N19815

Approval Letter And Related Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

G. Buehler
Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-815

SEP 6 1996

Roberts Pharmaceutical Corporation
Attention: Mr. Drew Karlan
Meridian Center II
Four Industrial Way West
Eatontown, NJ 07724-2274

Dear Mr. Karlan:

Please refer to your April 26, 1988 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ProAmatine (midodrine HCl) 2.5 and 5 mg Tablets.

We acknowledge receipt of your amendments and correspondence dated June 10, 14, 19 and 26, July 5, 8 and 15 and August 6, 13, 15 and 23 (two), 1996.

The new drug application provides for the use of ProAmatine for the treatment of symptomatic orthostatic hypotension (OH). The indication is based on ProAmatine's effect on increases in 1-minute standing systolic blood pressure, a surrogate marker considered likely to correspond to a clinical benefit. At present, clinical benefits of ProAmatine, principally improved ability to perform life activities, have not been established.

We have completed the review of this application including the submitted draft labeling, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve ProAmatine (midodrine HCl) 2.5 and 5 mg Tablets for use as recommended in the enclosed marked-up draft. Accordingly, the application is approved under 21 CFR 314.520. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations. In particular, we remind you that all promotional materials must be submitted at least 30 days prior to the intended time of initial dissemination of the labeling or the initial publication of the advertisement. Please submit one copy to NDA 19-815 and a second copy directly to the Division of Drug Marketing, Advertising, and Communications. Such submissions should be prominently labeled "Accelerated Approval Materials."

We remind you of your Phase 4 commitments specified in your submissions dated May 20 and August 15, 1996. These commitments, along with any completion dates agreed upon, are listed below.

As described under 21 CFR 314.570, approval under this section requires that you study the drug further to verify and describe its clinical benefit. The studies required to confirm the clinical benefit of midodrine were discussed at the July 18, 1996 meeting with the Agency. Draft protocols for the Phase 4 trials provided in your August 15, 1996 submission are currently under review. Our recommendations for the proposed studies will be provided under separate cover. Upon receipt of these

recommendations, the studies should be carried out with due diligence. The projected time for completion of these trials was estimated, at the July 18 meeting, to be 3 to 4 years, depending on rate of enrollment.

Protocols, data, and final reports should be submitted to your IND for this product with a copy of the cover letter submitted to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

If these studies do not provide verification of clinical benefit to conclude that the drug is safe and effective for an intended use, you will comply with the accelerated approval withdrawal procedures described in 21 CFR 314.530. Additional studies, including treatment IND protocols, could proceed after such a withdrawal if the data supported continued trials.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 19-815. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

APPLICATION SUMMARY

NDA 19-815 Proamatine (Midodrine HCl) 2.5 and 5 mg Tablets

Roberts Pharmaceutical Corporation
Meridian Center III
6 Industrial Way West
Eatontown, NJ 07724

Date of Submission: April 26, 1988

Not-Approvable Letters: October 22, 1993
July 31, 1991
February 13, 1990

Approvable Letter: June 6, 1996

Date of Major Amendment: September 25, 1995

Due Date: March 23, 1996

BACKGROUND

Upon receipt of the February 13, 1990 not approvable letter, Roberts requested that they be considered for approval under subpart H, approval based on a surrogate endpoint. Because of midodrine's effect on blood pressure, the decision was made to consider approval under subpart H. The Division met with Roberts to review their data supporting the use of increase in standing blood pressure as a surrogate for clinical benefit and decided that approval based on this surrogate could be considered. An approvable letter issued on June 6, 1996.

Please refer to previous CSO overview for further background on this application.

MEDICAL - Dr. Gordon

Dr. Gordon has done a comprehensive review of the latest 3 studies (201, 320 and 318) submitted by Roberts. While she found that all showed a statistically significant effect on raising blood pressure, the effect on symptoms was not impressive and only one trial (318) even looked at standing time. She was also troubled by the incidence of adverse events, specifically the high incidence of hypertension seen, and the fact that 5 times as many patients in the midodrine group dropped out of study 320 compared to the placebo group.

DSI Audits

Three audits were recently done on the 320 study (Low Gilden and Freeman). All found the conduct of the study centers acceptable

STATISTICS - Dr. Mahjoob

The efficacy of midodrine was measured by elevation of standing systolic blood pressure and improvement of major symptoms. Dr. Mahjoob concluded that midodrine therapy substantially elevated the standing systolic blood pressure from pre-dose to 1-hour post dose, but study 320 does not provide a full characterization with respect to the risk/benefit of the therapy for a 24 hour duration. He stated that the trials showed that midodrine showed significant superiority over placebo in improving the dizziness/ lightheadedness/unsteadiness (DLU) symptoms with respect to placebo.

BIOPHARMACEUTICS - Dr. Borga

Although he identified many deficiencies in the trials submitted by the firm, Dr. Borga found the application basically approvable provided that certain changes in labeling be made and that the firm commit to doing a phase IV study of the mechanisms of renal elimination and potential for drug-drug interaction for desglymidodrine.

CHEMISTRY - Dr. Mittal

Deficiencies listed in review #7 were related to Methods Validation and Dr. Wolters asked that they not be included in the decision letter. The firm has received these deficiencies, but they were informed that they will not affect approval.

Chemistry review #8 found the application approvable.

Establishment Inspection

An acceptable establishment inspection was issued on May 16, 1996.

Environmental Assessment

A satisfactory environmental assessment was submitted. A FONSI was prepared.

PHARMACOLOGY - Dr. Link et al

Initial pharmacology submission was reviewed by Dr. Lathers. She found the application approvable, except that she stated that if the indication was expanded to patients with less serious disease (non-Shy-Drager patients), they should have carcinogenicity studies. Carcinogenicity studies were submitted and reviewed by Dr. Link.

Dr. Lipicky did not believe that the further animal studies recommended by Dr. link need be performed.

Statistical Review of Carcinogenicity Studies - Dr. Cui

Review was completed by Dr. Cui. He deferred evaluation of the results to the reviewing pharmacologist. Dr. Link stated that the studies met minimal regulatory requirements; results were not significant.

SUMMARY

We have met with the firm to discuss their labeling, protocols and promotional material. There has been agreement on draft labeling. It is ready to send with an approval letter. Protocols for phase 4 trials have been submitted and are being reviewed. Promotional material has been submitted to DDMAC. An approval on draft labeling letter has been prepared for Dr. Temple's signature.

Gary Buehler

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

913

Food and Drug Administration
Rockville MD 20857

JUN - 6 1996

NDA 19-815

Roberts Pharmaceutical Corporation
Attention: Mr. Drew Karlan
Meridian Center III
6 Industrial Way West
Eatontown, NJ 07724

Dear Mr. Karlan:

Please refer to your April 26, 1988 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proamatine (midodrine HCl) 2.5 and 5 mg Tablets.

We acknowledge receipt of your correspondence and amendments dated March 12, 14, 18, 22, and 29, April 11, and 25, and May 13, 15, and 20, 1996.

As provided under 21 CFR 314.102(d), a meeting was held on May 22, 1996 between representatives of your firm and the Agency. Based upon discussions at that meeting, I have reconsidered the approvability of this application and have determined that it is approvable under 21 CFR Subpart H - Accelerated approval of new drugs for serious or life-threatening illnesses, specifically under 21 CFR 314.510 - Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity. Before Proamatine can be approved, however, the following additional information is needed:

1. Labeling: Please submit draft labeling revised to state clearly that the approval of this new drug is based on its effect on a surrogate endpoint, one-minute standing blood pressure, and that additional trials are underway to verify and describe the clinical benefits of midodrine. The labeling should include descriptions of the completed trials and endpoints used as surrogates upon which the approval is based. The labeling must be candid about what has not been established with respect to the clinical manifestations associated with orthostatic hypotension in the indicated population as well as the potential risk of supine and sitting blood pressure elevation.

   Accelerated approval applies only to products that are used to treat serious or life-threatening illnesses. The patient population for which this drug should be indicated should therefore be identified as those whose lives are considerably impaired, even after optimal clinical care; i.e., people who have not responded adequately to nonpharmacologic treatment (life-style alterations) and fluid expansion.

2. Promotional Materials: As required by 21 CFR 314.550, you should submit for consideration during the preapproval review period, three copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days following marketing approval. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

After 120 days following marketing approval you must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement.

3. Protocol(s): Please submit protocol(s) that will be carried out with due diligence after approval to verify and describe the clinical benefit of midodrine (see below). Please include a proposed schedule for initiation and completion of the trial(s) and for submission of the completed study report(s).

Protocol Design

As we explained in our March 22, 1996 not-approval letter, we have concluded that midodrine has a clear pressor effect in both the supine and standing position for 7 hours when administered q3h and for 1 hour after the first (or second) dose of the day when given for up to 3 weeks at 10 mg t.i.d. in an asymmetric regimen. Under an accelerated approval, additional trial(s) will be needed to show the clinical benefit in the treatment of orthostatic hypotension and define the time course of that benefit. In conducting these trials it is critical to consider the lessons of previous efforts. Please refer to the March 22, 1996 letter for details of our conclusions on previously conducted trials. We believe it will be very important for us to meet with you and your consultants to discuss the design of the additional trials.

There are several approaches to consider in seeking evidence of clinical benefit. The principal goals of the trial(s) are to show that midodrine provides a clinical benefit and to develop information that will allow the drug to be used with greater safety and effectiveness. Certain design considerations are applicable to all of the trials we suggest below.

All trials should be randomized, double-blind, placebo-controlled, parallel-group design studies with primary endpoint(s) identified clearly in the protocol. The principal protocol-stated analysis should be one that uses data from all patients given drug. It should be clear how patients not completing the study will be handled.

The following are our proposals for the trials that may be used to generate the necessary information; it may be possible to combine or "nest" some of these:

A Randomized Withdrawal Trial to Establish Clinical Benefit:

The most critical trial is one to establish that the recommended dosage of Proamatine has clinical benefit in a defined population. We believe the best, and most efficient, way to do this is to identify patients who are known midodrine responders and who can tolerate the side effects of midodrine and study them using a randomized withdrawal design. Patients should be identified on the basis of a morning blood pressure response, possibly a morning standing time response, and one important activity that the patient perceives as significantly improved by midodrine. The activity would be defined for each patient but described on a common scale (e.g., 10 cm VAS). At the start of the trial, all patients would receive midodrine (for a minimum amount of time, such as 2 weeks) at a defined dose (e.g., t.i.d. with at least 3 hours between doses). They would then be randomized to continued midodrine or placebo for a defined period (e.g., 3 weeks). Patients would be encouraged to remain in the trial but could terminate prematurely as failures for well-defined reasons (e.g., defined deterioration in ability to perform the important activity), or for other reasons. It would be critical to determine those reasons. Midodrine and placebo would be compared for effects on the critical activity and ability of patients to complete the trial. Blood pressure effects would be measured but would not be the primary endpoints of this trial.

The protocol should clearly define the questions that are to be asked during the patient evaluations, including the words used and the order in which they will be asked. Blood pressure measurements should be taken after the patients have answered the questions, and the person who records the blood pressure and collects side effects information should be different from the one who evaluates the clinical response. Each should be blind to the results obtained by the other and both recorders and patients should be blind to previously reported ratings. Patients could be asked to rate themselves periodically during a single day of treatment (e.g., the day before a clinic visit). In addition, it might be informative to have patients maintain diaries or record their scores frequently between visits.

Naive Patient Trial:

To gain a realistic assessment of risks and benefits of midodrine in an unselected population, study of a naive population would be useful. Patients on standard therapy for orthostatic hypotension, including nonpharmacologic management and fluid expansion, who remain symptomatic and have never taken midodrine, would be randomized to either placebo, a standard regimen of midodrine (10 mg t.i.d., at least 3 hours apart, with the last dose given by 6:00 p.m.), or a titrated regimen of midodrine (perhaps starting at 2.5 mg t.i.d. and increased to 10 mg t.i.d. or q.i.d. over 3 weeks). The titrated arm would allow one to know whether titration to a dose leads to fewer side effects than starting immediately on that dose. The primary efficacy endpoint, as in the randomized withdrawal trial, should be a daily life activity, but standing time measured over the course of the day would also be a reasonable endpoint. This trial should also measure one- and 3-minute standing blood pressures over the course of the study at intervals (e.g., weekly).

A High-Dose Study:

The effect on blood pressure of 20 mg is clearly greater than 10 mg. Unless there is good reason not to, doses higher than 10 mg should be explored. A trial could be performed in patients who have failed to respond adequately to standard doses of midodrine (10 mg t.i.d.); these patients would be randomized to greater and/or more frequent doses of midodrine or placebo. One possible design would be to randomize one group to placebo, one to 20 mg t.i.d., one to a regimen of 20 mg as the first dose of the day, followed by doses of 10 mg, and one group to 15 mg t.i.d. Again, endpoints should include an important life activity, one- and 3-minute standing blood pressure, and possibly standing time.

The following points should be considered in deciding on the design of the trial(s):

1. Standing time, in contrast to standing systolic blood pressure, is a clinically meaningful endpoint. When studied, standing time should be assessed over the course of a day (at least over the waking hours), and the effect of the initial daily dose assessed over time (e.g., weekly) with continuous dosing. These measurements might be performed in a well defined subgroup of any of the proposed trials.

2. Increases in supine and sitting blood pressure are substantial and are worrisome. It would be worthwhile to explore the effect of midodrine on blood pressure over a 24-hour time period (at

baseline and then after chronic dosing) using an automated device, at least in a subset of the treated population. This device, which can evaluate blood pressure under "daily living" conditions, has been used successfully in many studies evaluating antihypertensive agents.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
Telephone: (301) 594-5332

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

PATENT STATEMENT

Midodrine Hydrochloride is described in U. S. Patent 3,340,298 which issued on September 5, 1967. This patent expired on September 5, 1984.

study after randomization. This left 19 fentanyl and 17 placebo patients in the study.

The subjects were typical for the predominantly male VA patient population, with a mean age of 52 years, weight of 80-83 kg, and ASA class II. As a group, this population has a higher degree of alcohol and drug use and anesthetic and analgesic tolerance than other sub-samples of the population, and this would be expected to reduce the difference between the fentanyl and placebo group by altering the pharmacodynamics of fentanyl.

As the system was applied pre-operatively, an "intent-to-treat" analysis should include all patients, but the 3 subjects in the fentanyl group who were withdrawn all had non-drug related protocol changes or surgical cancellations. The same was true of the 3 peri-operative placebo withdrawals. In consequence, the most unbiased method of handling the patients who had systems but no surgery is not to extrapolate their values, the method used by the sponsor.

The same cannot be said for the 1 placebo patient who was removed for respiratory depression and 2 placebo patients who dropped out for inadequate analgesia as well. No predictable bias was likely to have been introduced by these withdrawals, but they do degrade the power of the trial.

Results and Analysis

The results of the study are shown on the accompanying pages. As may be seen from the plot of morphine use, the use of rescue medication in the experimental and control group differed to the greatest extent in the first hours of the trial, and while the use of morphine was always less in the active system group, this difference was never significant. While a significant difference favoring the TTS system was seen in 0-24 hour global pain ratings, hourly pain ratings and observer ratings did not differ to any appreciable extent.

Safety

Review of the pattern of side effects reported in the study shows no obvious pattern other than a higher incidence of urinary retention (5 fentanyl vrs 2 placebo) and of anxiety (2 fentanyl vrs 0 placebo).

There were three patients in the study who had episodes of serious respiratory depression :

SCN 170, a fentanyl patient, had an episode of apnea after extubation in the PAR (fentanyl level 1.85) and required naloxone.

SCN 125, placebo, had hypercarbia after pulmonary lobectomy and receiving 16 mg morphine.

SCN 130, fentanyl, had an episode of hypopnea after receiving 50 mg diphenhydramine IV for hives (fentanyl level 0.61).

None of these episodes appeared related to TTS fentanyl overdosage, but did seem related to the residua of anethesia, use of narcotic analgesics or the combination of narcotics with sedatives.

Topical effects from the system were as expected. Both fentanyl and placebo system patients had mild erythema lasting 24 hours post system removal, while one patient had mild irritant dermatitis with pustules lasting over 24 hours.

Pharmacologic Performance

There was considerable variation in peak blood level, Tmax, and 24 hour dose in this study. Examination of the group mean revealed that it required about 4-8 hours for the patients to reach analgesic blood levels of fentanyl even with the bolus dose, and the peak level was not reached until 2 hours after the system was removed at 24 hours (hour 26).

Case reports for two of the individuals with the lowest blood levels and two with the highest blood levels were reviewed to examine the pharmacokinetic exceptions. Subjects 115 & 127 had low blood levels of fentanyl and were found to be males who weighed 108.9 and 104.3 kilos respectively, who were having a total knee repair (3.5 hr) and a cholecystectomy (4.5 hr) respectively. Cases 122 & 174 (who had high blood levels) were also male, 90 & 85 kg respectively, and having a low anterior resection (4.5 hr) and a Knodt rod fusion (5.5 hr). No satisfactory explanation for the differences other than the 20 % weight difference and its probable relationship to [illegible] could be discerned.

Reviewer's Evaluation

The investigator failed to show any difference between TTS 100 and placebo on any of the major outcome variables in the study. Although TTS 100 fentanyl did consistently outperform placebo in both supplemental morphine requirements and pain intensity scores the difference was not of a magnitude such as to reach statistical significance given the power of the study. The safety findings are consistent with the efficacy outcome, and both seem to reflect the lack of sufficiently high blood levels of fentanyl to produce either analgesia or adverse effects. The claim of improved overall pain relief in the 0-24 hour ratings is not sufficiently robust to be accepted owing to the multiplicity of secondary variables.

Conclusion

This study gives useful information about the kinetics of the drug, but provides no information regarding either an analgesic effect or lack of toxicity in analgesic doses.

See Consult #58 Consult #362

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Ms. Yana Mille, Chair, (HFD-600) MPN II

FROM: Division of Cardio-Renal Drug Products HFD-110
Attention: Gary Buehler Phone 4-5332

DATE: 10/19/94

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Proamatine NDA/ANDA# 19-815

Company Name: Roberts Pharmaceutical

Established name, including dosage form: midodrine HCl tablets

Other trademarks by the same firm for companion products:
Gutron (european trade name)

Indications for Use (may be a summary if proposed statement is lengthy): Orthostatic hypotension

Initial comments from the submitter: (concerns, observations, etc.)
Refer to Consult #58 for previous discussion

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Oct. 93

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Mr. Kent Johnson, Chair, (HFD-600) MPN II

FROM: Division of Cardio-Renal Drug Products HFD- 110
Attention: Robert Wolters Phone: 443-0315

DATE: May 20, 1991

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Amatine NDA/ANDA # :19-815

Established name, including dosage form: Midodrine Hydrochloride 2.5 & 5 mg tablets

Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy): Alpha adrenergic agonist for idiopathic orthostatic hypotension

Initial comments from the submitter: (concerns, observations, etc.)

NOTE: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev Dec. 1990

Consult #58 (HFD-110)

Amatine Midodrine Hydrochloride Tablets

A review revealed two names which look or sound like the proposed name. The first, Emetine, an antiamebic, is an injection, not widely used, and is not thought to present a significant problem. However, the second conflicting name, Amantadine, is that of a well-recognized and widely used product which is frequently prescribed by established name.

The Committee finds the proposed name unacceptable since it is clearly misleading as described in 21 CFR 201.10(c)(5).

CDER Labeling and Nomenclature Committee

5-31-91

_____, Chair

Consult #362 (HFD-110)

PROAMATINE — Midodrine Hydrochloride Tablets

A review revealed several names which sound or look like the proposed name: Primatine, Persantine, and Pro-Banthine. However, the Committee does not believe any of these names are likely to be confused with the proposed name.

The Committee has no reason to find the proposed name unacceptable.

Yana Mille, Chair 11/7/94
CDER Labeling and Nomenclature Committee

COMPLETED

BIO Review

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

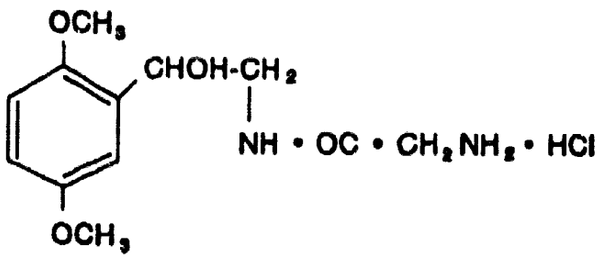
NDA No. 19-815
Submission Dates: 12/28/87, 05-14-93, 9-21-94, 9-22-95, 10-05-95, 12-27-95, 12-29-95, 01-04-96
Generic Name: Midodrine HCl
Brand Name: ProAmatine
Formulation: Tablets 2.5 and 5 mg.
Sponsor: Roberts Laboratories Inc., Eatontown NJ 07724
Type of Submission: New Drug Application **Status:** 1P
Reviewer: O. Borga, Ph.D.

TABLE OF CONTENTS

	Page
Background	2
Drug Substance	2
Drug Formulation	2
Composition of Pro-Amatine Tablets	3
Contents of Previous and Present Submissions	4
Summary of Pharmacokinetics and Pharmacodynamics	5
- Pharmacology of the Enantiomers	5
- Absorption	5
- Food Studies	5
- Distribution	6
- Half-lives	
- Kinetics of enantiomers	6
- Multiple-dose kinetics	6
- Renal Elimination	6
- Metabolism	7
- Dose Proportionality	7
- Clinical versus Market Formulation	7
- Pharmacokinetics in Target Population	7
- Elderly	8
- Gender Effects on Plasma Levels	8
- Pharmacokinetics in Special Populations	8
- PK-PD Relationship	8
Dissolution Method	9
Labeling Comments	9
Comments	11
Recommendations	12
Appendix 1. Review of individual studies:	
A dose proportionality and food effect study	13
Plasma levels in patients in clinical study	19
Pharmacokinetics of enantiomers	26
Absolute bioavailability of tablet and oral solution	31
Appendix 2. Proposed labeling with suggested changes	

Background: Midodrine HCl is the racemate of a chiral sympathomimetic agonist that binds to receptors of the arterial and venous vasculature, leading to an increase in vascular tone and elevation of blood pressure. While it has been shown to have in vitro activity of its own, it appears clear that the main active moiety is the metabolite desglymidodrine, which has an in vitro activity 15 times that of the parent compound. Desglymidodrine is formed by enzymatic hydrolysis of the glycineamide bond of midodrine. Midodrine is currently marketed in Europe under various brand names, its main indication being the treatment of orthostatic hypotension associated with autonomic failure. An effective treatment is still lacking for this indication. Midodrine has the status of an orphan drug.

Drug Substance: Midodrine is a mixture of two enantiomers. It has weak basic properties, the pK_a being 7.8. The hydrochloride has a solubility in water of 93 mg/mL. The solubility is 78 mg/mL at pH 1.0 (0.1N HCl) and 98 mg/mL at pH 7.3. Thus the solubility is high and quite independent of pH. The distribution coefficient between octanol and water is low, 0.019.



Drug Formulation: The tablets are immediate-release tablets of strengths 2.5 and 5 mg. The maximum daily dose is 30 mg. The quantitative composition of the formulations is presented in Table 1. Full-scale production batches have been used throughout the clinical and biopharmaceutical programs. Tablets have been supplied by Hafslund Nycomed Pharma, Norway, that manufactures and sells the product world-wide under the name of Alphamine, Amatine, Gutron, Hipertan, Metligine, and Midamine.

Table 1. Composition of Pro-Amatine (midodrine HCl) 2.5-mg and 5-mg tablets.

Strength	2.5-mg Tablet	5-mg Tablet
Midodrine HCl	2.5 *)	5.0 *)
Magnesium Stearate		
Talc		
Colloidal Silicon Dioxide		
Microcrystalline Cellulose		
Corn Starch		
FD&C Yellow 6 Lake		
Total Weight		

*) Corresponding to the actual content of midodrine HCl, from 98% to 102%, e.g. for 5-mg tablet: 4.9-5.1 mg.
**) In dependence of the actual content of active substance: 80.1-79.9 mg

Contents of Previous and Present Submissions: The 12/28/87 submission contained 6 studies and was reviewed by Dr J.B. Jenkins, who found this submission grossly deficient and unreviewable. Study 058-133b (only mentioned deficiency: chromatograms were not supplied) was one possible exception. I have reviewed this study; see Study 4. The 05/14/93 amendment contained one study that was reviewed by Dr R.S. Pradhan, who concluded that the study contained several unexplained findings. The Sponsor has later volunteered information that the assay used in that study was not measuring desglymidodrine as intended. The 09/21/94 amendment was not reviewed at the time, but rather the Sponsor was informed what information would still be needed before a review of the Biopharmaceutics part of the submission could be undertaken.

The present submissions (from 1995-96) contains one pilot study (Study 3) of the kinetics of the (+) and (-) isomers of midodrine and desglymidodrine after administration of the racemate. It also contains the response to the letter of 5/23/95 from FDA in which the outstanding biopharmaceutics issues were brought to the Sponsor's attention. The response addresses these issues, and refers to data excerpted from the previous submissions as well as data compiled from sources within the company and from the literature. Among missing information in the previous submissions was validation data for the bioanalytical procedures (e.g. chromatograms for Study 4)., which is now being presented. The new information is presented in 6 volumes as follows:

Volume 1
Physical/Chemical properties of the drug
Proposed Package Insert (PI)
References to PI (1-6)

Volumes 2 and 3
References to PI (7-36)

Volume 4
References to PI (37-41)
Summary of ADME & pharmacokinetic (PK) properties
Validation of bioanalytical methods
Dosage formulation information
In vitro drug dissolution
Metabolic pathways

Volume 5
Multiple dose kinetics in humans studied with chiral assay.
Toxicokinetic studies in rats and dogs using chiral assay.

Volume 6
Single-dose studies in patients. Plasma level data analyzed according to age and gender classification.

SUMMARY OF PHARMACOKINETICS AND PHARMACODYNAMICS

Reviews of the four pharmacokinetic studies most central to the pharmacokinetic issues are to be found in Appendix 2. Otherwise, the following summary will draw from previous reviews as well as from the material that was submitted by the Sponsor in direct response to the FDA letter of 5/23/95.

Pharmacology of the Enantiomers: *In vitro* effect studies, measuring the contractility of isolated rat aorta, showed that the EC 50 of the l(-)-enantiomer of desglymidodrine was two orders of magnitude lower than that of the d(+)-enantiomer. This demonstrates that only the l(-)-form is active. Comparing the EC50 of the l(-)-forms of midodrine and desglymidodrine, it was concluded that desglymidodrine was approximately 15 times more active. The slow *in vitro* onset of action with midodrine indicated that the effect was mediated by desglymidodrine formed in the *in vitro* test system. Selective blocking by prazosin indicates that the effect is via α_1-receptors. It is important to note that there is no interconversion *in vivo* between the two enantiomeric forms. Thus d(+)-midodrine is metabolized to d(+)-desglymidodrine which is completely inactive.

Absorption: The absorption of midodrine tablets is very fast with a T_{max} of about 0.5 hours. The absolute bioavailability of midodrine is approximately 50%. The absolute bioavailability of its active metabolite, desglymidodrine, has not been determined. Urinary data demonstrates that at least 34% of the dose is transformed to the active metabolite. While plasma levels of midodrine peaked after 0.5 hr, desglymidodrine plasma levels peaked after 1.1 hr. This indicates rapid conversion to desglymidodrine. A fraction of the dose appears to be converted already during the first passage of gut wall and/or liver. The absolute fraction of systemically available midodrine that is being converted to desglymidodrine is not known. The AUC for desglymidodrine after oral administration of midodrine amounts to 90% of the AUC of desglymidodrine formed after an intravenous administration of midodrine. However, as pointed out above, the absolute amount of desglymidodrine formed is not known in either case. Part of the biotransformation of midodrine is of hepatic origin, part of it is due to metabolic activity in blood and other tissues. The plasma levels of midodrine and desglymidodrine were virtually identical after the tablet (2.5 mg) and an oral solution of midodrine, indicating rapid *in vivo* dissolution. The tablet and the solution showed similar bioavailability.

Food Studies: A food effect study was undertaken with a 10-mg dose (2 x 5 mg). There was no effect of a medium-size meal (1 pkg Corn Flakes, 4 oz whole milk, 2 slices toast with butter and jam, plus coffee) on C_{max} and AUC_∞ of the active desglymidodrine,

whereas mean T_{max} was prolonged from 1.3 to 2.1 hours. T_{max} for midodrine was slightly prolonged (from 30 to 45 min), while mean C_{max} decreased from 42.6 to 29.1 ng/mL. In contrast, AUC of midodrine was increased on the average 25% by the meal. Since the decrease in C_{max} and increase in AUC was not propagated from midodrine to the active moiety, desglymidodrine, these effects are inconsequential.

Distribution: The protein binding of midodrine and desglymidodrine in human serum was of the order of 30%. The volume of distribution (model independent, V_β) of midodrine was approximately 70 L. The volume of distribution for desglymidodrine is not known.

Half-lives: After intravenous administration of midodrine, its half-life is approximately 0.4 hours, while that of formed desglymidodrine is about 3 hours. As discussed below, the half-lives for midodrine and desglymidodrine are difficult to define in a meaningful way, since the enantiomers have different half-lives.

Kinetics of enantiomers: A study using a chiral assay after oral administration of midodrine demonstrated large differences in apparent clearance and volume of distribution values for the two enantiomers. The true values for these parameters could not be determined due to uncertainties in the oral availabilities of the two enantiomers of midodrine, and in the percentages of the dose that get converted to the enantiomers of desglymidodrine. Nevertheless, the data demonstrated a longer half-life of the active (-)-form of the metabolite, 3.5 hours as compared to 2.1 hours for the inactive (+)-form. Plasma levels of the active form were also remarkably higher than those of the inactive form. The kinetics of separately administered enantiomers of midodrine have not been studied.

Multiple-dose kinetics: Since midodrine and desglymidodrine have short half-lives, accumulation is not expected to occur with administration bid. This was demonstrated to be true in a study in healthy volunteers that obtained 7.5 mg midodrine twice daily for 7 days. Plasma level data for days 1 and 7 was virtually superimposable. The Sponsor has suggested dosing 3 times a day with an interval of only 3 hours, but not provided any data with regard to accumulation for this regimen.

Renal Elimination: The renal elimination of midodrine is insignificant. The renal clearance for desglymidodrine is of the order of 385 mL/min. Since the unbound fraction in plasma is 70%, one can estimate glomerular filtration to be approximately 84 mL/min (0.7*120 mL/min). Thus about 80% of the renal elimination occurs by active renal secretion and about 20% by glomerular filtration. Since no mechanistic studies have been undertaken,

one can only speculate that the active secretion is by the base-secreting system responsible for the secretion of a number of drugs that are also bases (see Labeling: "Potential for Drug Interactions"). As noted above, the active l(-)-enantiomer of desglymidodrine is cleared slower in man than the inactive d(+)-enantiomer. It has not clarified whether this difference occurs on the level of renal secretion or metabolism or both. It is worth noting that for a structurally similar compound, the β_2-agonist terbutaline, the active l(-)-enantiomer had a lower renal clearance than the inactive d(+)-enantiomer (Borgstrom et al., Br.J.Clin.Pharmacol. 1989, 27:49-56).

Since the amount of desglymidodrine being formed has not been determined, the relative importance of the renal route for the elimination of desglymidodrine is not known. Thus the consequences of impaired renal elimination or drug-drug interaction at the renal level can not be predicted.

Metabolism: Midodrine is mainly converted to desglymidodrine, although other pathways apparently exist, which might decrease the bioavailability in terms of desglymidodrine. The main metabolic pathway for desglymidodrine is by demethylation of the methoxy group located in meta position to the amino side-chain. This metabolite (M-2) is deaminated to the corresponding glycol, which is the main metabolite (M-4) of desglymidodrine. Conjugated forms of midodrine, desglymidodrine, M-2, and M-4 exist, and could be either glucuronides or sulfates, since hydrolysis was brought about by use of preparations with β-glucuronidase plus sulfatase. (The means of identification is still unclear. The Sponsor has indicated that information on ^{14}C-study is underway). Neither midodrine nor desglymidodrine are substrates for monoamine oxidase.

Dose Proportionality: Using 2.5- and 5-mg tablets, dose proportionality was demonstrated for single doses of 2.5, 5, and 10 mg (2×5 mg) midodrine, both with regard to C_{max} and AUC_∞ of midodrine and desglymidodrine. Also, dose-normalized mean plasma levels of midodrine and desglymidodrine were virtually superimposable. Studies in patients showed a similar dose proportionality for single doses of 5, 10 (2×5), and 20 (4×5) mg.

Clinical versus Market Formulations: The Sponsor states that the clinical studies have been performed with the final formulation, which in all cases have been manufactured by Hafslund Nycomed Pharma.

Pharmacokinetics in Target Population: A study with limited sampling in 25 patients (of both sexes) with orthostatic hypotension indicated slightly higher plasma levels of desglymidodrine in the patients, as compared to young healthy male volunteers from another study. No formal analysis was

undertaken due to the fact that samples were taken only up to 6 hours after drug administration, but the average half-life in the patients was estimated at 4 hours. The average half-life of desglymidodrine in healthy subjects is 3 hours. Thus the pharmacokinetics in the target population does not seem to deviate dramatically from that in healthy subjects.

Elderly: Plasma level data for midodrine and desglymidodrine from 20 patients were divided according to patient age: <65 years (N=11) and ≥65 years (N=9). A cross-over design was used; each patient had received 2.5, 10, and 20 mg of midodrine. Both after doses of 10 and 20 mg mean plasma levels were virtually identical in the two age groups (if anything, the younger age group was slightly higher in terms of plasma levels).

Gender Effects on Plasma Levels: Data from 17 males and 23 females were compared with respect to plasma concentrations of midodrine and desglymidodrine. No differences were found after a 10-mg dose. After a 20-mg dose of midodrine, plasma levels of desglymidodrine tended to be higher (approximately 40%) in the females. The finding appears to be of little concern since the highest recommended daily dose is 30 mg, which is probably going to be divided into three dose administrations of 10 mg each per day. Midodrine plasma levels (20-mg dose) were also higher in the females than the males. This finding has no relevance *per se*, since midodrine itself has virtually no activity.

Pharmacokinetics in Special Populations: No studies have been performed in patients with impaired renal or hepatic function. As noted above, the consequences of renal impairment can not be predicted. Without quantitative data on the metabolism of desglymidodrine, the consequences for hepatically impaired patients are equally difficult to predict. These concerns need to be expressed in the labeling.

PK-PD Relationship: No attempt to analyze the relationship between plasma levels and hypertensive response has been undertaken by the Sponsor. Some sort of relationship is expected, since there is a clear-cut dose response, and plasma levels are proportional to dose. A factor that is bound to blur the picture is the lack of separate measurements of the active l(-)enantiomer and the inactive d(+)enantiomer. Since the clearance of the two is different, the ratio of the two will change with time. Thus the total plasma levels will not reflect the levels of the active enantiomer. In view of this limitation, and the high inter- and intra-variability in effect measurements, the undertaking of a PK-PD analysis by this reviewer was not considered meaningful.

DISSOLUTION METHOD

Product Dissolution Method

Dosage Form: Tablets
Dose Potencies: 2.5 and 5 mg
Apparatus:
Medium:
Volume:
Agitation:
Temperature:
Sampling Times:
Analytical:

Dissolution Specifications: The specification proposed by the Sponsor states "not less than dissolved within 30 minutes". The data submitted by the Sponsor demonstrates an average dissolution at 5 minutes of about (the lowest individual tablet was dissolved). The following sampling times are suggested: 5, 10, 15, and 30 minutes, with the specification be set to be "not less than within 15 minutes".

LABELING COMMENTS

A copy of the proposed labeling, including minor suggested changes pencilled in, is presented as Appendix 2. The Pharmacokinetics part has been completely redrafted as follows:

"**Pharmacokinetics:** ProAmatine is a prodrug, i.e., the therapeutic effect of orally administered midodrine is due to the major metabolite desglymidodrine, formed by deglycination of midodrine. After oral administration ProAmatine is rapidly absorbed. The plasma levels of the prodrug peak after about half an hour, and decline with a half-life of approximately 25 minutes. The absolute bioavailability of midodrine is approximately 50%. The absolute bioavailability of desglymidodrine has not been determined. Approximately the same amount of desglymidodrine is formed after intravenous and oral administration of midodrine. Urinary recovery data demonstrates that at least 34% of an oral dose of midodrine is transformed to the active metabolite. The plasma half-life of desglymidodrine is 3-4 hours. Peak levels of the active desglymidodrine are generally reached 1-2 hours after drug administration. After a 10-mg dose of ProAmatine, the mean peak level of desglymidodrine is approximately 20 ng/mL. A

desglymidodrine level higher than 10 ng/mL is generally maintained from 0.5 to 4 hours after drug intake, during which blood pressure is elevated. The bioavailability of desglymidodrine was similar when a 10-mg dose of ProAmatine was given with a meal or in a fasted state. Neither midodrine nor desglymidodrine is bound to plasma proteins to any significant extent (about 30%). The volume of distribution of midodrine is approximately 70 L. The value for the active metabolite is not known. The renal elimination of midodrine is insignificant. The relative importance of renal and non-renal elimination routes for desglymidodrine is not known. Thorough metabolic studies have not been conducted, but it appears that deglycination of midodrine to desglymidodrine takes place in many tissues, and both compounds are metabolized in part by the liver. Neither midodrine nor desglymidodrine are substrates for monoamine oxidase.

The renal clearance of desglymidodrine is of the order of 385 mL/min. The majority, or about 80%, is by active renal secretion. The actual mechanism of active secretion has not been studied, but it is quite possible that it occurs by the base-secreting pathway responsible for the secretion of several other drugs that are bases (See also Potential for Drug Interactions)."

The following should also be included in the labeling:

"*Potential for Drug Interactions:* It appears likely, although there is no experimental evidence, that the high renal clearance of desglymidodrine (a base) is due to active tubular secretion by the base-secreting system also responsible for the secretion of, e.g. metformin, cimetidine, ranitidine, procainamide, triamterene, flecainide, and quinidine. Thus there might be a potential for drug interactions at this level."

COMMENTS TO BE FORWARDED TO THE FIRM

1. The present view held by the Sponsor and presented in their draft of the Package Insert that "ProAmatine is rapidly and almost completely absorbed, with a mean absolute bioavailability (as desglymidodrine) of 93%" is incorrect and based upon misinterpretation of data from study 058-133b. Absolute bioavailability of desglymidodrine requires a study in which this entity is given intravenously.

2. Calculations of pharmacokinetic parameters in study 058-133b must take into account that doses are reported in mg of midodrine hydrochloride while plasma concentrations are reported as ng/mL of the free base. Also, as pointed out above, the proportion of desglymidodrine formed from midodrine is unknown. Hence the values reported for clearance and volume of distribution of desglymidodrine are incorrect.

3. In study GUH-1/94 the plasma levels were reported as ng/mL of the hydrochlorides of midodrine and desglymidodrine as opposed to reporting the free base concentration as done in the other studies. Thus plasma levels and C_{max} values are not comparable across studies.

4. In study GUH-1/94, due to oversight by the investigator, the calculations of V and CL did not take into account that the dose of each enantiomer is 3.75 mg, not 7.5 mg, which is the dose of the racemate. The latter contains equal amounts of the two enantiomers. A second mistake was not to compensate for the differences in molecular weights of midodrine and desglymidodrine. The dose in terms of each enantiomer of desglymidodrine*HCl is 6.028/2 mg taking into consideration that the molecular weight of desglymidodrine*HCl is a factor 0.8038 less than that of midodrine*HCl. A third mistake was not to consider that one does not know the actual percentage of the dose of midodrine that is being converted into desglymidodrine. Reported values for clearance and volume of distribution of desglymidodrine are thus incorrect.

4. Since it appears that the active metabolite is highly dependent on renal secretory mechanisms for its elimination, it is necessary to study these mechanisms further, in order to assess the potential for drug interactions. That can be done by using an inhibitor of base secretion, such as cimetidine, as a probe. A study of renal and metabolic clearance (cimetidine is also a blocker of mixed function oxidase) in the presence and absence of cimetidine is highly desirable. These studies will only be meaningful if analyzed with a chiral assay.

5. If the intended dosage regimen is 3 times daily with an interval of 3 hours, a multiple-dose study with this regimen

should be done. The study should focus on the active enantiomer of desglymidodrine.

6. *In vitro* studies to identify the isoenzyme(s) responsible for the metabolism of desglymidodrine are recommended.

7. In view of the different elimination rates of the two enantiomers; if future studies are considered of the disposition of midodrine, e.g. in patients with compromised renal or hepatic function, such studies should be performed with a chiral assay.

RECOMMENDATIONS

The following phase IV commitments are recommended:

The following is recommended with regard to *in vitro* dissolution testing: USP Apparatus II using 50 rpm and 900 mL of 0.1-N HCl. Specification: Q= at 15 minutes.

For the purpose of comparing dissolution profiles, sampling times at 5, 10, 15, and 30 minutes are suggested.

Upon implementation of the suggested labeling changes, and provided that further studies will be done as phase IV commitments as indicated above, the Sponsor's NDA 19-815 is approvable from the Office of Clinical Pharmacology and Biopharmaceutics' perspective.

2-16-96

Olof Borga, Ph.D. Date
Division of Pharmaceutical Evaluation I

FT Initialed by Patrick Marroum, Ph.D. 2/16/1996

Biopharm Day: 2/8/96 (Lazor, Marroum, Mehta, M.Gordon)

cc: NDA 19-815, HFD-110, HFD-860 (Malinowski, Borga, Mehta), HFD-870 (ML Chen), HFD-880 (Fleischer), Drug, FOI (HFD-19), Chron, HFD-340 (Viswanathan).

APPENDIX 1

REVIEW OF INDIVIDUAL STUDIES

REVIEW OF STUDY SUBMITTED AS AN AMENDMENT TO NDA 19-815

STUDY 1:

Study Title: A dose proportionality study of midodrine (2.5, 5, and 10 mg) and the effect of food on oral bioavailability in normal male subjects.

Protocol Number:

Report Number:

Investigators:

Study Site: Not reported.

Objectives: To study dose proportionality of midodrine and evaluate the effect of food on the availability of midodrine, 10-mg tablet.

Treatments: Each subject received four single doses of midodrine: 2.5 mg, 5 mg, and 10 mg midodrine orally were given during fasting conditions; 10 mg was given immediately after a "standard meal" containing 1 small package of Corn Flakes, 4 oz of whole milk, sugar for taste, 2 slices toast, lightly buttered with a standard package of jam or jelly. Tablets of the strength 2.5 mg and 5 mg were used.

Design: Open label, randomized, single-dose, 4-way crossover.

Study Subjects: 18 male subjects were studied. Age ranged from 20 to 49 years (mean 33), body weights from 60.5 to 102 kg (mean 81). Eight were Blacks, 8 were Whites, 2 were Hispanics. None was smoker. The subjects are referred to as patients, but it appears from the tabulated medical history that healthy volunteers were used.

Blood Sampling: Plasma was collected at the following times: 0 (blank), 10, 20, and 30 minutes, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours after dosing.

Analytical Methods: The principle of the assay was not described in earlier submissions, nor was any validation data. The present submission (10/05/95) presents validation data for parent drug and metabolite for Studies 1 and 2 that can be summarized as follows:

STUDY RESULTS: Plasma levels of the prodrug, midodrine, declined rapidly and, with one exception, levels were below limit of quantitation (LOQ), 0.5 ng/mL, at 4 hours after the 10-mg dose, earlier after the other doses (See Figure 1 for mean levels). The plasma levels of the active moiety, desglymidodrine, were above LOQ, 0.5 ng/mL, up to 12 hours in all subjects (See Figure 1 for mean levels). Pharmacokinetic parameters for the 3 doses are summarized in Table 1 for the prodrug and Table 2 for the active metabolite.

Table 1. Pharmacokinetic parameters for midodrine, mean (%CV), for 18 subjects dosed in the fasting state.

Parameter	Dose (mg)		
Dose	2.5 mg	5.0 mg	10.0 mg
C_{max} (ng/mL)	11.2 (24)	22.8 (29)	42.6 (27)
T_{max} (hr)	0.47 (32)	0.41 (29)	0.50 (42)
AUC_{∞} (ng*hr/mL)	9.42 (29)	19.6 (25)	36.6 (21)
t1/2 (hr)	0.49 (45)	0.46 (33)	0.44 (25)

Table 2. Pharmacokinetic parameters for desglymidodrine, mean (%CV), for 18 subjects dosed in the fasting state.

Parameter	Dose (mg)		
Dose	2.5 mg	5.0 mg	10.0 mg
C_{max} (ng/mL)	4.59 (16)	9.23 (21)	19.3 (25)
T_{max} (hr)	1.35 (41)	1.56 (49)	1.28 (43)
AUC_{∞} (ng*hr/mL)	23.9 (34)	53.2 (28)	107.7 (24)
t1/2 (hr)	3.32 (44)	3.14 (11)	3.03 (13)

Dose proportionality is obvious from C_{max} and AUC_{∞} values in Tables 1 and 2. Also, dose-normalized mean plasma levels of midodrine and desglymidodrine were virtually superimposable (see Figure 2).

In terms of C_{max} and AUC_{∞} the effect of food was only pronounced on midodrine, whereas the food-effect was negligible on the active metabolite, desglymidodrine (Tables 3 and 4).

Table 3. Pharmacokinetic parameters for midodrine, mean (%CV), in 18 subjects after 10-mg tablet given without and with food.

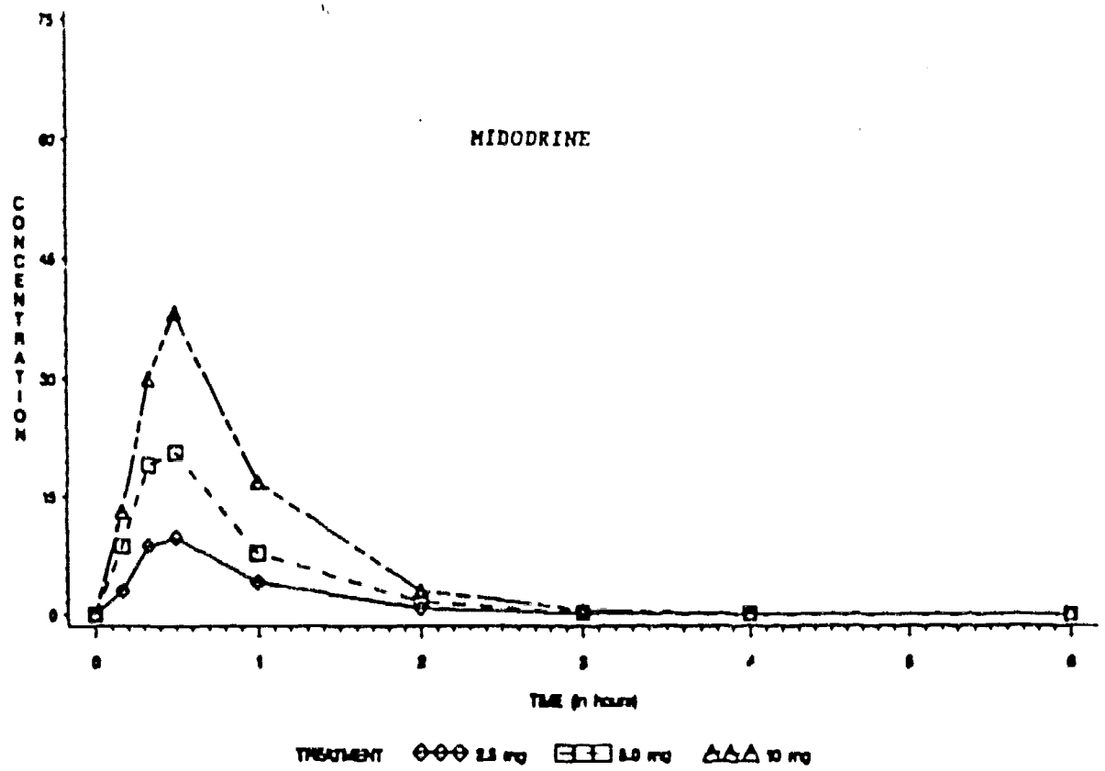
Parameter	Fasted	Fed	p-value; fed vs fasted
C_{max} (ng/mL)	42.6 (27)	29.1 (30)	0.0002
T_{max} (hr)	0.50 (42)	0.76 (37)	0.0084
AUC_{∞} (ng*hr/mL)	36.6 (21)	46.3 (28)	0.0001

Table 4. Pharmacokinetic parameters for desglymidodrine, mean (%CV), in 18 subjects after 10-mg tablet given without and with food.

Parameter	Fasted	Fed	p-value; fed vs fasted
C_{max} (ng/mL)	19.3 (25)	18.6 (19)	0.3910
T_{max} (hr)	1.28 (43)	2.06 (26)	0.0004
AUC_{∞} (ng*hr/mL)	107.7 (28)	107.5 (23)	0.9251

Figure 1

Mean Plasma Levels of Midodrine (ng/mL) and Desglymidodrine (ng/mL) after Single Oral Doses of 2.5, 5, and 10 mg of Midodrine Hydrochloride to 18 Fasting Subjects



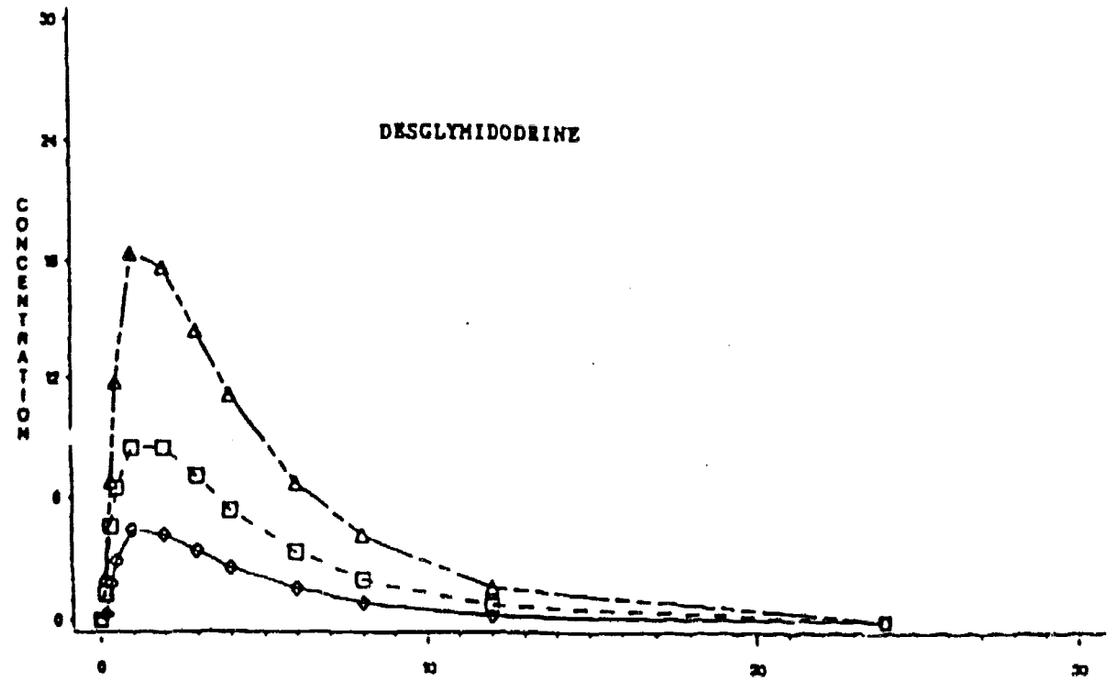
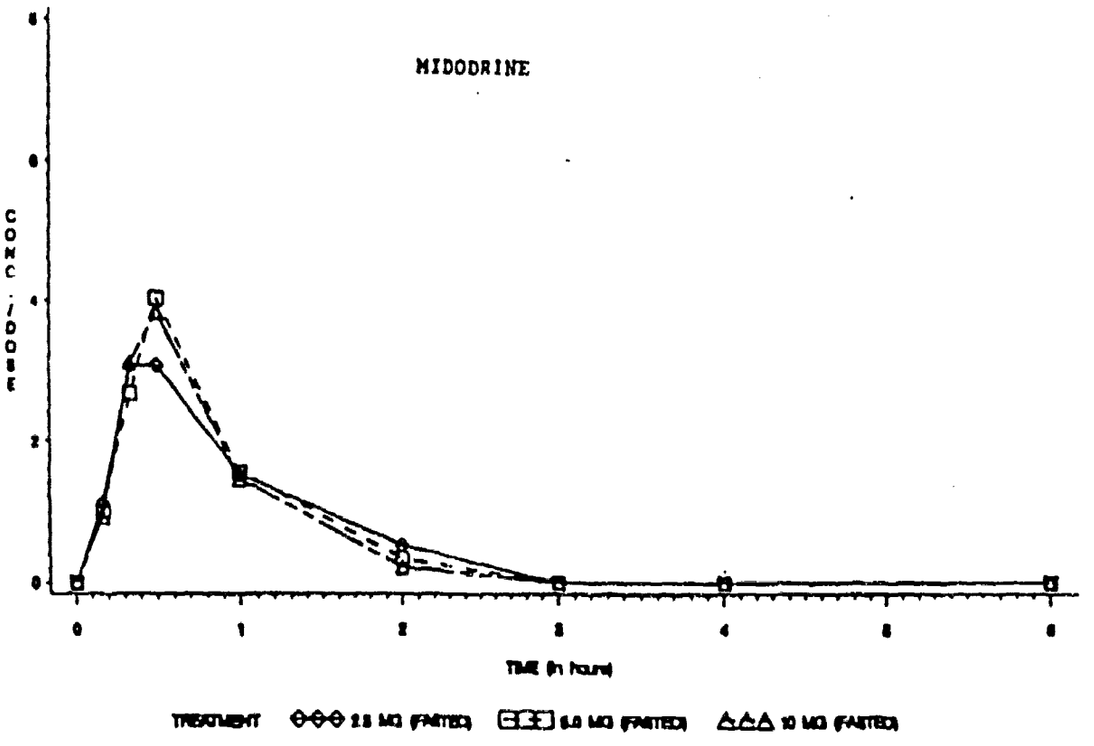
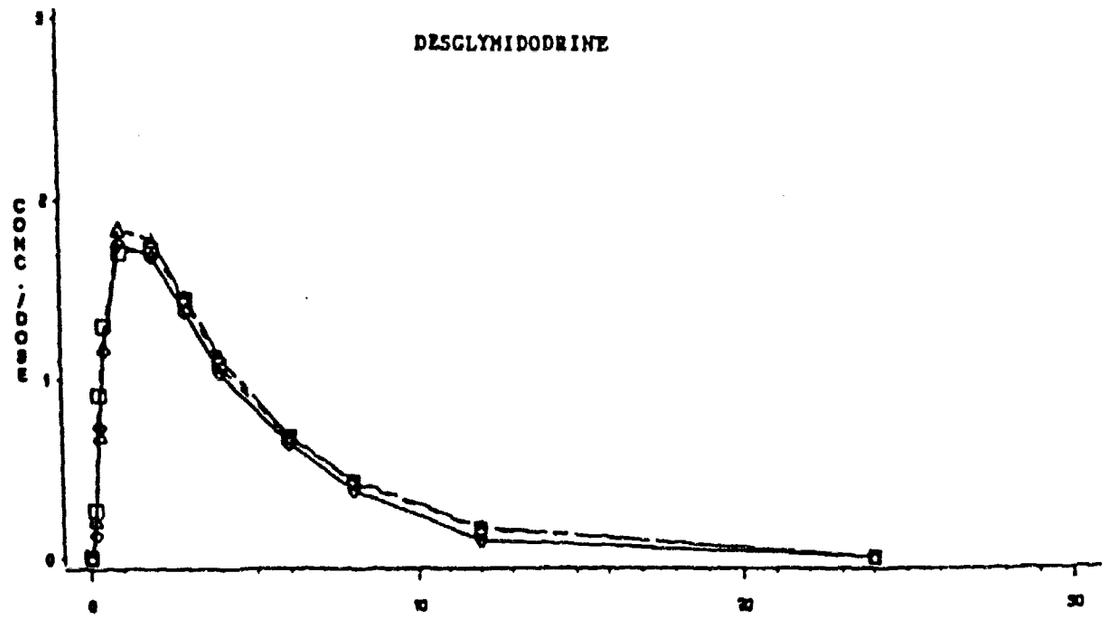


Figure 2

Mean Plasma Levels of Midodrine (ng/mL) and Desglymidodrine (ng/mL) Normalized for Dose (concentration/dose) after Single Oral Doses of 2.5, 5, and 10 mg of Midodrine Hydrochloride to 18 Fasting Subjects





REVIEW OF PLASMA LEVEL DATA OBTAINED IN CLINICAL STUDY IN HYPOTENSIVE PATIENTS

STUDY 2:

Study Title: A double-blind randomized dose response study of midodrine in patients with neurogenic orthostatic hypotension

Protocol Number:

Report: Submission 7-25-95

Authors: Shawk

Investigators:

Objectives: To assess dose response to single doses of midodrine.
To examine duration of action.
To gain information in patients with orthostatic hypotension on blood levels of midodrine and desglymidodrine.

Subjects: Twenty-five patients, 11 males, aged 38-78 years, and 14 females, aged 40-70 years, participated.

Design: Double-blind, randomized, 4-way complete cross-over.

Treatments: Each subject was studied on 4 occasions, on 4 consecutive days. Oral doses of placebo, 2.5 mg, 10 mg, and 20 mg as tablets (2.5-mg and 5-mg) were administered in the morning.

Blood and Urine Sampling: Samples of blood were taken hourly over 6 hours.

Analytical Method: See review of Study 1.

STUDY RESULTS: The mean plasma levels in the 4 study groups are presented in Table 1. The reason for plasma levels of midodrine even in the placebo group can be traced back to one single patient in which midodrine levels in the range 46-65 ng/mL were obtained after placebo administration, while his plasma levels of desglymidodrine were 0 at the same times. Obviously, the Sponsor should have excluded this patient when calculating mean levels.

The data clearly shows the dose proportionality both for midodrine and desglymidodrine.

The data was examined with relation to gender effects (Figures 1 and 2). No differences were found after a 10-mg dose. After a 20-mg dose of midodrine, plasma levels of desglymidodrine tended to be higher (approximately 40%) in the females. The finding appears to be of little concern since the highest recommended daily dose is 30 mg, which is probably going to be divided into three dose administrations of 10 mg each per day. Midodrine plasma levels (20-mg dose) were also higher in the females than the males. While this indicates a lower clearance in the females, it has no relevance *per se*, since midodrine itself has virtually no activity.

The plasma level data was also examined according to patient age: <65 years (N=11) and ≥65 years (N=9). Both after doses of 10 and 20 mg mean plasma levels were virtually identical in the two age groups (if anything, levels in the younger age group were slightly higher). See Figures 3 and 4. The Sponsor made no formal pharmacokinetic evaluation of the data, probably in view of the limited sampling time that would not allow accurate determinations of half-life and AUC and parameters derived from these. However, a comparison with the data in healthy subjects in Study 4 at corresponding time-points shows that the elimination of desglymidodrine on the average is slower in the patients; a rough estimate based on average data indicates a half-life of about 4 hours as opposed to 3 hours in the healthy subjects.

TABLE 1:
PLASMA LEVELS OF MIDODRINE AND DESGLYMIDODRINE (ng/mL)
Midodrine Study

Hour	Placebo N = 20	Midodrine 2.5 mg N = 20	Midodrine 10 mg N = 19	Midodrine 20 mg N = 20
Plasma Levels Midodrine (ng/mL)				
0	0.00 ± 0.00	0.04 ± 0.04	0.23 ± 0.14	0.11 ± 0.09
0.25	2.70 ± 2.58	8.82 ± 2.07	48.36 ± 8.57	82.23 ± 18.27
0.5	2.85 ± 2.85	12.04 ± 2.28	47.72 ± 6.18	89.43 ± 14.00
1	2.83 ± 2.69	7.35 ± 1.78	27.08 ± 3.74	47.47 ± 5.30
2	3.27 ± 3.27	4.93 ± 2.68	13.09 ± 3.31	21.18 ± 2.96
4	2.95 ± 2.95	3.04 ± 2.58	4.61 ± 2.74	5.64 ± 2.47
6	2.41 ± 2.31	1.98 ± 1.80	3.00 ± 1.97	3.26 ± 1.94
Plasma Levels Desglymidodrine (ng/mL)				
0	0.51 ± 0.15	0.39 ± 0.15	0.34 ± 0.15	0.15 ± 0.08
0.25	0.45 ± 0.13	1.53 ± 0.34	7.74 ± 1.55	11.08 ± 2.18
0.5	0.42 ± 0.13	3.54 ± 0.54	14.97 ± 2.25	24.49 ± 3.58
1	0.39 ± 0.12	4.51 ± 0.45	19.28 ± 2.02	35.64 ± 3.79
2	0.30 ± 0.11	4.65 ± 0.35	20.89 ± 1.84	39.40 ± 2.75
4	0.24 ± 0.09	3.33 ± 0.18	14.32 ± 1.05	28.38 ± 1.58
6	0.08 ± 0.06	2.45 ± 0.16	10.13 ± 0.54	19.92 ± 1.04

FIGURE 1
PLASMA LEVELS (ng/mL) OF MIDODRINE BY GENDER

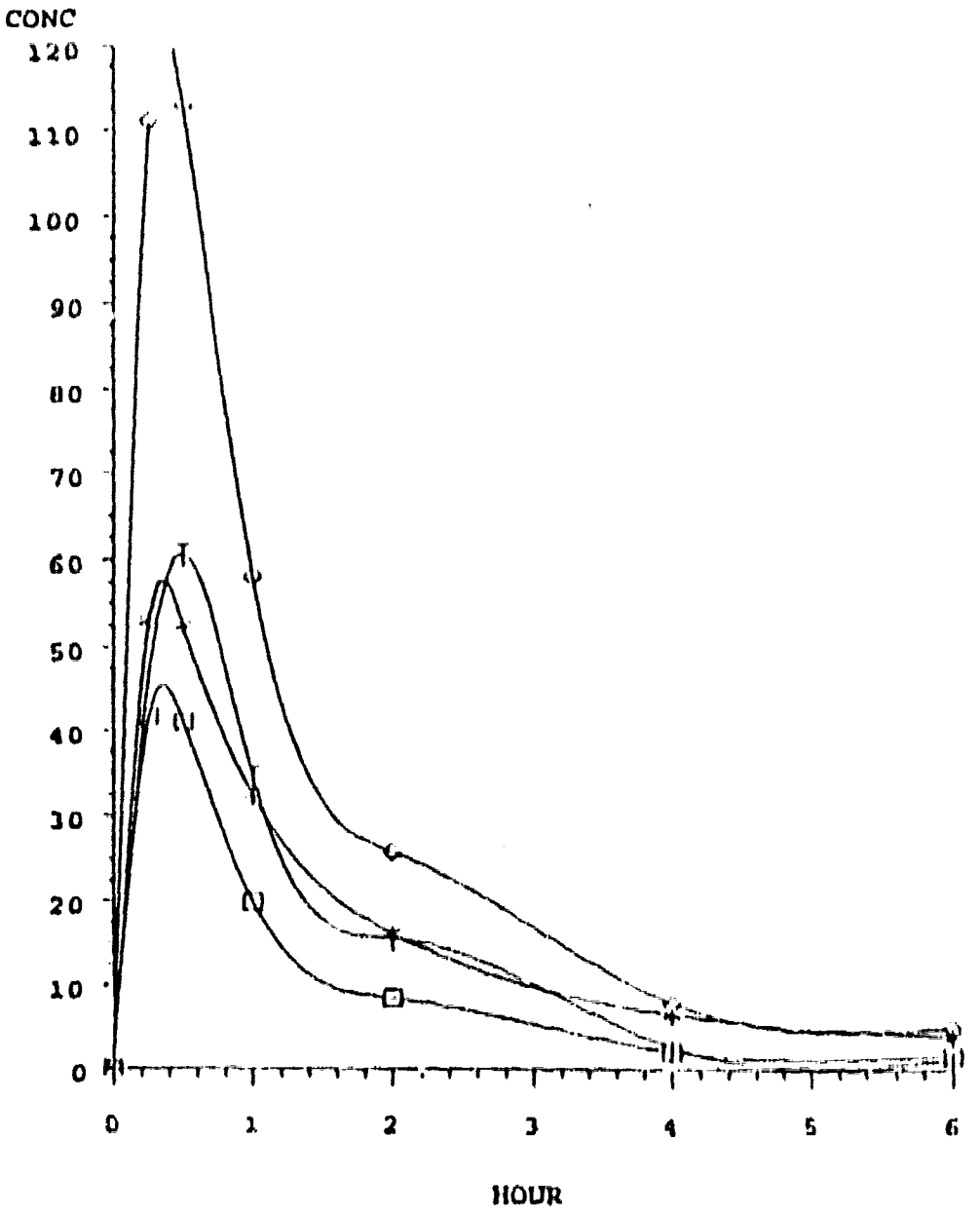


FIGURE 2
PLASMA LEVELS (ng/mL) OF DESGLYMIDODRINE BY GENDER

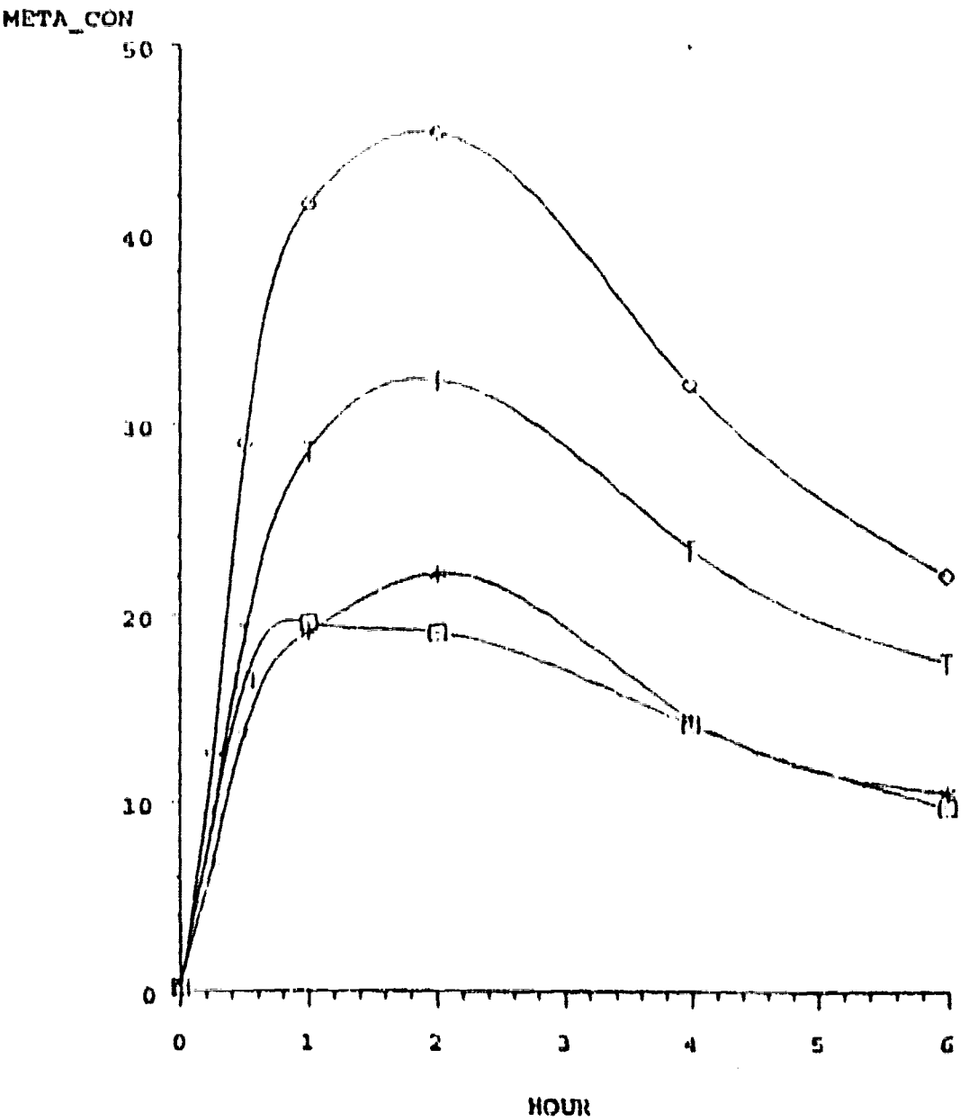


FIGURE 3
PLASMA LEVELS (ng/mL) OF MIDODRINE BY AGE

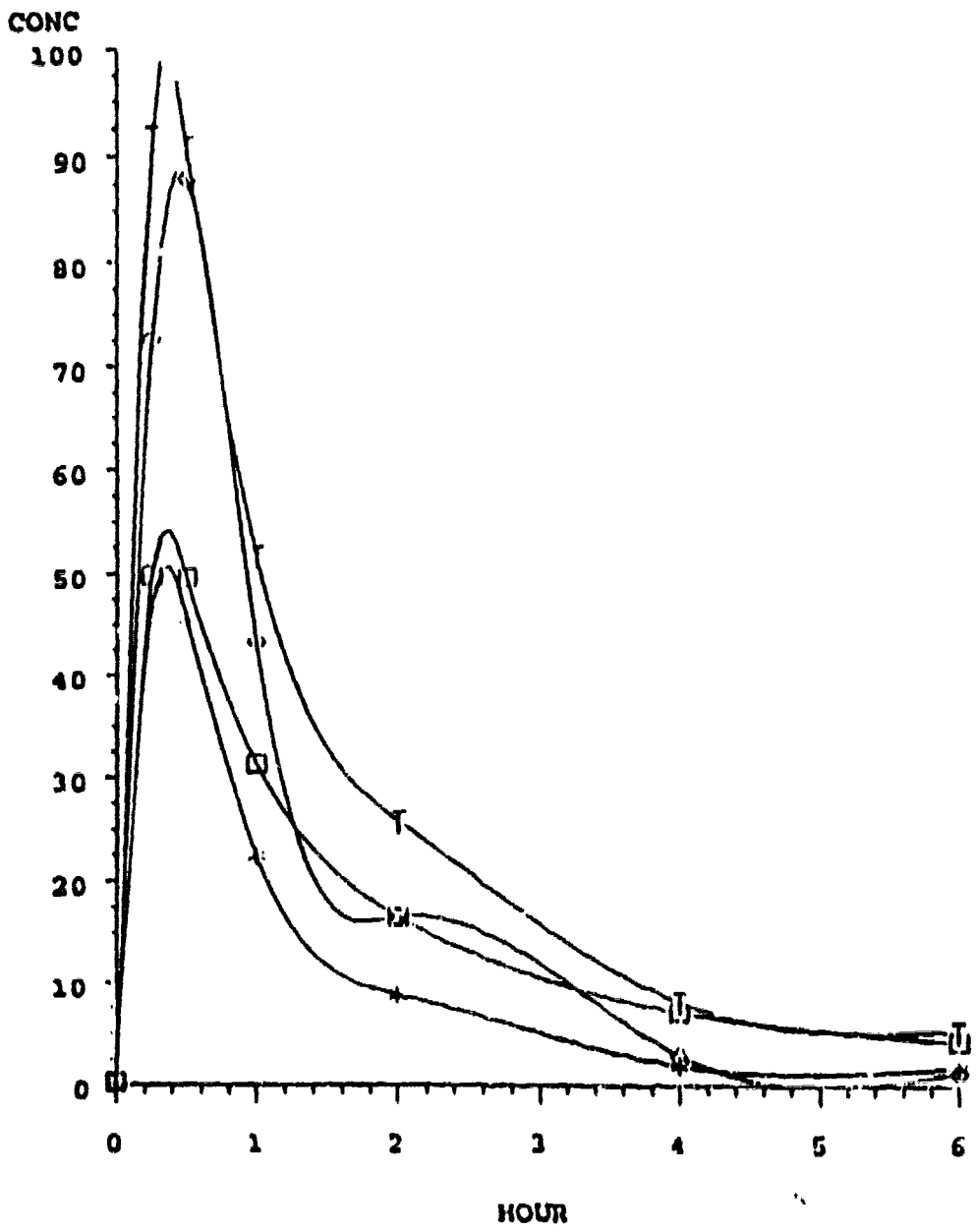
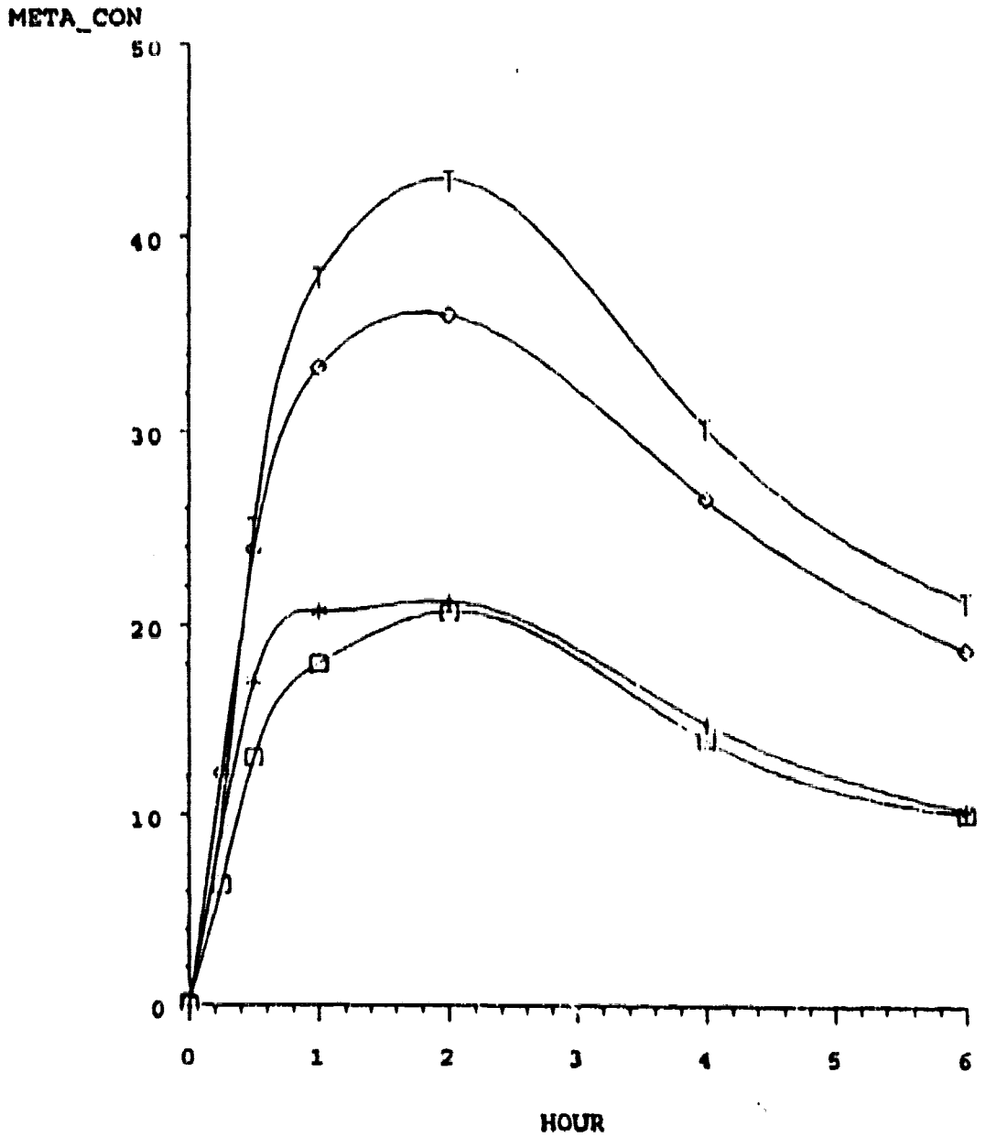


FIGURE 4
PLASMA LEVELS (ng/mL) OF DESGLYMIDODRINE BY AGE



REVIEW OF STUDY IN PRESENT SUBMISSION

STUDY 3:

Study Title: Unicenter phase I study to investigate the pharmacokinetics of Midodrine after single and repeated p.o. administration in male healthy volunteers (n=6).

Protocol Number:

Report Number: submitted 10/05/95

Investigators:

Study Site: See above.

Objectives: To study the pharmacokinetics of the different enantiomers of midodrine and desglymidodrine in healthy subjects.

Treatments: Subjects received 13 oral doses of 7.5 mg midodrine as tablets, doses were given twice daily.

Design: Open label, nonrandomized, repeated doses.

Study Subjects: Six healthy normal male caucasian volunteers aged 26 to 37 years. Two were smokers.

Blood Sampling: Fifteen blood samples were drawn over a period of 24 hours after dose on days 1 and 7.

Analytical Method:

Pharmacokinetic Evaluation: Noncompartmental analysis was undertaken. Due to oversight by the investigator, the calculations of volume of distribution and clearance do not take into account that the dose of each enantiomer is 3.75 mg, not 7.5 mg, which is the dose of the racemate in terms of the hydrochloride salt. In Table 1 below I have corrected this mistake. Calculations of apparent total clearance and volume of distribution of desglymidodrine were based on the assumption that the "dose" of desglymidodrine hydrochloride was 7.5 mg. Correcting for the actual content of each enantiomer this becomes 7.5/2. But there is an additional mistake introduced at this stage, since the dose in terms of desglymidodrine*HCl is 6.028/2 mg taking into consideration that the molecular weight of desglymidodrine*HCl is a factor 0.8038 less than that of midodrine*HCl. Finally, one does not know the actual percentage of the dose of midodrine that is being converted into desglymidodrine. Clearance and volume of distribution, reported as CL and V by the Sponsor, will in the following be designated as CL/F and V/F to indicate this fact.

STUDY RESULTS: Dramatic differences in kinetics of the enantiomers were observed both with midodrine and desglymidodrine (See Table 1 and Figure 1). Apparent clearance of (-)-midodrine was approximately 65% higher than for (+)-midodrine. Apparent volume of distribution was approximately twice as high for the (-)-enantiomer. As a result, half-life was slightly longer for this enantiomer. These results were in contrast to the results obtained with the metabolite, for which clearance of the (+)-enantiomer was approximately twice that of the (-)-enantiomer.

While the volumes of distribution were similar for the two enantiomers of the metabolite, the half-life was shorter for the (+)-enantiomer, 2.1 as compared to 3.5 hours for the (-)-form. The data in Table 1 refers to the first dose (day 1). There was no accumulation of drug after repeated administration, and the data obtained on day 7 was very similar to that of day 1.

Discussion: The different kinetics for the two enantiomers of midodrine is difficult to interpret, due to the uncertainty in the bioavailability factor, F. While the oral absorption is probably complete for midodrine, there is a substantial first-pass formation of desglymidodrine (see Study 4), which could differ between the enantiomers. Thus part of the differences in apparent clearance and volume of distribution noted for the two enantiomers of midodrine might actually be due to differences in first-pass metabolism.

The interpretation of the different kinetics of the two enantiomers of desglymidodrine is also not straight forward because the fraction F of the parent drug that is actually forming the metabolite is not known (Note: This is a different F than above). The observed differences are only true if F is the same for the two enantiomers. However, the most important fact is that the half-life of the active (-)-metabolite enantiomer is considerably longer and the plasma levels are higher. This has implications for the duration of action of the drug. Also, the apparent kinetics of desglymidodrine, as studied by a non-chiral assay, will be dominated by the (-)-enantiomer at later time points.

Specific information for the metabolism and renal clearance of the enantiomers of desglymidodrine can not be obtained in the present study. However, it is interesting to note that for a structurally similar compound, the β_2-agonist terbutaline, the active l(-)-enantiomer had a lower renal clearance than the inactive d(+)-enantiomer (Borgstrom et al., Br.J.Clin.Pharmacol. 1989, 27:49-56).

Table 1. Mean pharmacokinetic parameters (%CV) of midodrine and its active metabolite after oral administration of (racemic) 7.5 mg midodrine*HCl to healthy volunteers (day 1 of 7 days of repeated administrations).

Parameter	midodrine enantiomer		desgly-midodrine enantiomer	
	(+)	(-)	(+)	(-)
C_{max} (ng/mL)	37.3 (35%)	17.3 (36%)	9.6 (17%)	10.0 (18%)
T_{max} (hr)	0.33 (31%)	0.42 (22%)	0.75 (81%)	1.25 (40%)
t1/2 (hr)	0.28 (27%)	0.36 (23%)	2.1 (22%)	3.5 (6%)
Clearance/F (L/hr)	200 (25%)	329 (38%)	108 (11%)	56 (15%)
V_β/F (L)	77.3 (24%)	165 (34%)	328 (18%)	285 (9%)

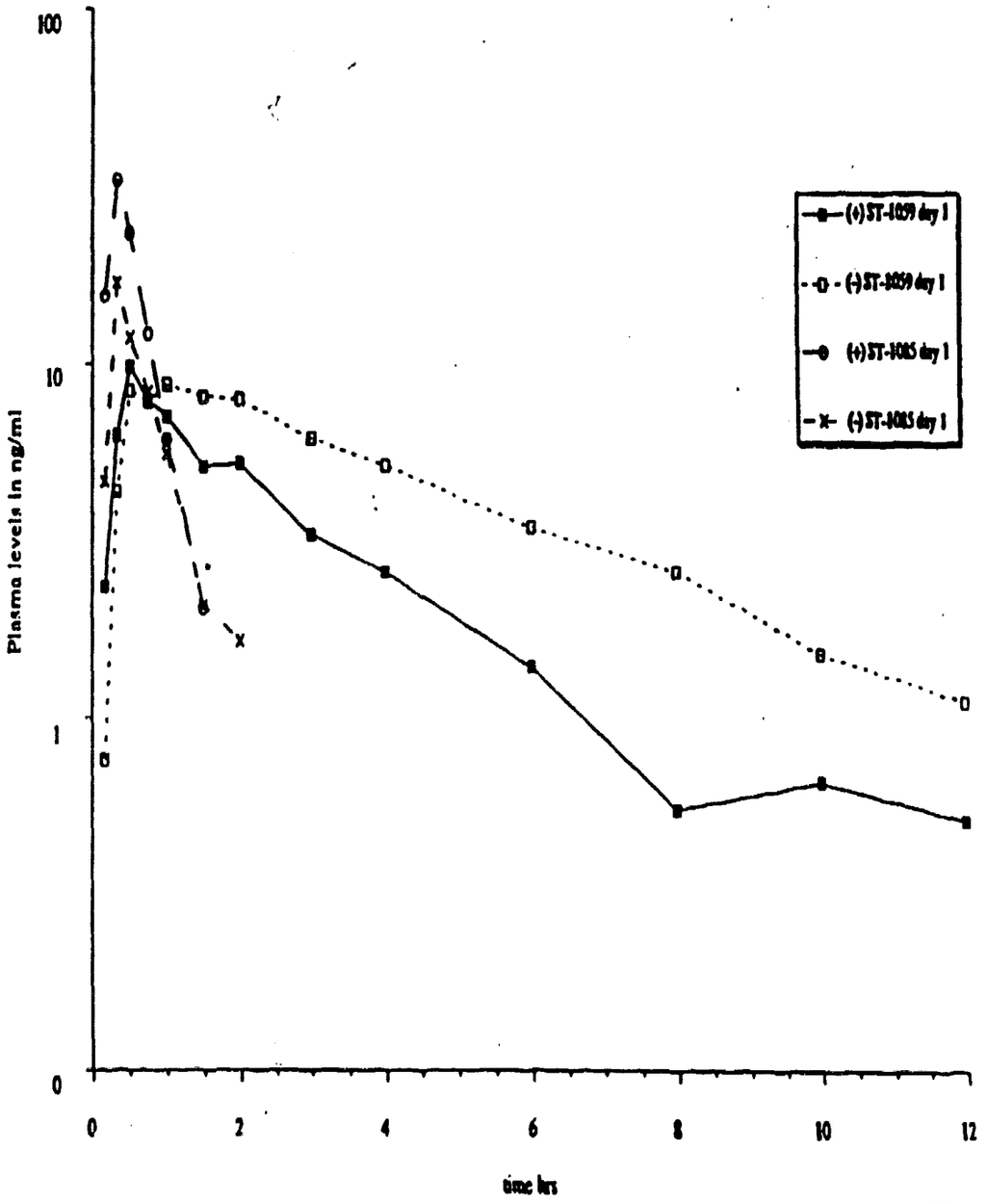


Figure 1. Median plasma levels of the enantiomers of midodrine and desglymidodrine on day 1 (n=6).
Legend: x-x-x (-)-midodrine
o-o-o (+)-midodrine
□-□-□ (-)-desglymidodrine
■-■-■ (+)-desglymidodrine

REVIEW OF STUDY IN ORIGINAL SUBMISSION OF NDA 19-815

STUDY 4:

Study Title: Studies on the bioavailability of midodrine and alpha-2,5-dimethoxyphenyl-beta-aminoethanol hydrochloride.

Protocol Number:

Report: See original NDA, volume 9, pp. 150-166D.

Investigators:

Objectives: To determine the absolute bioavailability of the active metabolite of midodrine (ST 1059) after administration of 2.5 mg of midodrine either as a solution or as a 2.5-mg tablet. The relative bioavailability of the tablet as compared to the solution was also determined.

Subjects: Twelve healthy males, aged 21-26 years, participated. Data is available in 11 of them.

Treatments: Each subject was studied on 3 occasions separated by one week. Fasted subjects received single 2.5-mg doses of midodrine intravenously, as a solution, or as a 2.5-mg tablet. The solution was prepared in mineral water, volume 125 mL. The tablet was administered together with 125 mL of mineral water. Subjects were given breakfast 2 hours after drug administration.

Design: Randomized, cross-over.

Blood and Urine Sampling: 15 samples of blood were taken over 24 hours. Urine was collected in 6 fractions over 24 hours.

Analytical Method:

STUDY RESULTS: The mean plasma level data for midodrine and desglymidodrine are presented in Tables 1 and 2 respectively. The elimination half-life of midodrine after intravenous administration was short, approximately 25 minutes, and midodrine reached its LOQ after about 3 hours. From the mean values in the table one may estimate CL at approximately 120 L/hr and V_β at approximately 70 L.

After oral administration, the mean C_{max} of midodrine was approximately 11 ng/mL after both tablet and oral solution, T_{max} being approximately 25 minutes (see Table 3 for pharmacokinetic parameters of midodrine). The ratio of oral and intravenous AUCs indicate that the oral bioavailability in terms of midodrine is approximately 50%.

Figure 1 shows the mean plasma profiles of desglymidodrine after the three administrations. Plasma levels could be followed up to 10 hours after all three administrations before reaching the LOQ. Mean C_{max} was approximately 5 ng/mL after the oral administrations, T_{max} was approximately 1 hour. Pharmacokinetic parameters for desglymidodrine are presented in Table 4. Note the high apparent clearance of desglymidodrine, approximately 54 L/hr or 1200 mL/min.

The bioavailability of desglymidodrine after the oral administrations, using the AUC of desglymidodrine formed after an intravenous dose of midodrine as the reference, was 0.90 for the oral solution (95% C.I.: 0.78-1.02) and 0.93 for the tablet (95% C.I.: 0.84-1.08).

Table 1. Mean plasma concentration of midodrine hydr ɔnloride (ng/mL) after administration of 2.5 mg to 11 healthy volunteers.

Time	Intravenous	Oral solution	Tablet
5 min	56.6	3.4	-
10 min	21.6	8.0	4.9
20 min	11.3	9.7	9.4
30 min	7.6	8.0	9.9
45 min	4.4	5.3	6.2
1 hr	3.2	3.5	4.0
1.5 hr	1.8	1.8	2.1
2 hr	-	1.1	1.3

Table 2. Mean plasma concentration of desglymidodrine hydrochloride (ng/mL) after administration of 2.5 mg midodrine hydrochloride to 11 healthy volunteers.

Time	Intravenous	Oral solution	Tablet
5 min	8.1	-	-
10	5.1	2.0	-
20	5.2	3.1	2.5
30	5.1	3.5	3.6
45	5.4	3.9	4.3
1 hr	5.4	4.3	4.7
1.5	4.9	4.1	4.4
2	4.5	4.2	4.2
3	3.3	3.2	3.3
4	2.6	2.6	2.6
6	1.6	1.5	1.6
8	1.1	1.2	1.0
10	0.7	0.8	0.7

Table 3. Mean pharmacokinetic parameters (%CV) for midodrine after administration of 2.5 mg of midodrine hydrochloride to 11 healthy volunteers by 3 different routes.

Parameter	Intravenous	Oral solution	Tablet
T_{max} (hr)	-	0.38 (61%)	0.45 (44%)
C_{max} (ng/mL)	-	10.9 (27%)	11.2 (35%)
$t_{½}$ (hr)	0.41 (20%)	0.45 (27%)	0.49 (24%)
AUC_{∞} (ng*hr/mL)	18.6	8.71 (20%)	9.46 (22%)
CL (L/hr)	118	-	-
V_{β} (L)	70	-	-
$U_{0\text{-}24\,hr}$ (% of dose)	3.6 (36%)	2.2 (18%)	2.2 (27%)
Absolute Bioavailability (%)	100 (ref)	47	51

Table 4. Mean pharmacokinetic parameters (%CV) for desglymidodrine after administration of 2.5 mg of midodrine hydrochloride to 11 healthy volunteers by 3 different routes. The fraction (Fr) of systemically available midodrine that actually forms desglymidodrine was set at 0.9 in the calculations of clearance and V_{β}.

Parameter	Intravenous	Oral solution	Tablet
T_{max} (hr)	-	1.1 (45%)	1.1 (45%)
C_{max} (ng/mL)	-	4.6 (22%)	5.0 (32%)
$t_{½}$ (hr)	3.1 (16%)	3.0 (13%)	3.0 (17%)
AUC_{∞} (ng*hr/mL)	28.7 (23%)	25.7 (26%)	25.6 (24%)
CL/Fr (L/hr)[*]	54 (19%)	-	-
V_{β}/Fr (L)[*]	240 (19%)	-	-
$U_{0\text{-}24\,hr}$ (% of dose)	39.3 (10%)	34.4 (8%)	34.4 (13%)

[*] Fr is the unknown fraction of midodrine that is being converted to desglymidodrine.

DISCUSSION

The oral absorption rate of midodrine is obviously very high. The completeness is more difficult to judge. The fraction of the dose being transformed to desglymidodrine can not be estimated, since there was no systemic administration of this entity. The absolute oral bioavailability of midodrine was approximately 50%. The relative (not absolute as believed by the Sponsor) oral availability of desglymidodrine, using the AUC of desglymidodrine after intravenous midodrine as the reference, was more than 90%. This indicates that there is a fraction of the dose that is lost on oral absorption of midodrine which is actually forming desglymidodrine by first-pass biotransformation in the gut and/or liver. Since the fraction of the dose eventually forming desglymidodrine is not known, no quantitative statement can be made with regard to how much of the first-pass metabolism is due to formation of desglymidodrine, and how much is due to formation of other metabolites and/or due to incomplete absorption. The present numbers were interpreted by the Sponsor to indicate a 90% absorption of midodrine. While the reasoning was not presented in the report, it was probably based upon the notion that the metabolic fate of midodrine should be the same irrespective of administration route. However, if presystemic formation of desglymidodrine were to occur predominantly by gut wall metabolism, this may compensate for a loss due to incomplete absorption of midodrine. In other words; the present data on desglymidodrine levels can not be used to draw conclusions with regard to absorption of midodrine.

The systemic clearance of midodrine is very high, approximately 120 L/hr. That systemic and presystemic clearance may not necessarily be exclusively hepatic has been shown in rats; metabolic transformation of midodrine to desglymidodrine was found in blood, lung, intestine and other organs.

CONCLUSIONS

The stated goal to determine the absolute bioavailability of the active metabolite, desglymidodrine, can not be achieved with the present design. It would require the administration of intravenous desglymidodrine. In terms of quantitation of the formation of desglymidodrine, the present data on urinary recovery demonstrate that at least 34% of an oral dose of midodrine, i.e., one third of the dose, is transformed to the active moiety.

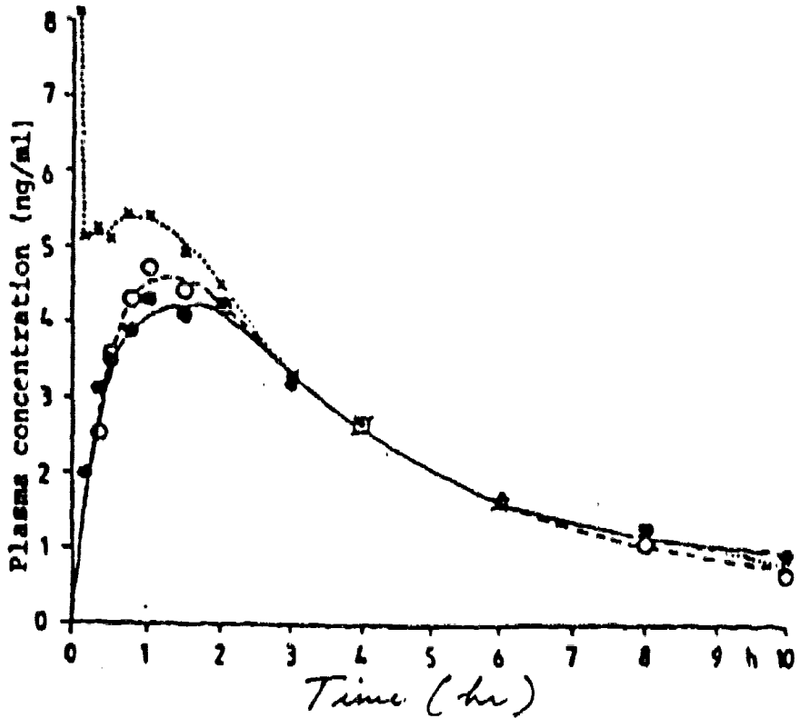


Figure 1. Mean plasma concentration of desglymidodrine after administration of 2.5 mg midodrine hydrochloride to 10 healthy volunteers: x = i.v.; ● = p.o. solution; o = tablet.

MAY 2 4 1995

MAR 30 1995

NDA No. 19-815
Submission Dates: 12/28/87, 05-14-93, 9-21-94
Generic Name: Midodrine HCl
Brand Name: Amatine
Formulation: Tablets; 2.5, 5, and 10 mg.
Sponsor: Roberts Laboratories Inc.,
Eatontown NJ 07724
Type of Submission: Amendment to NDA **Status:** 1P
Reviewer: O. Borga, Ph.D.

BACKGROUND:

Midodrine HCl is the racemate of a chiral sympathomimetic agonist that binds to receptors of the arterial and venous vasculature, leading to an increase in vascular tone and elevation of blood pressure. While it has been shown to have in vitro activity of its own, it appears clear that the main active moiety is the metabolite desglymidodrine, which has an in vitro activity 15 times that of the parent compound. Desglymidodrine is formed by enzymatic hydrolysis of the glycineamide bond of midodrine. Midodrine is currently marketed in Europe under the brand name Gutron®, its main indication being treatment of orthostatic hypotension associated with autonomic failure. Clinical studies are ongoing in this country for this indication for which an effective treatment is still lacking. For this reason, midodrine has the status of an orphan drug. I have been unable to find any information with regard to the biologic activity of the two optical isomers.

In the amendment submitted 9-21-94, the firm submitted three studies, one of which is of biopharmaceutic relevance. The original submission was reviewed by Dr Janice Barnett Jenkins, Division of Biopharmaceutics. As a whole, it was considered unreviewable because of a large number of deficiencies. The present review consists of an examination of the newly submitted study plus a reevaluation of one study (with a minor deficiency) in the original submission.

RECOMMENDATION

Even after the present submission and reevaluation of the previous submission there remain a number of biopharmaceutical issues that should be adequately addressed by the Sponsor:

Physical/chemical properties of the drug: These should include information about solubility in water and some common organic solvents, pK_a, and, if available, octanol-water partition coefficient at pH 7.4.

Proposed package insert: This should contain a summary of the

basic ADME and pharmacokinetic (PK) properties of the drug, with references that support the specific claims done by the Sponsor.

Validation of bioanalytical methods: All assays of drug or drug metabolites have to be validated with regard to specificity, sensitivity, linearity, accuracy and precision. Samples of chromatograms should also be provided. The stability during storage of midodrine and desglymidodrine in actual biological samples has to be established. This could be done by repeating the analyses of previously analyzed samples after some months and comparing the results. In addition to the validation of the assay *per se*, the **in-study performance** of the assay has to be documented, e.g. by including quality control samples of known concentration as unknowns in each assay performed.

Dosage formulation information: For the midodrine tablets, the following information should be provided: Composition of the formulation. Batch/lot numbers and information to indicate if the batch is from a full scale production size batch made on the same kind of production equipment using the same manufacturing procedures that will be used for making the final market product at the proposed site of manufacture. If the batch is not a full scale production size batch, it should ideally represent 10% of the number of dosage units for what a full scale production size batch will be or dosage units, whichever is greater.

For the batch/lot of the midodrine being tested in-vivo, content uniformity data should be provided. For the individual tablets to be administered to subjects in the study, the tablets should be randomly selected, i.e., there must not be any prescreening of tablets from a batch/lot.

In vitro drug dissolution: A pH-solubility profile for the drug itself should be submitted. For the midodrine tablet, the following information should be provided: Dissolution profiles in simulated gastric fluid (without enzymes), simulated intestinal fluid (without enzymes), water and other media (i.e., different pHs, surfactants, etc.) as appropriate. In media where sink conditions exist, dissolution profiles should be carried out to where at least of the drug is dissolved. For the water dissolution medium, its pH should be determined before and after drug dissolution. Twelve dosage units per tablet per dissolution medium should be provided. Individual as well as average results should be submitted.

Metabolic pathways: Identification of main metabolite(s) by unequivocal methodology, e.g. mass spectrometry, with comparisons with synthetic reference compounds. The ongoing mass balance study will hopefully address this issue.

Stereoisomers: The present guidelines request the Sponsor to describe the behavior of each isomer separately. (Copy of guideline will be provided upon request).

Single dose PK studies: A previous submission contained an acceptable study comparing 3 formulations (i.v., oral solution and tablet) after single dose that presented data on absolute bioavailability of the tablet. The study also presents basic information on clearance, volume of distribution and half-life for both the parent drug and the active metabolite. The ~~only deficiency~~ With this study ~~is that~~ chromatograms were not supplied for the assay validation.

Bioequivalence study(ies): If clinical studies have been undertaken with preliminary experimental formulations, their bioequivalence with the to-be-marketed formulation should be ascertained. If clinical studies in this country were in fact performed with the final formulation, this is not an issue.

The combined **dose-proportionality and food study**, presented in this submission, is adequate to characterize the single-dose profile of midodrine. However, the Sponsor needs to submit an assay validation report for the assay used in this study.

Special populations: The Division of Biopharmaceutics recommends studies in elderly, in patients with renal disease, and patients with hepatic disease.

Gender analysis: Gender must not be an exclusion criteria in PK studies. Whenever PK data are available in both sexes, an analysis should be undertaken of possible gender effects on the PK.

Most of the requests should present little problem, since they only deal with compilation of information that should be easily available to the Sponsor. With regard to studies in special populations, the Division of Biopharmaceutics is cognizant of the fact that it might present practical difficulties to undertake such studies. However, a lack of such information will be addressed in the labeling.

APPENDIX-/ Summary of studies
Copy of original review by Dr. Jenkins.

Olof Borga 5/30/95
Olof Borga, Ph.D. Date
Pharmacokinetics Review Branch

FT Initialed by Ameeta Parekh, Ph.D. Ameeta Parekh 5/30/95

cc: NDA 19-815, HFD-110, HFD-426 (Fleischer, Borga), Drug, FOI (HFD-19), Chron, HFD-340 (Vishwanathan), F

APPENDIX 1

1) SUMMARY OF STUDIES

2) ORIGINAL REVIEW BY DR. JENKINS

REVIEW OF STUDY SUBMITTED AS AN AMENDMENT TO NDA 19-815

STUDY 1:

Study Title: A dose proportionality study of midodrine (2.5, 5, and 10 mg) and the effect of food on oral bioavailability in normal male subjects.

Protocol Number:

Report Number:

Investigators:

Study Site: Not reported.

Objectives: To study dose proportionality of midodrine and evaluate the effect of food on the availability of midodrine, 10-mg tablet.

Treatments: Each subject received four single doses of midodrine: 2.5 mg, 5 mg, and 10 mg midodrine orally were given during fasting conditions; 10 mg was given immediately after a "standard meal". The time of the day or the length of fasting was not reported, nor was the composition of the "standard meal". Also, it is not clear whether the same (e.g. 2.5-mg) or different tablet strengths were used, or, in fact, whether tablets were used at all. It follows, that other pertinent data such as batch numbers, batch sizes etc. were not presented.

Design: Open label, randomized, single-dose, 4-way crossover.

Study Subjects: 18 male subjects were studied. Age ranged from 20 to 49 years (mean 33), body weights from 60.5 to 102 kg (mean 81). Eight were Blacks, 8 were Whites, 2 were Hispanics. None was smoker. The subjects are referred to as patients, but it appears from the tabulated medical history that healthy volunteers were used.

Blood Sampling: Plasma was collected at the following times: 0 (blank), 10, 20, and 30 minutes, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours after dosing.

Analytical Methods: The principle of the assay is not described, nor are any validation data presented. Assays were undertaken by (address not given). The method is said to be presented in the following document:"The Analysis of Midodrine and ST-1059 in Plasma" but the document is not included in this submission.

Pharmacokinetic Evaluation: A standard, noncompartmental analysis was performed.

STUDY RESULTS: Plasma levels of the prodrug, midodrine, declined rapidly and, with one exception, levels were below limit of quantitation (LOQ), 0.5 ng/mL, at 4 hours after the 10-mg dose, earlier after the other doses (See Figure 1 for mean levels). The plasma levels of the active moiety, desglymidodrine, were above LOQ, 0.5 ng/mL, up to 12 hours in all subjects (See Figure 2 for mean levels). Pharmacokinetic parameters for the 3 doses are summarized in Table 1 for the prodrug and Table 2 for the active metabolite.

Table 1. Pharmacokinetic parameters for midodrine, mean (%CV), for 18 subjects dosed in the fasting state.

Parameter	Dose (mg)		
Dose	2.5 mg	5.0 mg	10.0 mg
C_{max} (ng/mL)	11.2 (24)	22.8 (29)	42.6 (27)
T_{max} (hr)	0.47 (32)	0.41 (29)	0.50 (42)
AUC_∞(ng*hr/mL)	9.42 (29)	19.6 (25)	36.6 (21)
t1/2 (hr)	0.49 (45)	0.46 (33)	0.44 (25)

Table 2. Pharmacokinetic parameters for desglymidodrine, mean (%CV), for 18 subjects dosed in the fasting state.

Parameter	Dose (mg)		
Dose	2.5 mg	5.0 mg	10.0 mg
C_{max} (ng/mL)	4.59 (16)	9.23 (21)	19.3 (25)
T_{max} (hr)	1.35 (41)	1.56 (49)	1.28 (43)
AUC_∞(ng*hr/mL)	23.9 (34)	53.2 (28)	107.7 (24)
t1/2 (hr)	3.32 (44)	3.14 (11)	3.03 (13)

Dose proportionality is obvious from C_{max} and AUC_∞ values in tables 1 and 2. Also, dose-normalized mean plasma levels of midodrine and desglymidodrine were virtually superimposable (see Figures 3 and 4).

In terms of C_{max} and AUC_{∞} the effect of food was only pronounced on midodrine, whereas the food-effect was negligible on the active metabolite, desglymidodrine (Tables 3 and 4).

Table 3. Pharmacokinetic parameters for midodrine, mean (%CV), in 18 subjects after 10-mg tablet given without and with food.

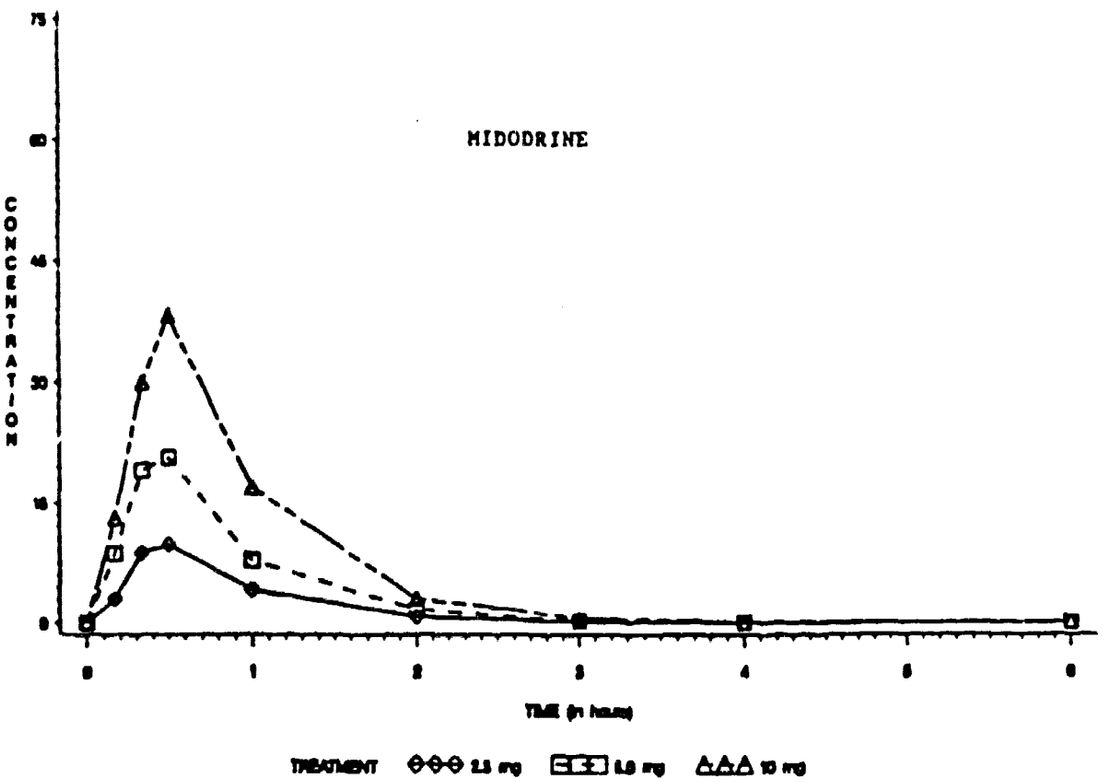
Parameter	Fasted	Fed	p-value; fed vs fasted
C_{max} (ng/mL)	42.6 (27)	29.1 (30)	0.0002
T_{max} (hr)	0.50 (42)	0.76 (37)	0.0084
AUC_{∞} (ng*hr/mL)	36.6 (21)	46.3 (28)	0.0001

Table 4. Pharmacokinetic parameters for desglymidodrine, mean (%CV), in 18 subjects after 10-mg tablet given without and with food.

Parameter	Fasted	Fed	p-value; fed vs fasted
C_{max} (ng/mL)	19.3 (25)	18.6 (19)	0.3910
T_{max} (hr)	1.28 (43)	2.06 (26)	0.0004
AUC_{∞} (ng*hr/mL)	107.7 (28)	107.5 (23)	0.9251

Figure 1

Mean Plasma Levels of Midodrine (ng/mL) and Desglymidodrine (ng/mL) after Single Oral Doses of 2.5, 5, and 10 mg of Midodrine Hydrochloride to 18 Fasting Subjects



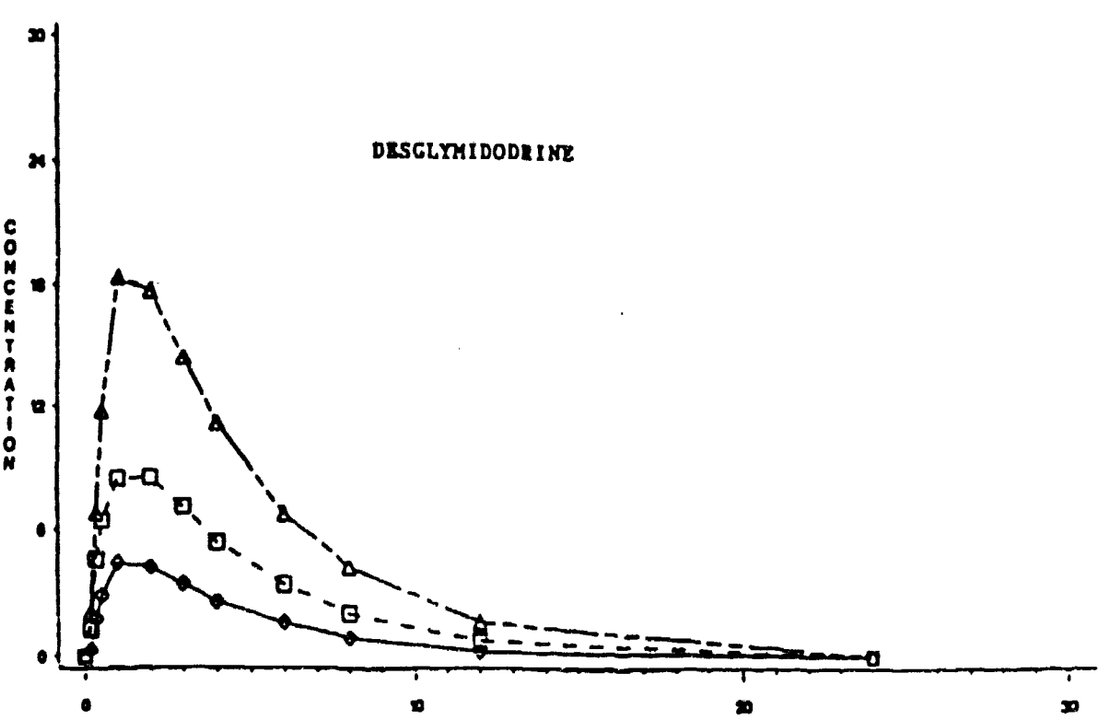
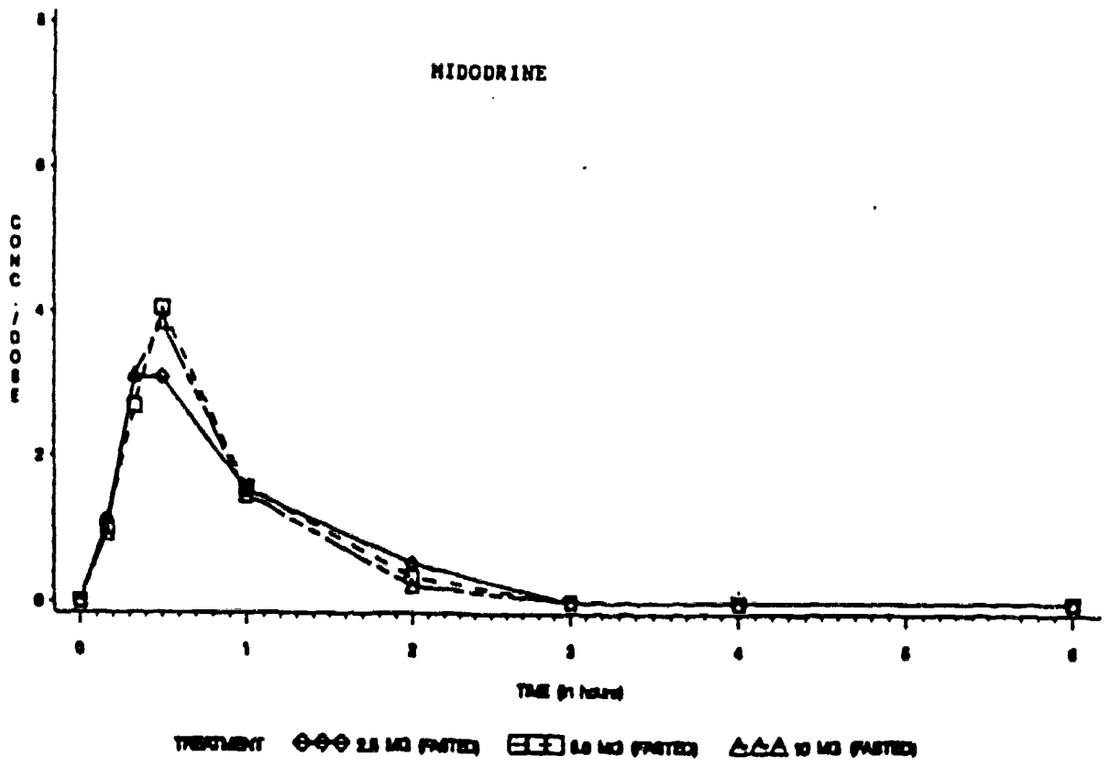
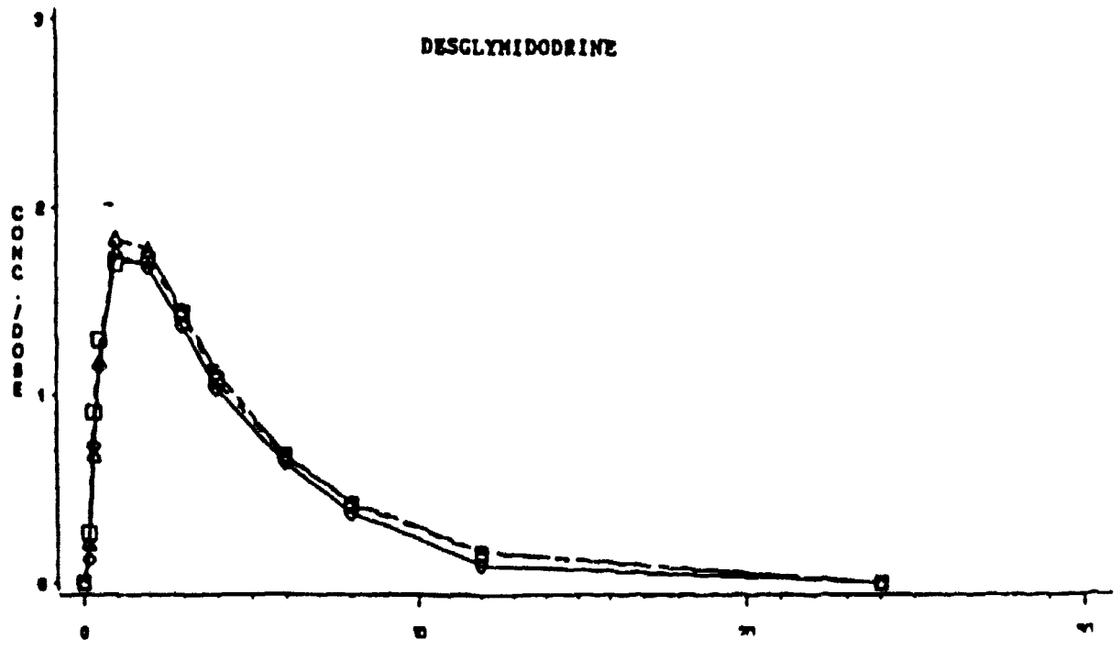


Figure 2

Mc Plasma Levels of Midodrine (ng/mL) and Desglymidodrine (ng/mL) Normalized for Dose (concentration/dose) after Single Oral Doses of 2.5, 5, and 10 mg of Midodrine Hydrochloride to 18 Fasting Subjects





REVIEW OF STUDY IN ORIGINAL SUBMISSION OF NDA 19-815

STUDY 2:

Study Title: Studies on the bioavailability of midodrine and alpha-2,5-dimethoxyphenyl-beta-aminoethanol hydrochloride.

Protocol Number:

Report: See original NDA, volume 9, pp. 150-166D.

Investigators:

Objectives: To determine the absolute bioavailability of the active metabolite of midodrine (ST 1059) after administration of 2.5 mg of midodrine either as a solution or as a 2.5-mg tablet. The relative bioavailability of the tablet as compared to the solution was also determined.

Treatments: Each subject was studied on 3 occasions separated by one week. Fasted subjects received single 2.5-mg doses of midodrine intravenously, as a solution, or as a 2.5-mg tablet. The solution was prepared in mineral water, volume 125 mL. The tablet was administered together with 125 mL of mineral water. Subjects were given breakfast 2 hours after drug administration.

Design: Randomized, cross-over.

Blood and Urine Sampling: 15 samples of blood were taken over 24 hours. Urine was collected in 6 fractions over 24 hours.

STUDY RESULTS: The individual plasma level data for midodrine and desglymidodrine are presented in Tables 1 and 2 respectively. The elimination half-life of midodrine after intravenous administration was short, approximately 25 minutes, and midodrine

reached its LOQ after about 3 hours. From the mean values in the table one may estimate CL at approximately 170 L/hr and V_β at approximately 100 L.

After oral administration, the mean C_{max} of midodrine was approximately 11 ng/mL after both tablet and oral solution, T_{max} being approximately 25 minutes (see Table 3 for pharmacokinetic parameters of midodrine).

Figure 1 shows the mean plasma profiles of desglymidodrine after the three administrations. Plasma levels could be followed up to 10 hours after all three administrations before reaching the LOQ. Mean C_{max} was approximately 5 ng/mL after the oral administrations, T_{max} was approximately 1 hour. Pharmacokinetic parameters for desglymidodrine are presented in Table 4. Note the high clearance of desglymidodrine, approximately 72 L/hr or 1200 mL/min.

The bioavailability of desglymidodrine after the oral administrations, using the AUC of desglymidodrine formed after an intravenous dose of midodrine as the reference, was 0.90 for the oral solution (95% C.I.: 0.78-1.02) and 0.93 for the tablet (95% C.I.: 0.84-1.08).

Table 1. Mean plasma concentration of midodrine hydrochloride (ng/mL) after administration of 2.5 mg to 11 healthy volunteers.

Time	Intravenous	Oral solution	Tablet
5 min	56.6	3.4	-
10 min	21.6	8.0	4.9
20 min	11.3	9.7	9.4
30 min	7.6	8.0	9.9
45 min	4.4	5.3	6.2
1 hr	3.2	3.5	4.0
1.5 hr	1.8	1.8	2.1
2 hr	-	1.1	1.3

Table 2. Mean plasma concentration of desglymidodrine hydrochloride (ng/mL) after administration of 2.5 mg midodrin hydrochloride to 11 healthy volunteers.

Time	Intravenous	Oral solution	Tablet
5 min	8.1	-	-
10	5.1	2.0	-
20	5.2	3.1	2.5
30	5.1	3.5	3.6
45	5.4	3.9	4.3
1 hr	5.4	4.3	4.7
1.5	4.9	4.1	4.4
2	4.5	4.2	4.2
3	3.3	3.2	3.3
4	2.6	2.6	2.6
6	1.6	1.5	1.6
8	1.1	1.2	1.0
10	0.7	0.8	0.7

Table 3. Mean pharmacokinetic parameters (%CV) for midodrine after administration of 2.5 mg of midodrine hydrochloride to 11 healthy volunteers by 3 different routes.

Parameter	Intravenous	Oral solution	Tablet
T_{max} (hr)	-	0.38 (61%)	0.45 (44%)
C_{max} (ng/mL)	-	10.9 (27%)	11.2 (35%)
$t_{½}$ (hr)	0.41 (20%)	0.45 (27%)	0.49 (24%)
AUC_{∞} (ng*hr/mL)	14.6 (32%)	8.71 (20%)	9.46 (22%)
$U_{0\text{-}24\ hr}$ (% of dose)	3.6 (36%)	2.2 (18%)	2.2 (27%)

Table 4. Mean pharmacokinetic parameters (%CV) for desglymidodrine after administration of 2.5 mg of midodrine hydrochloride to 11 healthy volunteers by 3 different routes.

Parameter	Intravenous	Oral solution	Tablet
T_{max} (hr)	-	1.1 (45%)	1.1 (45%)
C_{max} (ng/mL)	-	4.6 (22%)	5.0 (32%)
$t_{\frac{1}{2}}$ (hr)	3.1 (16%)	3.0 (13%)	3.0 (17%)
AUC_{∞} (ng*hr/mL)	28.7 (23%)	25.7 (26%)	25.6 (24%)
CL (L/hr)	72 (19%)	-	-
V_{β} (L)	319 (19%)	-	-
$U_{0\text{-}24\ hr}$ (% of dose)	39.3 (10%)	34.4 (8%)	34.4 (13%)

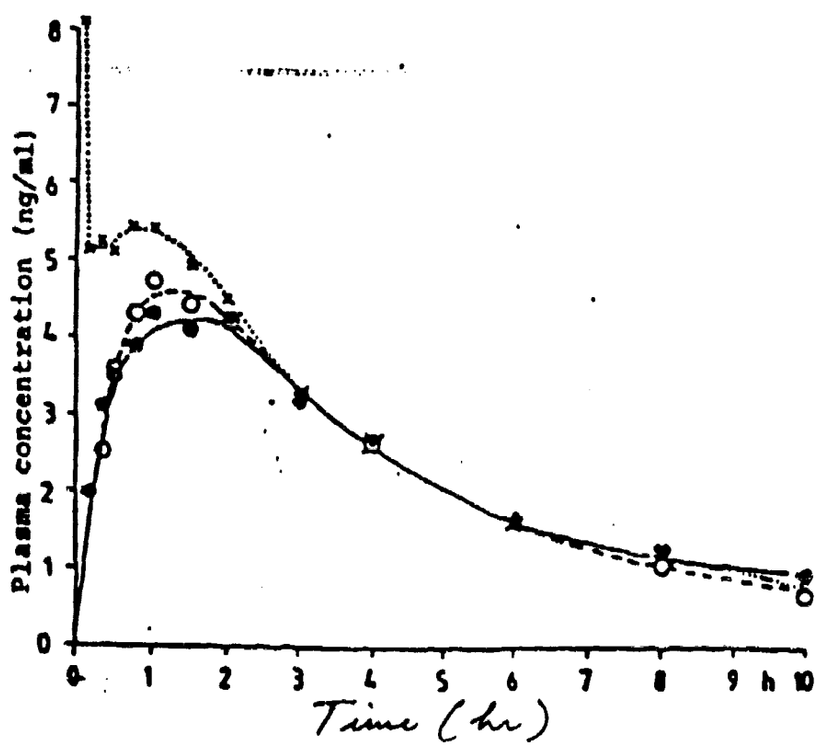


Figure 1. Mean plasma concentration of desglymidodrine after administration of 2.5 mg midodrine hydrochloride to 10 healthy volunteers: x = i.v.; ● = p.o. solution; o = tablet.

NDA 19-815 Category 1P Submission Date:05-14-1993
Midodrine tablets
Amatine®,
Sponsor: Roberts Laboratories, Inc. Reviewer: Rajendra S. Pradhan
Type of Submission: Amendment

Background: Midodrine is a specific α_1 sympathomimetic agonist that is claimed to bind to the receptors of the arteriolar and venous vasculature, leading to an increase in vascular tone and elevation of blood pressure. It is also claimed to stimulate the α receptors in the bladder neck and proximal urethra leading to an improvement in involuntary micturition. The pharmacologically active metabolite of midodrine is desglymidodrine, which is formed by enzymatic cleavage of a glycine residue. Midodrine is under investigation for the indication of treating patients with orthostatic hypotension associated with autonomic failure and patients with stress urinary incontinence.

In this amendment the firm submitted a relative bioavailability study between to-be-marketed tablet formulation and solution. This submission is amending the previous submission (12-28-1987), which was reviewed by Dr. Janice Barnett Jenkins (Division of Biopharmaceutics). Dr. Jenkins's review is attached in the appendix I. The latter submission was found deficient on several issues, and considered unreviewable by the Division of Biopharmaceutics. The current submission has only one study and addresses only one issue i.e. relative bioavailability.

Recommendation: The following studies are needed to be submitted to the Division of Biopharmaceutics. The required information/studies are divided into 1. Critical for evaluation of biopharmaceutic aspects of the drug and 2. Recommended but not mandatory for Div. of Biopharmaceutics's evaluation.

1.

Drug physical/chemical properties

Proposed package insert

Dosage formulation information

Radiolabelled ADME studies

Metabolism information

Single dose PK studies

Multiple dose PK studies

Dose Proportionality

Bioequivalence study

In vitro drug dissolution

Gender Analysis

2.
Food effect study

PK/PD study

Special population

Protein binding

Assay-Validation

Metabolic identification/Isozymes characterization

The firm so far has satisfied only the requirement of relative bioavailability study. The solution was found bioequivalent to the tablet. In this relative bioavailability study there were several unexplained findings. First, the parent compound was not detected. Second, the level of desglymidodrine showed a second peak at 36 hr post drug administration. The firm has confirmed that the peak seen at 36 hr is not due to a compound other than desglymidodrine using The Division suggests that the firm run a to make sure that it is desglymidodrine. The firm has concluded that the drug is getting metabolized extensively in the gut wall to desglymidodrine. It is recommended to identify the exact mechanism of this conversion. This is important especially because firm has quoted two references where total conversion of midodrine to desglymidodrine did not take place in the gut wall. It is quite clear that some properly designed basic pharmacokinetic studies are necessary to understand midodrine disposition e.g. pharmacokinetics and mass-balance study of radiolabelled midodrine.

The Division of Biopharmaceutics is willing to work with the sponsor in designing the above studies.

10/22/93

Rajendra S. Pradhan, Ph.D.
Division of Biopharmaceutics

Initialed by Ameeta Parekh, Ph.D. Ameeta Parekh 10/22/93

cc: NDA 19-815, HFD 110, HFD 426 (Fleischer, Parekh, Pradhan), Chron, Drug, FOI (HFD 19), HFD 340 (Viswanathan), MET.

Appendix I

Relative-Bioavailability of Midodrine Tablet with respect to Aqueous Solution

Objective: To compare the oral bioavailability of a 5 mg dose of midodrine in the tablet and the aqueous solution.

Study Treatments: Tablet (5 mg) Lot# 293511.
Aqueous solution (5 mg) Lot# 110553

Study Design: Open, randomized, two-way cross-over trial conducted at a single center. 18 healthy male subjects received one of two treatments and subjects remained fasted for 4 hr following drug administration. The wash out period was 5 days.

Specimen: Blood, at 0, 10, 20, 30, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hr after the administration of the drug.

Results: The parent compound midodrine was not detected in the plasma. Mean concentrations of desglymidodrine versus time plot is shown in fig 1. The profile showed two peaks, one at 20 min and the other one at 36 hr. Table 1 shows pharmacokinetic parameters at several time points. In this table AUC was calculated from 0-3, 0-8, 0-12, 0-24, 0-36 and 0-48 hr. The following table shows the 90% confidence intervals for desglymidodrine pharmacokinetic parameters (log transformed)

Aqueous solution/Tablet	90% CI
AUC_{0-t}	82.99-115.49
Cmax	84.86-105.48
Tmax	-22.19-351.55

Comments: There were several unexplained findings in this study. First, the parent compound was not detected. Second, the level of desglymidodrine showed a second peak at 36 hr post drug administration. The firm has confirmed that the peak seen at 36 hr is not due to a compound other than desglymidodrine using . The Division suggests that the firm run a · to make sure that it is desglymidodrine. The firm has concluded that the drug is getting metabolized extensively in the gut wall to desglymidodrine. It is recommended to identify the exact mechanism of this conversion. This is important especially because firm has quoted two references where total conversion of midodrine to desglymidodrine did not take place in the gut wall. It is quite clear that some basic pharmacokinetic studies are necessary to understand midodrine disposition e.g. pharmacokinetics and mass-balance study of radiolabelled midodrine.

Conclusion: Midodrine 5 mg tablet and aqueous solution are bioequivalent.

FIGURE 1

CONCENTRATION OF DESGLYMIDODRINE IN THE PLASMA
5 mg Tablet vs. Solution

(n = 18). Values represent the Mean. A dose of 5 mg midodrine, either tablet or solution midodrine was given at Hour 0.

TABLE I
BIOAVAILABILITY
5 mg Tablet vs. Solution

TIME (hr)	SOLUTION	TABLET
C_{max} (mcg/ml x 10^{-1})		
3		
8		
12		
24		
36		
48		
T_{max} (hours)		
3		
8		
12		
24		
36		
48		
AUC (mcg.hr/ml)		
3		
8		
12		
24		
36		
48		

(n = 18) Pharmacokinetic parameters (Medians) for desglymidodrine in the plasma.

Drug: Midodrine tablets
Amatine®
Roberts Laboratories, Inc.

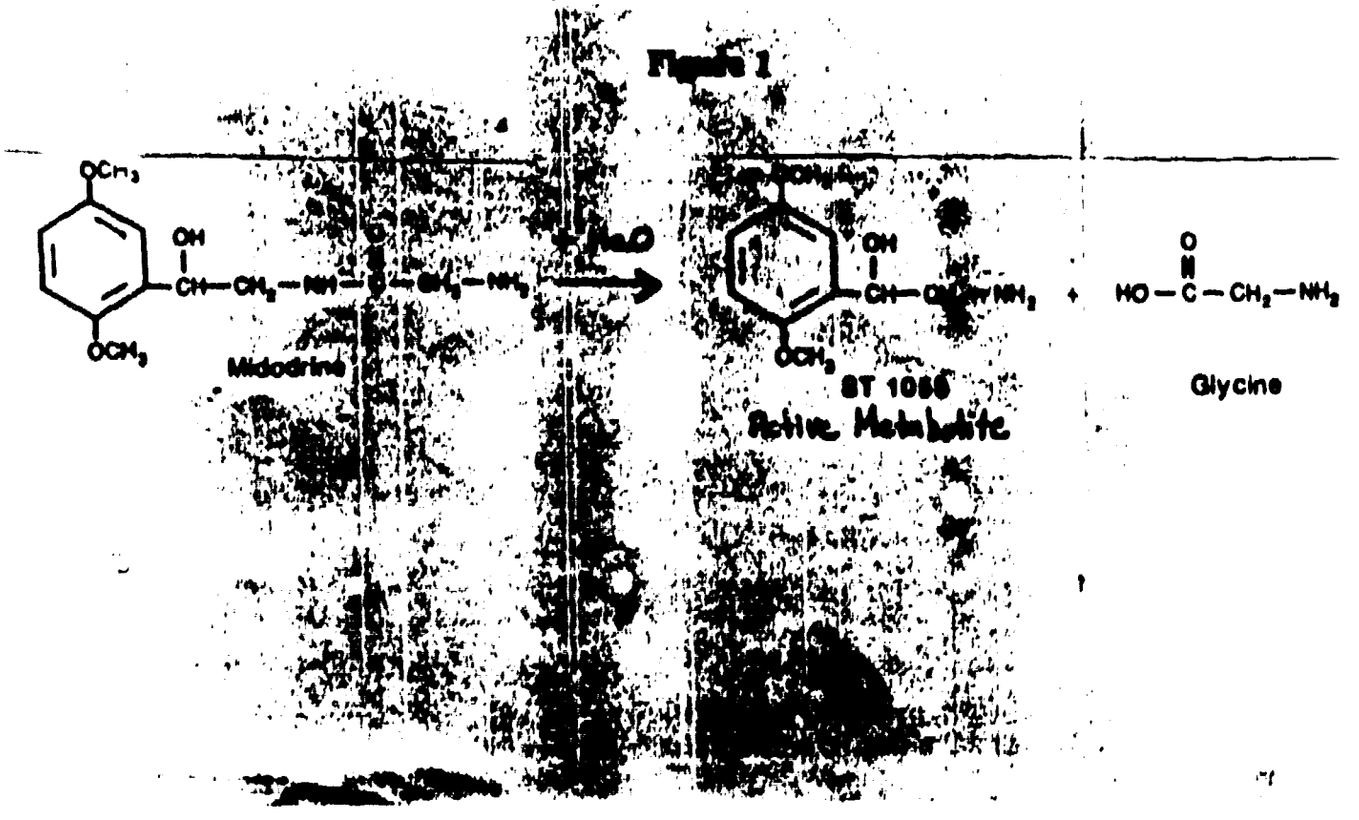
Reviewer: Janice Barnett Jenkins

Type of submission: Original NDA

Background:

The sponsor has submitted 6 studies which examine the metabolism and bioavailability of midodrine (ST 1085). Midodrine is a prodrug of desglymidodrine (ST 1059) which is an alpha-receptor sympathomimetic stimulant (Figure 1). The sponsor does not mention what the intended indication is for midodrine, however, conversations with the CSO (Gary Buehler) reveal that midodrine will be used to treat patients suffering from idiopathic orthostatic hypotension. This condition is quite rare, making it difficult to recruit significant numbers of study subjects. Clinical studies are also hindered by the fact that patients with this disorder are virtually bedridden because of the hypotension and when they experience the positive effects from midodrine they are reluctant to participate in placebo phases of studies. According to Gary Buehler, the dose that has been found to be effective is 10 mg. Midodrine is currently marketed in Europe under the brand name Gutron®. The studies submitted by the sponsor were conducted in Europe under the sponsorship of the At best, the details of the submitted studies are sketchy, containing very few specific details of the methods used for sample and data analysis. Therefore, a scientifically based biopharmaceutics review cannot be undertaken at this time. A brief description of the studies and results will be included in the Appendix. Also, the conclusions drawn by the sponsor will be included. It should be noted throughout that the conclusions are not those of the reviewer, but of the sponsor. Because of the many deficiencies in the submitted studies, a reasonable review cannot be undertaken at this time.

Figure 1



DEFICIENCIES:

There are a number of deficiencies in the present submission which need to be addressed before a biopharmaceutics review can take place. Below is a summary of the information needed for each study and information that is needed but not included in the submission.

QUESTIONS

(1) What is the proposed indication for use?
(2) What strength(s) and dosage form(s) will be marketed?
(3) What is the dose, dose range and dosing interval, and how do these relate to effect?
(4) Has an effective plasma concentration been identified and has a pharmacokinetic/pharmacodynamic relationship been established?
(5) What is the proposed labeling for the product?
(6) How is product labeled in Europe?
(7) Where will the final product be manufactured, and what will the batch size be?
(8) What is the composition of the formulation(s) used in the studies and intended for marketing?
(9) Has the market image tablet been studied in clinical trials, if not, has bioequivalency been established between the clinical formulation and market image tablet?
(10) What are the dissolution characteristics and proposed dissolution specification for the
(11) Is there interconversion between the enantiomers?
(12) What is the stability of midodrine in blood samples collected from study subjects (i.e. is there any in vitro metabolism of midodrine in blood/plasma)? midodrine formulations intended for marketing?
(13) What studies have been done to define the pharmacokinetics of midodrine in terms of dose proportionality and the effect of food? What were the findings of such studies?
(14) Are there other metabolites besides ST 1059? If so, have they been identified and their pharmacokinetics and pharmacodynamic effects defined?
(15) Are studies planned to examine the pharmacokinetics of 10 mg doses of midodrine, if this is to be the labeled dose?
(16) Have the pharmacokinetics of midodrine been studied in patients and special populations, such as elderly, hepatic and renal dysfunction?
(17) Are there any significant interactions with other renally cleared drugs?
(18) It was reported that most of the subjects in the submitted studies experienced formication (see definition below*) following the administration of midodrine. Is this side effect dose and/or concentration related? Also, do patients experience this side effect?
(19) Is midodrine protein bound to a significant extent and if so, what protein(s) is/are involved?

*Formication: A tactile hallucination in which there is a sensation of tiny insects crawling over the skin; most commonly seen in cocaine or amphetamine intoxication. (from 27th edition of Dorland's Illustrated Medical Dictionary)

INFORMATION REQUIRED FOR INDIVIDUAL STUDY REVIEW

(1) Source of study drug
- manufacture site
- manufacture date
- batch size
- lot number
- expiration
- dosage form

(2) Assay method
- specify method
- range of standard curve
- linearity, specificity, sensitivity, accuracy and precision of assay
- range of quality control samples
- inter- and intraday variability
- stability under frozen conditions
- were the samples analyzed within the range of the standard curve
- were samples diluted

(3) Data analysis
- statistical methods used
- use ln transformed data
- provide 90% confidence intervals

(4) Other
- study dates
- investigator(s)
- provide data sets for each study subject

Comments (To be sent to firm):

In study UL/4095 " Report on pharmacokinetic trials with ^{3}H-labelled midodrine in man (Part 1)", the measured total radioactivity is converted to midodrine plasma concentrations, however, the method used for this conversion is not detailed. Furthermore, it is not clear how such a conversion could be done based on total radioactivity, since active metabolite and residual activity are included in total radioactivity. The rationale for such conversion needs to be explained by the sponsor.

Any information which has been published regarding the pk/pd of a drug for which approval is sought should be included in the application submitted by the sponsor. At least one publication has been identified which was not included in the submission (Pharmacodynamics of midodrine, an antihypotensive agent. Zachariah PK, et. al., CPT, 39:586-591, 1986).

Recommendation:

The biopharmaceutics package for NDA 19-815 is found to be grossly deficient. The studies submitted to the Division of Biopharmaceutics as part of NDA 19-815 have not been documented in a manner which allows for appropriate biopharmaceutics review. In addition, other pertinent information relative to the drug has not been included in this submission. It is therefore recommended that the listed deficiencies contained herein be forwarded to the firm in order to provide guidance in putting together a reviewable biopharmaceutics package. Furthermore, if there is clinical interest in pursuing the approval of this application or if there is the possibility of a resurgence of this application, the Division of Biopharmaceutics would be willing to work with the sponsor to expedite the approval of this 1P orphan drug.

Janice Barnett Jenkins

Janice Barnett Jenkins, Ph.D.

RD initialed by Ameeta Parekh, Ph.D. 4/21/93
FT initialed by Nicholas Fleischer, Ph.D. Ameeta Parekh 5/5/93

cc: NDA 19-815, HFD 110, HFD 426 (Jenkins, Fleischer), Chron, Drug, FOI (HFD 19), MET.

d,l-ST 1085.HCl (MIDODRINE, GUTRON®) urinary excretion of the metabolite ST 1059 after one single oral dose of ST 1085.HCl to volunteers.

Study: Volume: 9 Pages: 28 - 37

SUMMARY

Six healthy male volunteers 27 to 59 years of age and weighing 68 to 90 kg participated in this study. Each subject received a single 5 mg dose of midodrine (batch No. 566319) with 250 ml of mineral water. A urine sample was collected prior to dosing and complete urine collection was carried out in intervals of 0 - 2, 2 - 4, 4 - 8, and 8 - 12 hours after drug administration. The samples were stored frozen until analysis. The active metabolite, ST 1059, was quantitated by fluorometric determination.

Note: About 1 hour after administration, formication of the scalp occurred. Analogous symptoms occurred in the shoulders and back. The symptom wanes after about 4 hours.

Based on the data from this study, the sponsor reached the following conclusions:
(1) ST 1085 (midodrine) seems to be rapidly absorbed from the tablets.
(2) ST 1085 is rapidly metabolized to ST 1059.
(3) Within a period of 8 hours, an average (n=6) of 30.2% of the administered dose is excreted as ST 1059 in the human urine (Tables 1 & 2).
(4) The temporary course of the excretion is identical with the duration of the subjective effect

Table 1

Summary of excretion of ST 1059 (active metabolite) in the individual urine fractions following an oral dose of 5.0 mg ST 1085.HCl (midodrine) each to test persons (i.e. 66.9 mcg/kg ST 1085.HCl (n=6)), expressed as micrograms of ST 1059 excreted per fraction.

Subject #	0 - 2 hours	2 - 4 hours	4 - 8 hours	8 - 12 hours	Total
1					
2					
3					
4					
5					
6					
mean	**525.83**	**320**	**178.68**	**0**	**1024.52**
sd	**121.61**	**34.43**	**130.74**	**0**	**176.23**
% cv	**23.13**	**10.76**	**73.17**	**0**	**17.20**

Table 2

Summary of excretion of ST 1059 (active metabolite) in the individual urine fractions following an oral dose of 5.0 mg ST 1085.HCl (midodrine) each to test persons (i.e. 66.9 mcg/kg ST 1085.HCl (n=6)), expressed as percent of the administered dose (n=6).

Subject #	0 - 2 hours	2 - 4 hours	4 - 8 hours	8 - 12 hours	% of Total Dose
1					
2					
3					
4					
5					
6					
mean	**15.5**	**9.42**	**5.28**	**0**	**31.03**
sd	**3.59**	**1.03**	**3.86**	**0**	**5.75**
% cv	**23.18**	**10.94**	**73.05**	**0**	**18.53**

COMMENTS:

(1) The sponsor has not submitted specific details regarding the analytical procedure used in this study.

(2) The sponsor calculated the total percent (30.2) of the dose excreted as ST 1085 in the urine by adding the average percents excreted in each urine fraction. I calculated the value (31.03) by taking the average of the individual total values for each study subject.

(3) The table in the submission reports "% of dose as ST 1085", I think it should be ST 1059 and I have changed the above tables to reflect this?

(4) The firm reports that the urinary excretion of ST 1059 can be correlated to a subjective effect, however, the subjective effect is not specifically stated.

d,l-ST 1085.HCl (MIDODRINE, GUTRON®). Urinary excretion of the metabolite ST 1059 after repeated administration of ST 1085.HCl to volunteers.

Study: Volume: 9 Pages: 38 - 48

SUMMARY:

The same 6 healthy male volunteers who were in the preceding single dose study participated in the present study. The subjects received three 5 mg doses of ST 1085.HCl (midodrine) (batch no. 566319). The dosing interval was 4 hours. Urine samples were collected prior to drug administration and over intervals of 0 - 4, 4 - 8, 8 - 12, and 12 - 24 hours. Samples were frozen until the time of analysis. The metabolite ST 1059 was quantitated using fluorometric determination.

Note: About 1 hour after the administration of the 1st tablet, formication of the scalp appeared, spreading to the shoulders and back. About half an hour after the administration of the 2nd tablet, this formication and chill covers practically the whole body. After administration of the 3rd tablet, a moderate reddening of the skin of the face is seen. All symptoms last until about 20.30 h.

Based on the data from the study, the sponsor reached the following conclusions:
(1) ST 1085 seems to be rapidly absorbed from the tablets.
(2) ST 1085 is rapidly metabolized to ST 1059.
(3) Within a period of 24 hours an average (n=6) of 44.9% of the administered total dose is excreted as ST 1059 in the human urine (Table 1).
(4) The amount of ST 1059 excreted in urine, over the reported intervals, after three doses of ST 1085 was similar to what was observed after single dose administration. There is apparently no accumulation of the substance within the observation period; so the chosen dosing interval can reasonably be considered as adequate.
(5) The temporary course of the total excretion can be correlated approximately with the duration of the subjective effects.

Table 1

Summary of excretion of ST 1059 (active metabolite) in the individual urine fractions (expressed in micrograms) following 3 oral doses ST 1085 (5mg) and percent of total dose excreted as ST 1059.

Subject #	0 - 4 h	4 - 8 h	8 - 12 h	12-24 h	Total	% of dose
1						
2						
3						
4						
5						
6						
mean	**968**	**1476**	**1445**	**685**	**4573**	**44.9**
sd	**121**	**246**	**297**	**706**	**873**	**8.6**
% cv	**12**	**17**	**21**	**103**	**19**	**19.1**

Comments:

See comments #1 & #4 from previous study,

Studies on the pharmacokinetics and the metabolism of d,l-^{3}H-ST 1085/HCl (midodrine) after i.v. administration to man

Study: Volume: 9 Pages: 49 - 81

SUMMARY:

One male subject participated in this study (age; 43, hgt; 186cm, wgt; 85kg). A solution of d,l-^{3}H-ST 1085/HCl (purity 95%) in normal saline was prepared and a 5.11 mg dose administered intravenously to the study subject. Blood samples were collected prior to and at the following times after drug administration; 3, 6, 10, 15, 30, 60 (mins), 2, 3, 6, 8, 24, 48, 72, and 96 (hr). Urine was collected over the following intervals; 0-2, 2-4, 4-6, 6-8, 8-12, 12-24, 24-36, 36-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours. Complete stools were collected at 24 hour intervals, over a 4 day period. All samples were frozen until analysis.

Liquid scintillation counting was used to measure total activity. The method of internal standardization was used for the calculation of the absolute activities. About 93% of the administered activity was excreted via the urine within 168 hours (7 days), therefore, analysis of the stool samples was not done. The distribution of metabolites in plasma and urine following drug administration was confined to a separation of the bases and neutral substances divided into 3 fractions; ST 1085 (midodrine), ST 1059 (active metabolite) and residual activity. The separation involved extraction, thin layer chromatography, elution and counting (dpm). The distribution of metabolites was also determined after incubation of urine samples with the enzymes beta-glucuronidase/arylsulfatase (

Note: Within a period of 1.5 to 4 hours after the administration of the test drug to the study subject, he experienced shivers of the whole body with piloerection. During the collection period of the two first urine fractions, a markedly increased desire to urinate with concomitant slight micturition difficulties was observed. The observed effects and their course meet approximately with the course of action of active concentration of ^{3}H-ST 1059 in the plasma and urine.

Results:

Based on plots of total activity (TA) versus time (Figs. 1 & 2), the sponsor presumes that 3 different kinetic processes are occurring. The first is rapid distribution of the TA which ends at about 30 minutes, and is presumed to correspond to an accumulation of the substance in a depot (Fig. 2). This is followed by a fall of the TA with a half life of about 5 - 6 hours (Fig. 1). Subsequently, there is a very slow fall of a residual activity which is concealed for the first two days, and becomes manifest from about 48 hours after drug administration (Fig. 1). The sponsor notes that the plasma and urine levels of residual activity reach equilibrium at the same time and that this portion of the TA can reasonably be attributed to ^{3}HHO, which cannot be further concentrated by the kidney. The ^{3}HHO has a half life of about 7 - 9 days via the urine.

Distribution of metabolites (DM) in plasma was only done within the 0 - 120 minutes after drug administration. The TA was separated into 3 portions (Fig. 3); unchanged d,l-^{3}H-ST 1085 (midodrine), d,l-^{3}H-ST 1059 (active metabolite) and residual activity, calculated as the difference to 100% of the TA. Plasma d,l-^{3}H-ST 1085 had rapid elimination from the plasma. The plasma level of d,l-^{3}H-ST 1059 fell rapidly for the initial 15 minutes, then rose to practically constant values within a period of 60 - 120 minutes.

The urine data is summarized in Table 2 and Figure 4. Within 4 hours after drug administration, 50% of the TA was excreted in urine. Within 168 hours after drug administration, 93% of the TA was excreted in the urine. Distribution of metabolites was measured in the first 4 urine fra tions (covering 0 - 8 hr). The TA was separated into 3 parts as described above. After the conjugates were split, the activity of each of the three parts was evaluated again. Both before and after splitting of the conjugates, only a small percent of the TA was attributable to ST 1085 (midodrine).

Table 1

Activity levels of the fractions ST 1085, ST 1059 and "residual activity" (for 0 to 120 minutes only) and total activity in plasma, expressed as dpm/ml.

Sampling Time	Total Activity dpm/ml plasma	Fraction of ST 1085 dpm/ml	Fraction of ST 1059 dpm/ml	Fraction of "Residual Activity" dpm/ml
3 min	62186	37480	7848	16858
6 "	32607	18726	4131	9749
10 "	25115	13075	3325	8715
15 "	20712	10466	3030	7216
30 "	17327	4375	4373	8579
60 "	16373	1793	7867	6708
2 hr	15921	446	8741	6736
3 "	13768	--	--	--
6 "	9686	--	--	--
8 "	7051	--	--	--
24 "	2178	--	--	--
48 "	599	--	--	--
72 "	528	--	--	--
96 "	489	--	--	--

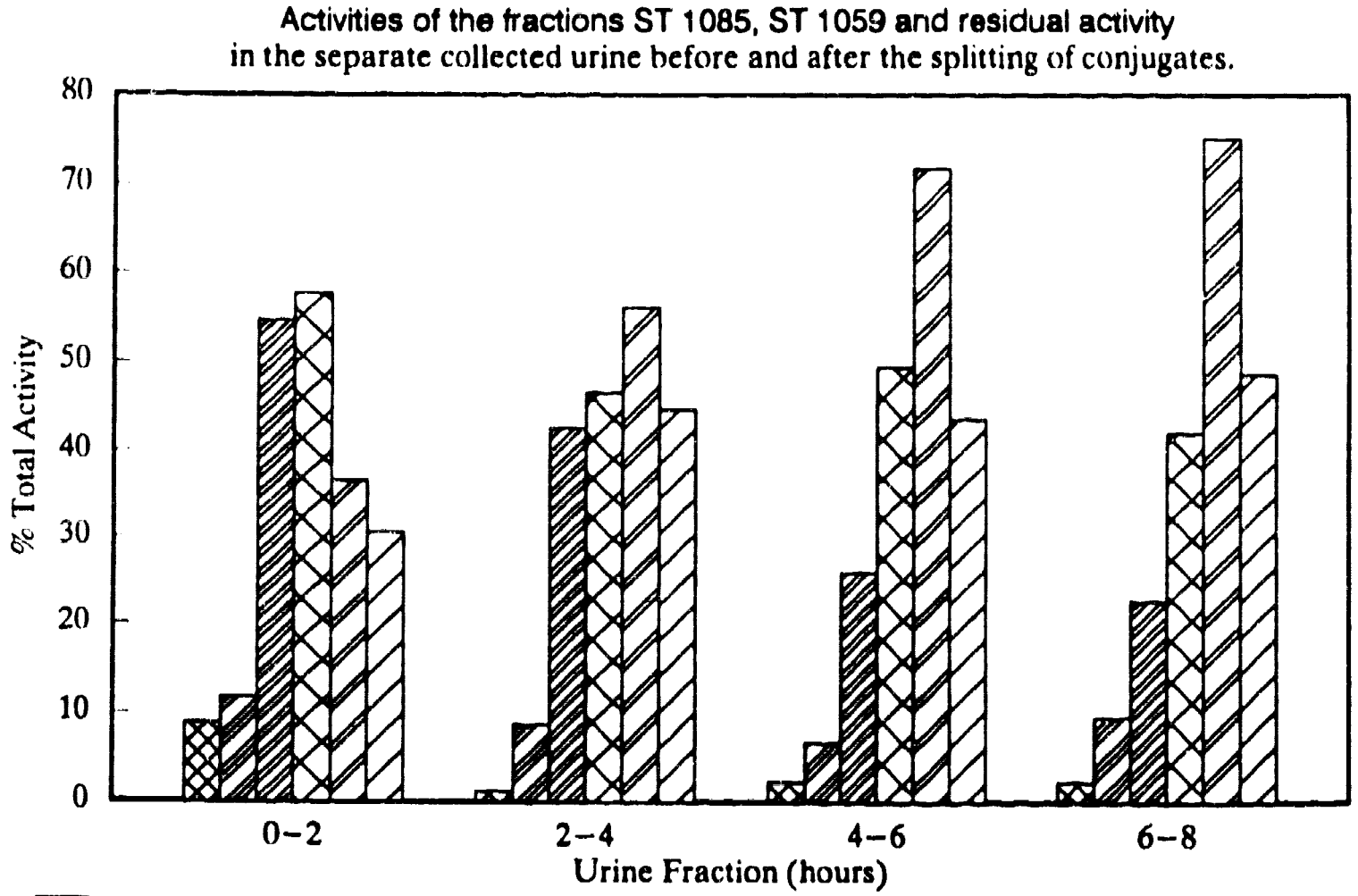
3 pages
purged

Table 2

Excretion of total activity (expressed in dpm/ml) in the separate urine collections

Urine Fraction in hours	dpm/ml of urine	dpm for total urine	% of excreted total activity in urine	Total excreted activity in urine
0 - 2	821900	508760873	29.97	--
2 - 4	1392300	284733106	16.77	46.74
4 - 6	1972400	225852768	13.30	60.04
6 - 8	764300	160519360	9.46	69.50
8 - 12	501150	195719217	11.53	81.03
12 - 24	199280	161420740	9.51	90.54
24 - 36	24241	26665614	1.57	92.11
36 - 48	10379	5707977	0.336	92.45
48 - 72	2438	3761834	0.222	92.67
72 - 96	1203	1785549	0.105	92.77
96 -120	892	1302465	0.077	92.85
120 -144	812	983004	0.058	92.91
144 -168	477	590860	0.035	92.94

Figure 4


Activities of the fractions ST 1085, ST 1059 and residual activity
in the separate collected urine before and after the splitting of conjugates.
% Total Activity
80
70
60
50
40
30
20
10
0
0–2
2–4
4–6
6–8
Urine Fraction (hours)
ST 1085(before)
ST 1085(after)
ST 1059(before)
ST 1059(after)
Residual Activity(before)
Residual Activity(after)

Report on pharmacokinetic trials with ^{3}H-labelled midodrine in man (part 1)

Study: Volume: 9 Pages: 82 - 110

SUMMARY:

In this study, plasma and whole blood levels and the excretion via urine and feces of ^{3}H-midodrine were measured in healthy male and female subjects after intravenous and oral administration, in order to confirm oral absorption. Three male and 3 female students ranging in age from 20 to 27 years participated in the study. The subjects fasted overnight prior to the study day. The subjects received either 5 mg or 5.3125 mg of ^{3}H-midodrine either intravenously or as an oral solution, respectively, in a randomized crossover study design. The study days were separated by 2 weeks. The drug was supplied by

For oral adminstration, the solution was injected into soft gelatin capsules and the capsules were ingested by the study subjects. Blood samples wee collected prior to and at 5, 10, 20, 40 and 60 min as well as 2, 4, 8, 12, 24, 48 and 72 hours after intravenous administration of drug. With the exception of the 5 minute sample, blood was collected according to the same schedule after oral administration. Both after the intravenous and the oral administration the urine was collected in 2 hour fractions until the 6th hour, which was followed by one period until the 12th hour, by another period until the 24th hour, afterwards the urine was collected in 24 hour fractions until day 7. In both trials feces were taken in 24-hour fractions until day 4.

Total activity was measured in whole blood, plasma, urine and feces.

Results:

The total activity was converted to ng/ml of midodrine and the mean results after intravenous and oral drug administration are presented in Table 1, along with their deviations. Table 1 also contains the theoretical plasma concentrations which were determined by using a multiple feathering computer program (Wagner, 1975; Fundamentals of Clinical Pharmacokinetics, Drug Intelligence Publications Inc., Hamilton). Figure 1 shows the theoretical plasma concentration curves. The predicted midodrine plasma concentrations correlate with the observed values after both routes of administration.

Mean whole blood concentrations after intravenous and oral drug administration are shown in Table 2. Table 3 has the mean excretion of midodrine in urine and feces after intravenous and oral administration of midodrine. The predominant percentage of the administered dose was excreted in the urine, with only a very small amount being excreted in the feces.

The plasma data following intravenous and oral administration of midodrine were fit to a two- and one-compartment model, respectively, using the computer program referenced above. The results are in Tables 4a, 4b, 5a and 5b. The mean absorption rate after oral administration was calculated by Dost's proposition and turned out to be 109%.
The individual data for Tables 1 - 5 are included in the appended tables A - D.

Table 1

Mean plasma concentrations of midodrine and their deviations after intravenous and oral administration of 5 mg and 5.3 mg of ^{3}H-midodrine, respectively, calculated from the ^{3}H-total activity and converted to ng/ml. The predicted concentrations derived from fitting the iv and oral data to two- and one-compartment models, respectively, is included.

Time	IV mean (ng/ml)	IV deviation (SEM)	IV predicted (ng/ml)	PO mean (ng/ml)	PO deviation (SEM)	PO predicted (ng/ml)
5 min	94.25	10.19	91.35	---	---	---
10 "	60.77	8.07	62.31	13.58	6.69	13.58
20 "	46.16	5.45	46.08	30.25	5.42	30.25
40 "	39.62	3.30	41.00	50.70	5.06	45.00
60 "	36.87	2.68	38.57	50.12	4.66	48.46
2 h	33.64	2.21	32.27	47.54	4.99	43.23
4 "	24.00	1.72	22.58	31.43	3.47	29.65
8 "	11.71	0.57	11.06	14.92	1.58	13.81
12 "	4.88	0.32	5.41	5.95	0.75	6.43
24 "	0.65	0.10	0.64	0.65	0.13	0.65
48 "	0.0	--	0.01	0.0	---	0.01
72 "	0.0	--	0.00	0.0	---	---

ng/ml

Figure 1

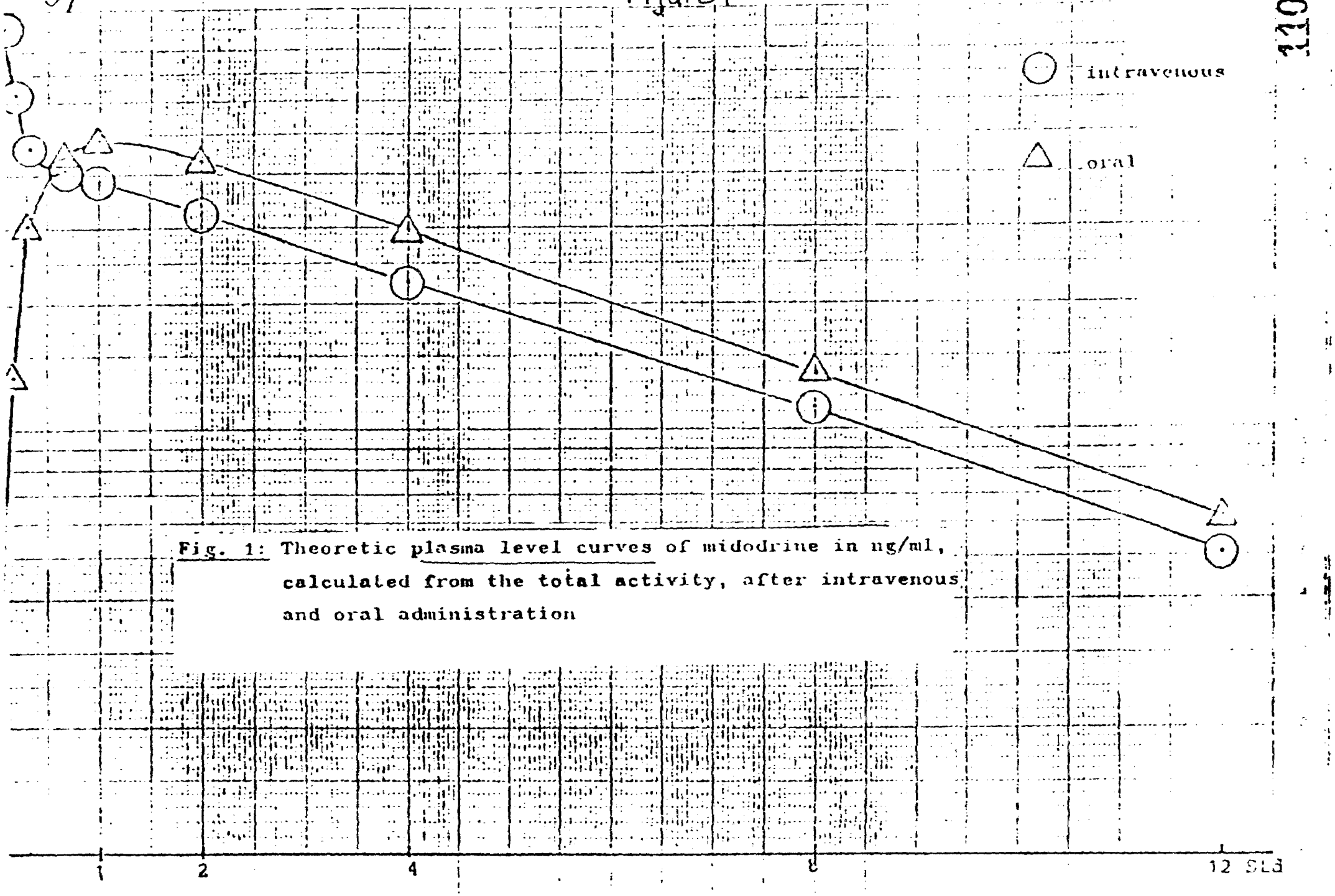


Fig. 1: Theoretic plasma level curves of midodrine in ng/ml, calculated from the total activity, after intravenous and oral administration

hrs

Table 2

Mean whole blood levels of midodrine in ng/ml after intravenous and oral administration (5.0 and 5.3 mg, respectively), calculated from the ^{3}H-total activity.

Time	IV mean (ng/ml)	IV deviation (SEM)	PO mean (ng/ml)	PO deviation (SEM)
5 min	109.82	18.35	---	---
10 "	69.56	13.06	14.21	7.28
20 "	50.50	8.77	29.82	7.13
40 "	40.42	5.84	45.91	3.06
60 "	38.18	5.14	41.61	1.99
2 hr	32.81	4.50	37.74	3.47
4 "	22.93	2.75	25.47	2.54
8 "	11.40	1.19	11.35	1.14
12 "	4.91	0.56	4.64	0.56
24 "	0.53	0.14	0.45	0.14
48 "	0.0	---	0.0	---
72 "	0.0	---	0.0	---

Table 3

Mean excretion of midodrine in urine and feces after intravenous and oral administration, as percentage of the dose given.

	Time	IV mean % of dose	IV deviation	PO mean % of dose	PO deviation
URINE	0 - 2 h	34.49	1.14	26.46	1.64
	2 - 4 h	18.60	1.86	20.61	0.91
	4 - 6 h	13.85	1.90	12.38	0.84
	6 - 12 h	6.77	1.59	7.90	2.03
	12 - 24 h	7.02	1.92	7.82	2.00
	2 days	1.17	0.27	1.17	0.15
	3 days	0.17	0.04	0.18	0.04
	4 days	0.01	---	0.04	0.02
	5 days	0.0	---	0.01	0.01
	6 days	0.0	---	0.0	
	7 days	0.0	---	0.0	
TOTAL URINE		**82.08**		**76.57**	
FECES	1 day	0.04	0.02	0.42	0.33
	2 days	0.32	0.15	0.69	0.44
	3 days	0.35	0.16	0.83	0.24
	4 days	0.07	0.06	0.17	0.16
TOTAL FECES		**0.78**		**2.11**	
TOTAL URINE AND FECES		**82.86**		**78.68**	

ad tables 4a and 4b

ß : slow disposition constant

α : rapid disposition constant

B : intersection of the mono-exponential ß-straight line with the ordinate

A : intersection of the mono-exponential α-straight line with the ordinate

C : fictitious concentration in the plasma at time O

k_{12} : distribution constant

k_{21} : distribution constant

k_{13} : elimination constant

$t_{1/2ß}$: biological half life (= half life of ß-phase)

$t_{1/2\alpha}$: half life of α-phase

AUC : area under blood level curve

Cl_{tot} : total clearance

V_c, V_{dss}, V_{darea} : distribution volumes

Table 4a: Pharmacokinetic results for midodrine after intravenous administration of 5 mg, calculated according to an open two-compartiment-model. The table shows the individual results for each test person, the means and deviations

Test person	β h^{-1}	B ng/ml	$t_{1/2\beta}$ h	α h^{-1}	A ng/ml	$t_{1/2\alpha}$ h
1						
2						
3						
4						
5						
6						
$\bar{x}$	0.1803	46.01	3.87	15.26	168.29	0.06
$s_{\bar{x}}$	0.0061	3.13	0.12	3.06	29.61	0.01

Table 40 : Pharmacokinetic results for midodrine after intravenous administration of 5 mg, calculated according to an open two-compartiment-model. The table shows the individual results for each test person, the means and deviations

Test person	C ng/ml	k_{12} h^{-1}	k_{21} h^{-1}	k_{13} h^{-1}	Cl_{tot} ml/min	$AUC^{0-\infty}$ $\frac{ng \cdot h}{ml}$	V_c ml	V_{dss} ml	V_{darea} ml
1									
2									
3									
4									
5									
6									
$\bar{x}$	214.30	11.38	3.2251	0.8588	319.60	268.67	25.03	101.60	106.21
$S_{\bar{x}}$	28.18	2.71	0.3365	0.1271	26.45	19.37	2.62	6.95	7.11

ad tables 5a and 5b

k_{el} : elimination constant

k_{ab} : absorption constant

$t_{1/2el}$: biological half life (= half life of ß-phase)

$t_{1/2ab}$: absorption half life

C_p^o : fictitious concentration in the plasma at time 0

t_o : time-lag of absorption

t_{max} : time of maximal concentration

c_{max} : maximal concentration

AUC : area under blood level curve

V_d, V_{darea}: distribution volumes

f : fraction of absorbed dose (x 100 = percentage)

JEC 2/10/88

Table 5a Pharmacckinetic results for midodrine after ~~intravenous~~ oral administration of a solution o .3 mg, calculated according to an open one-compartiment-model. The table shows the individual results for each test person, the means and deviations

Test person	k_{el} h^{-1}	$A=B=C_p^o$ ng/ml	$t_{1/2el}$ h	k_{ab} h^{-1}	$t_{1/2ab}$ h	t_o h	t_{max} h	c_{max} ng/ml
1								
2								
3								
4								
5								
6								
$\bar{x}$	0.1965	64.24	3.58	4.5822	0.22	0.13	0.66	53.91
$S_{\bar{x}}$	0.0102	5.93	0.19	1.4827	0.04	0.04	0.12	4.00

JEC 2/10/88

Table 5b . Pharmacokinetic results for midodrine after ~~intravenous~~ oral administration of a solution of 5.3 mg, calculated according to an open one-compartiment-model. The table shows the individual results for each test person, the means and deviations

Test person	$AUC^{0-\infty}$ $\frac{ng \cdot h}{ml}$	f $0 < ; \leq 1$	V_d $ml \cdot 10^3$	V_{darea} $ml \cdot 10^3$
1				
2				
3				
4				
5				
6				
$\bar{x}$	307.93	1.09	93.83	100.11
$s_{\bar{x}}$	25.93	0.07	11.34	12.59

Comments:

(1) The oral midodrine dose was 5.3125 mg instead of 5.0 mg because gravimetric determination found that the subjects received 0.425 ml instead of 0.400 ml of the dosing solution.

(2) When the data is examined based on gender, there does not appear to be any difference (Table 6, Figure 2). However, the small number of subjects does not allow for concrete conclusions to be drawn.

Table 6

Mean (std. dev.) plasma concentrations of midodrine (ng/ml) after intravenous and oral administration to 3 female and 3 male volunteers.

Time	IV FEMALE	IV MALE	PO FEMALE	PO MALE
5 min	106.0 (29.0)	82.5 (17.4)	---	---
10 "	71.4 (22.3)	50.1 (11.7)	7.8 (12.4)	19.4 (20.4)
20 "	54.1 (13.4)	38.2 (8.6)	28.7 (17.5)	31.9 (11.2)
40 "	45.6 (5.3)	33.7 (5.3)	59.6 (11.3)	41.9 (4.7)
60 "	40.6 (5.3)	33.1 (6.1)	56.3 (10.7)	44.0 (9.8)
2 h	36.9 (3.2)	30.4 (5.5)	54.7 (11.4)	40.4 (9.5)
4 "	26.5 (3.8)	21.5 (3.5)	35.0 (9.4)	27.9 (7.3)
8 "	12.4 (0.6)	11.1 (1.8)	14.5 (3.8)	15.3 (4.7)
12 "	5.2 (0.3)	4.5 (1.0)	5.4 (1.7)	6.5 (2.1)
24 "	0.7 (0.2)	0.6 (0.3)	0.5 (0.2)	0.8 (0.4)

Figure 2

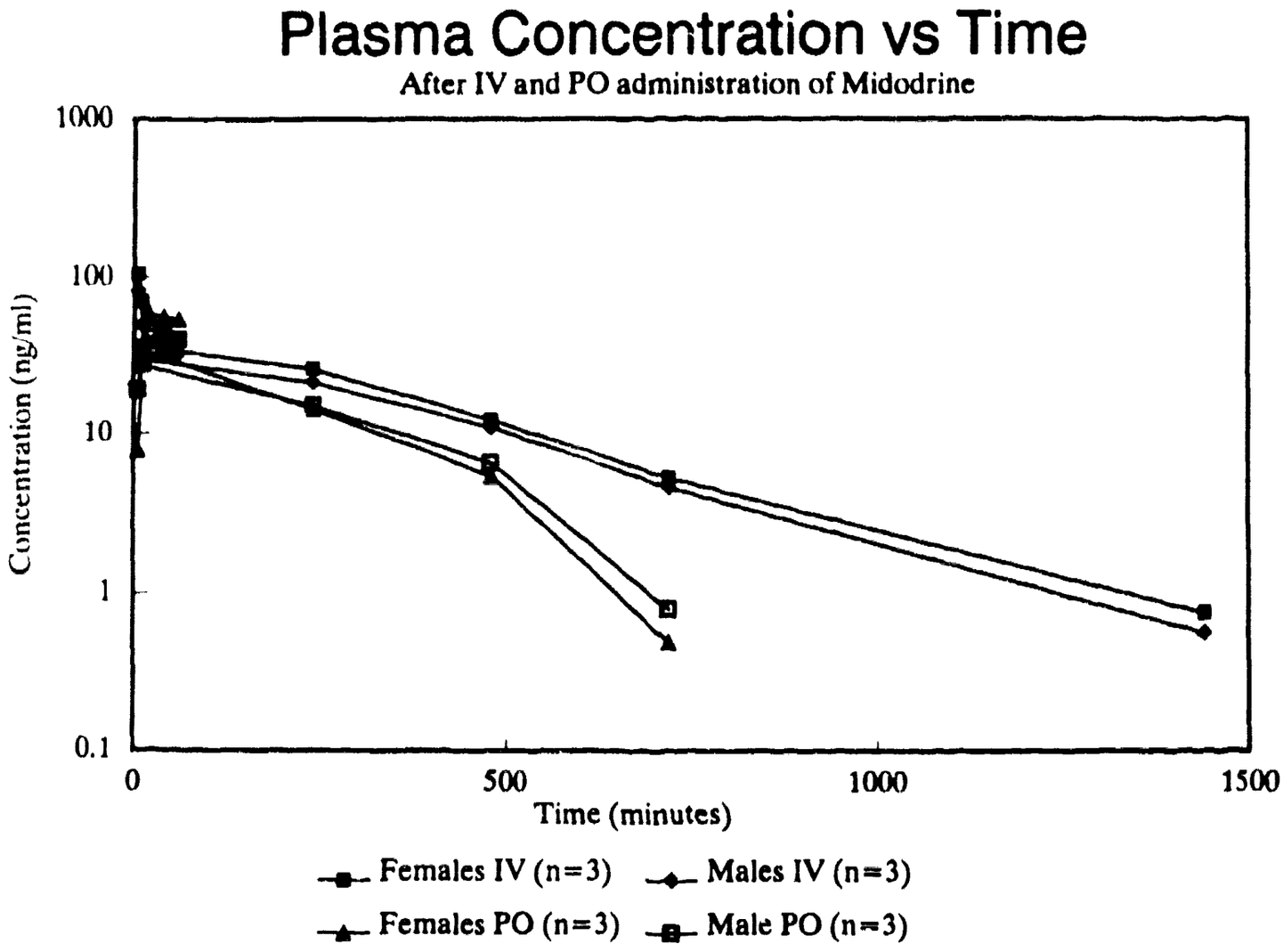

Plasma Concentration vs Time
After IV and PO administration of Midodrine
1000
100
10
1
0.1
Concentration (ng/ml)
0
500
1000
1500
Time (minutes)
Females IV (n=3)
Males IV (n=3)
Females PO (n=3)
Male PO (n=3)

Table A. Individual results to table 1

intravenous

Time	1 ♀	2 ♀	3 ♀	4 ♂	5 ♂	6 ♂
5 min	72.49	121.98	123.43	64.64	99.43	83.50
10 min	45.94	87.61	80.72	41.72	63.47	45.14
20 min	38.74	63.24	60.40	31.14	47.84	35.59
40 min	39.77	46.75	50.22	29.69	39.73	31.55
60 min	34.45	43.50	43.91	26.11	36.09	37.13
2 h	33.26	38.91	38.62	24.39	35.34	31.34
4 h	22.38	27.23	29.76	18.55	25.32	20.75
8 h	11.73	12.39	12.99	9.70	13.06	10.41
12 h	5.14	5.59	4.96	3.89	5.71	3.99
24 h	0.79	0.92	0.53	0.24	0.79	0.65
48 h	0	0	0	0	0	0
72 h	0	0	0	0	0	0

Table B: Individual results to table 1

oral

Time	1 ♀	2 ♀	3 ♀	4 ♂	5 ♂	6 ♂
10 min	1.29	0	22.03	42.11	2.48	13.54
20 min	23.04	14.60	48.31	44.30	22.73	28.52
40 min	66.96	65.13	46.56	36.68	45.70	43.18
60 min	61.95	62.95	43.95	33.13	52.38	46.35
2 h	57.59	64.39	42.13	29.42	45.90	45.79
4 h	39.36	41.48	24.17	19.42	31.96	32.19
8 h	15.95	17.41	10.19	10.77	20.18	15.01
12 h	6.17	6.50	3.42	4.94	8.94	5.70
24 h	0.68	0.57	0.24	0.78	1.17	0.43
48 h	0	0	0	0	0	0
72 h	0	0	0	0	0	0

Table C Individual results to table 2

intravenous

Time	1 ♀	2 ♀	3 ♀	4 ♂	5 ♂	6 ♂
5 min	108.52	163.85	158.65	45.88	90.33	91.69
10 min	69.84	117.45	94.56	28.88	50.74	55.86
20 min	57.06	82.80	61.91	20.92	39.76	40.56
40 min	43.66	60.02	50.80	19.40	35.56	33.09
60 min	42.78	56.13	44.07	18.97	32.55	34.59
2 h	38.85	47.21	37.74	15.38	27.47	30.19
4 h	27.35	30.40	25.35	10.97	22.31	21.18
8 h	13.59	14.39	11.68	6.28	12.31	10.13
12 h	6.25	5.64	5.22	2.50	5.66	4.18
24 h	0.83	0.82	0.37	0	0.83	0.34
48 h	0	0	0	0	0	0
72 h	0	0	0	0	0	0

Table D. Individual results to table 2

oral

Time	1 ♀	2 ♀	3 ♀	4 ♂	5 ♂	6 ♂
10 min	0.50	0	24.73	45.04	2.62	12.36
20 min	15.71	13.08	50.11	53.03	20.82	26.17
40 min	44.70	60.52	45.80	43.20	41.56	39.66
60 min	35.73	49.29	43.35	37.01	42.06	42.21
2 h	38.22	49.97	37.94	23.32	39.32	37.68
4 h	22.30	34.03	25.16	15.62	28.86	26.86
8 h	8.56	13.08	11.13	7.92	15.34	12.07
12 h	3.35	4.90	4.43	3.16	6.98	5.00
24 h	0.10	0.22	0.37	0.23	0.82	0.94
48 h	0	0	0	0	0	0
72 h	0	0	0	0	0	0

Report on pharmacokinetic trials with ^{3}-labelled midodrine in man. Part 2

Study: Volume: 9 Pages: 111 - 130

SUMMARY

The plasma and urine samples from the previous study were analyzed for midodrine (ST 1085) and its active metabolite (ST 1059) using radio-thin-layer-chromatography. Plasma samples collected at 20 min, 60 min, 2 h, 4 h and 12 h after iv and oral drug administration were assayed. The urine fractions: 0 - 2 h, 2 - 4 h, 4 - 6 h, 6 - 12 h and 12 - 24 h were also assayed. Urinary metabolites were also measured following a 24 hour incubation with an enzyme mixture (betagluconidase/arylsulphatase). The activity in the thin layer bands corresponding to ST 1085 and ST 1059 was determined and the remaining activity was the residual activity. Data was expressed as the percent of total activity.

The mean activities of the 3 fractions, after oral and intravenous administration of midodrine, in the separate plasma samples and urine fractions are presented in Tables 1 & 2, respectively.

Table 1: Mean activities of fractions "ST 1085", "ST 1059" and "residual activity" in the separate plasma specimens - expressed as percentages of total activity - after intravenous and oral administration of 5 mg midodrine in subjects No. 1 - 6

	Intravenous			Oral		
Plasma (time)	ST 1085	ST 1059	Residual activity	ST 1085	ST 1059	Residual activity
20 min	31.5 ± 2.14	29.5 ± 9.65	38.8 ± 8.88	52.8 ± 4.38	27.5 ± 5.21	19.5 ± 4.04
60 min	0	34.8 ± 3.11	65.2 ± 3.11	0	25.2. ± 12.03	74.8 ± 12.03
2 h	0	37.2 ± 5.33	62.7 ± 5.42	0	0	100+
4 h	—	—	—	—	—	—
12 h	—	—	—	—	—	—

+ N = 5

124

Table 2: Mean activities of fractions "ST 1085", "ST 1059" and "residual activity" in the separate collected urines - expressed as percentages of total activity - after intravenous and oral administration of 5 mg midodrine in subjects No. 1 - 6

Before cleavage of conjugates

	Intravenous			Oral		
Urine (h)	ST 1085	ST 1059	Residual activity	ST 1085	ST 1059	Residual activity
0 - 2	11.5 ± 2.29	56.5 ± 3.52	31.7 ± 3.78	13.2 ± 1.35	57.0 ± 2.31	29.8 ± 2.59
2 - 4	3.1 ± 0.72	53.7 ± 2.60	42.8 ± 2.23	4.2 ± 1.28	55.3 ± 3.09	40.5 ± 2.17
4 - 6	1.6 ± 0.74	51.0 ± 1.71	47.0 ± 1.51	2.8 ± 1.05	54.2 ± 3.59	42.5 ± 3.13
6 - 12	2.1 ± 1.80	51.2 ± 3.24	46.8 ± 2.12	2.3 ± 0.91	50.6 ± 2.91	47.0 ± 2.53
12 - 24	0.2 ± 0.15	66.2 ± 5.32	33.7 ± 5.25	0.4 ± 0.32	54.7 ± 3.6	44.8 ± 3.30

After cleavage of conjugates

0 - 2	14.3 ± 1.38	60.2 ± 1.94	25.2 ± 1.49	13.0 ± 1.39	55.3 ± 4.06	31.7 ± 3.21
2 - 4	3.0 ± 0.52	54.7 ± 2.95	42.3 ± 3.12	4.6 ± 1.27	53.7 ± 3.03	41.2 ± 2.89
4 - 6	3.0 ± 0.37	55.3 ± 3.81	41.7 ± 3.90	4.8 ± 1.33	53.5 ± 2.72	41.5 ± 3.08
6 - 12	3.2 ± 1.08	55.0 ± 5.34	41.2 ± 4.93	6.6 ± 0.93	51.0 ± 3.27	42.2 ± 3.12
12 - 24	0.7 ± 0.42	64.0 ± 6.63	35.2 ± 6.60	1.8 ± 0.60	54.2 ± 3.28	43.5 ± 2.78

Studies on the bioavailability of midodrine and alpha-2,5-dimethoxyphenyl-beta-aminoethanol hydrochloride

Study: Volume: 9 Pages: 150 - 166D

Investigators:

Objectives:

The purpose of this study was to examine the absolute bioavailability of the active metabolite of midodrine (ST 1059) when administered as a drinkable solution of 2.5 mg of midodrine and also when administered as a 2.5 mg midodrine tablet. The bioavailability of the tablet relative to the solution was also examined.

Formulation:

The formulations were manufactured by

Study Design:

Twelve (12) healthy, male volunteers between the ages of 21 and 26 years (median = 23), weighing from 63 to 88 kg (median = 76) and from 175 to 190 cm tall (median = 185) participated in this randomized crossover design study. On 3 occasions, each separated by one week, fasted subjects received single 2.5 mg doses of midodrine either as iv, oral solution or tablet preparations. The solution was prepared in mineral water and had a final volume of 125 ml. The tablet was administered with 125 ml of mineral water. Subjects were given breakfast two hours after drug administration. Ten (10) ml blood samples were collected immediately before drug adminstration or injection and 5 min (only after iv), 10 min, 20 min, 30 min, 45 min and 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours after drug administration. Urine samples were collected before adminstration and for the following intervals after drug administration: 0 - 2 h, 2 - 4 h, 4 - 6 h, 6 - 8 h, 8 - 10 h and 10 - 24 h. Plasma and urine samples were stored frozen at -70° C until assayed.

1 page
purged

Results:

After oral administration, the mean plasma concentrations of midodrine peaked at 10 ng/ml in about 20 - 30 minutes, for both preparations, and midodrine was no longer detected in plasma after 3 hours (Tables 1 & 3). The calculated pharmacokinetic parameters for midodrine are presented in Table 1.

Figure 1 shows the mean plasma concentrations versus time profiles for ST 1059 following the administration of 2.5 mg of 3 different midodrine formulations (iv, oral solution, oral tablet). At about 1 hour, concentrations of ST 1059 peaked at 4.3 and 4.7 ng/ml for the solution and tablet formulations, respectively. Plasma concentrations of ST 1059 could be detected up to 10 hours after midodrine administration in most subjects. Pharmacokinetic parameter estimates and mean plasma concentrations for ST 1059 are presented in Tables 2 and 4.

The absolute bioavailability (F) (mean $\pm$ sd) of ST 1059 as the drinkable solution was 0.9 (95% C.I.: 0.78 - 1.02) and F for the tablet was 0.93 (95% C.I.: 0.84 - 1.08). The mean relative bioavailability of the tablet compared to the solution was 1.09 (95% C.I.: 0.90 - 1.22).

FIGURE 1

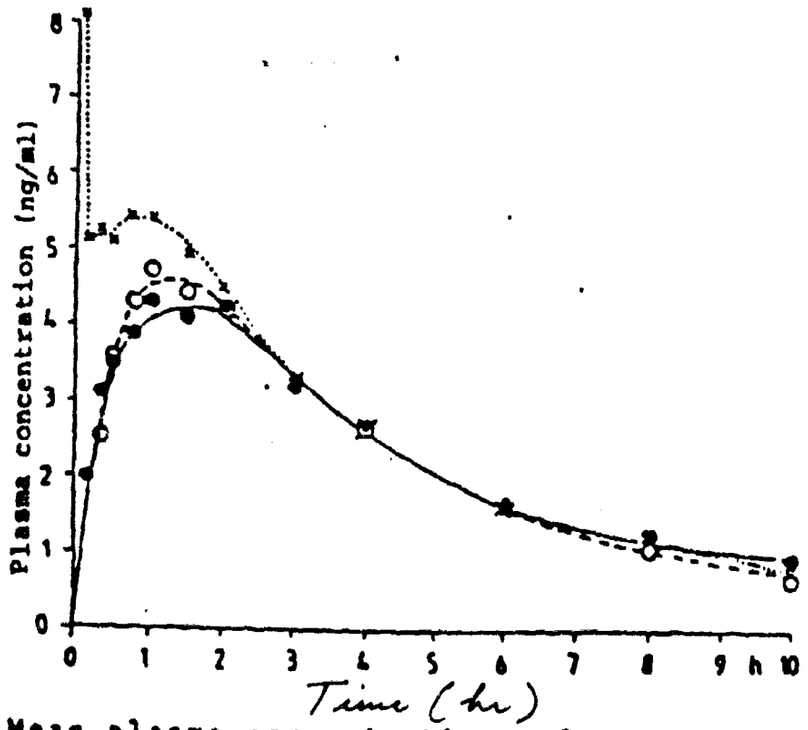


Figure 1: Mean plasma concentrations of ST 1059 after administration of 2.5 mg midodrine hydrochloride in each case to 10 healthy volunteers. x i.v.; • p.o. (solution); o p.o. (tablet).

Table 1

Pharmacokinetic parameters of midodrine hydrochloride after administration of a 2.5 mg dose to healthy volunteers.

Parameter	Intravenous	Oral Solution	Oral Tablet
Tmax (min)	-	23 ± 14	27 ± 12
Cmax (ng/ml)	-	10.9 ± 2.9	11.2 ± 3.9
$t_{1/2}$ (h)	0.41 ± 0.08	0.45 ± 0.12	0.49 ± 0.12
AUC (ngxh/ml)	14.6 ± 4.6	8.71 ± 1.78	9.46 ± 2.09
$U_{0\text{-}24\,h}$ (% of dose)	3.6 ± 1.3	2.2 ± 0.4	2.2 ± 0.6

$U_{0\text{-}24\,h}$ = excretion in 24 hours

Table 2

Pharmacokinetic parameters of ST 1059 after administration of 2.5 mg midodrine to healthy volunteers.

Parameter	Intravenous	Oral Solution	Oral Tablet
Tmax (h)	-	1.1 ± 0.5	1.1 ± 0.5
Cmax (ng/ml)	-	4.6 ± 1.0	5.0 ± 1.6
$t_{1/2}$ (h)	3.1 ± 0.5	3.0 ± 0.4	3.0 ± 0.5
AUC (ngxh/ml)	28.7 ± 6.6	25.7 ± 6.6	25.6 ± 6.2
Cl (ml/min)	1200 ± 229	1392 ± 378	1378 ± 319
Volume (l)	319 ± 61	355 ± 81	352 ± 80
$U_{0\text{-}24\,h}$ (% of dose)	39.3 ± 3.8	34.4 ± 2.6	34.4 ± 4.5

$U_{0\text{-}24\,h}$ = excretion in 24 hour urine

Table 3: Plasma concentrations of midodrine hydrochloride (ST 1085/HCl, ng/ml) after administration of 2.5 mg Gutron to 11 volunteers.

Time	Dosage form		
	Intravenous	Oral	
		Solution	Tablet
5 min	56.6 ± 22.2	3.4 ± 1.9[1]	–[4]
10	21.6 ± 6.2	8.0 ± 4.2	4.9 ± 3.2[1]
20	11.3 ± 3.1	9.7 ± 3.4	9.4 ± 3.6
30	7.6 ± 2.0	8.0 ± 2.0	9.9 ± 4.3
45	4.4 ± 1.1	5.3 ± 1.9	6.2 ± 2.2
1 h	3.2 ± 1.2	3.5 ± 1.1	4.0 ± 0.9
1.5	1.8 ± 0.5[1]	1.8 ± 0.5	2.1 ± 0.5
2	–[4]	1.1 ± 0.2[1]	1.3 ± 0.3[1]

[1] n = 9; [2] n = 6; [3] n = 7; [4] Most of the values below the limit of detection of 1.0 ng/ml.

Table 4: Plasma concentrations of ST 1059/HCl (ng/ml) after administration of 2.5 mg Gutron to 11 volunteers.

Time	Dosage form		
	Intravenous	Oral	
		Solution	Tablet
5 min	8.1 ± 2.1	–	–
10	5.1 ± 1.0	2.0 ± 1.0[1]	–[4]
20	5.2 ± 1.1	3.1 ± 1.2	2.5 ± 1.0
30	5.1 ± 1.0	3.5 ± 1.3	3.6 ± 1.4
45	5.4 ± 1.2	3.9 ± 1.3	4.3 ± 2.0
1 h	5.4 ± 1.0	4.3 ± 1.1	4.7 ± 1.5
1.5	4.9 ± 0.8	4.1 ± 1.0	4.4 ± 1.2
2	4.5 ± 0.7	4.2 ± 0.9	4.2 ± 1.1
3	3.3 ± 0.7	3.2 ± 0.8	3.3 ± 0.7
4	2.6 ± 0.5	2.6 ± 0.6	2.6 ± 0.6
6	1.6 ± 0.3	1.5 ± 0.4[1]	1.6 ± 0.4
8	1.1 ± 0.2[1]	1.2 ± 0.4[1]	1.0 ± 0.2
10	0.7 ± 0.2	0.8 ± 0.2	0.7 ± 0.2

[1] n = 9; [2] n = 10; [3] n = 7; [4] Most of the values below the limit of detection of 0.5 ng/ml.

midodrine HCl
Amatine® Tablets
2.5 mg, 5.0 mg
NDA 19-815
Reviewer: Ching-Leou C. Teng, Ph.D.
SP

Roberts Laboratories, Inc.
Eatontown, New Jersey 07724
Submission Date:
April 26, 1988

DEC 29 1989

Review of an NDA

Midodrine HCl is the glycine analog of a potent alpha sympathomimetic agent. Following oral administration, midodrine is bioactivated by hydrolysis of the glycine ester to des-gly-midodrine which is the active alpha receptor agonist.

According to Dr. Cheryl J. Graham (medical officer, HFD-110), the NDA was disapproved. Therefore, the Division of Biopharmaceutics will not review this NDA at this time. A brief description of studies is included as a reference.

DESCRIPTION OF STUDIES:

1. Single oral dose urinary excretion study to evaluate midodrine metabolites.

Six healthy male volunteers each received 5 mg midodrine tablet. Urinary concentrations of desglymidodrine (active metabolite) were determined by fluormetric assay.

2. Multiple oral dose urinary excretion study to evaluate midodrine metabolites.

Six healthy male volunteers received a total of three doses of 5 mg midodrine.

3. Single I.V. dose to evaluate midodrine metabolites.

One subject received 5.11 mg of midodrine (764.6 uCi of tritium label, 3 ml) by intravenous injection. was used to separate unchanged midodrine and its metabolites in plasma and urine samples.

4-5. Midodrine single dose I.V./P.O. study, 2-way crossover metabolic study.

Six subjects received an i.v. dose of 5 mg of midodrine labeled with 268.1 uCi of tritium (3 ml) and an oral dose of 5.3 mg midodrine labeled with 266.0 uCi in 0.4 ml. Total radioactivity was measured in whole blood, plasma, urine, and feces (study 4). Plasma and urine specimens were extracted by methanol. The extracts were then subjected to

6. Single dose midodrine bioavailability study.

Twelve healthy male volunteers received 2.5 mg i.v., 2.5 mg solution (p.o.), and 2.5 mg tablet (p.o.) according to a randomized 3-way crossover design.

Ching-Leou C. Teng 12-29-89

Ching-Leou C. Teng, Ph.D.
Pharmacokinetics Evaluation Branch

FT Initialed by Mei-Ying Huang, Ph.D. MYH 12-29-89

cc: NDA 19-815 Orig., HFD-110(2), HFD-426(Teng), HFD-344(Turner, HFD-19(FOI), Chron, and Drug Files.

CLCT,clct, PC: 12/29/89

END

BT

J.H.M. Research & Development, Inc., 5776 Second Street, N.E., Washington, D.C. 20011

Chemist Review

AUG 2 1988

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
CHEMIST REVIEW #1

A. 1. NDA No.: 19-815 Date Completed: 7/28/88

Applicant: Roberts Laboratories, Inc.
Eatontown, NJ 07724
(AF 63-036)

2. Product Name: Amatine (midodrine hydrochloride) Tablets

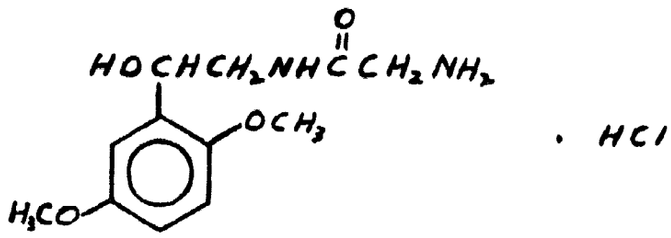
Proprietary: Amatine
Nonproprietary: Midodrine Hydrochloride
USAN: Midodrine Hydrochloride
Compendium: -
Code: ST 1085/HCl

3. Dosage Form & Route of Administration; Rx or OTC: Tablets for oral administration containing 2.5 and 5 mg of midodrine hydrochloride per tablet; Rx.

4. Pharmacological Category and/or Principal Indication: Antihypotensive. Proposed indication: Idiopathic orthostatic hypotension.

5. Structural Formula & Chemical Name:

$[C_{12}H_{18}N_2O_4 \cdot HCl \quad 290.75]$



2-Amino-N-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]acetamide hydrochloride

or

2-Amino-N-(2,5-dimethoxy-beta-hydroxyphenethyl)acetamide hydrochloride

or

1-(2',5'-dimethoxyphenyl)-2-glycinamidoethanol hydrochloride

B. 1. Initial Submission (Manufacturing & Controls): 12/28/87 (Rec'd. 12/30/87; assigned 12/31/87).

2. Remainder of NDA (Including changes in mfg & controls): 4/26/88

3. Supporting INDs, NDAs, DMFs & Letters of Authorization (LA):

4. Related Documents (INDs, NDAs):

This in only a partial list of the several INDs filed by individual investigators.

C. Remarks: The Pre-NDA submission (12/28/87) was supposed to be "a complete manufacturing/controls section and validation package ...". However, the remainder of the application as submitted under date of 4/26/88 (rec'd. 4/28/88) includes additional information on manufacturing and controls.

The drug was developed by . It was filed as IND . At that time sponsor stated that the drug was being marketed in some dozen countries in Europe, South America and the Far East. The proprietary name used initially was "Gutron." Sponsorship of IND was transferred to Roberts Laboratories, Inc. on 10/1/84. FDA letter dated 6/21/85 advised sponsor that the drug had qualified for the orphan drug designation in the treatment of idiopathic orthostatic hypotension. It is for this same indication that applicant is seeking approval via the subject NDA.

The bulk and finished products will be manufacturing by Present plans call for all testing, packaging, labeling operations, etc., to be performed by

D. Conclusions and/or Recommendations: This NDA shows some deficiencies in the Manufacturing and Controls information, and a few changes are necessary in the draft labeling submitted. The controls deficiencies and requested changes in draft labeling are summarized in "Draft of Chemist's Part of Letter to Applicant" which follows the Review Notes.

Methods validation in our laboratories will be requested after agreement is reached on methods and specifications.

GMP evaluation of the manufacturing facility, has been requested

A.J. Thompson, Jr.

cc: Orig
HFD-102/CKumkumian
HFD-110
HFD-110/CSO
HFD-110/AThompson
clb/7/29/88/0904C
R/D init: RWolters/7/29/88

JUN 3 1993

DIVISION OF CARDIO-RENAL DRUG PRODUCT
Review of Chemistry, Manufacturing, and Control

NDA #: 19-815 **CHEM.REVIEW #:** 2 **REVIEW DATE:** 28-MAY-93

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	01-OCT-92	05-OCT-92	07-OCT-92

NAME & ADDRESS OF APPLICANT: Roberts Pharmaceutical Corporation
Merdidian Center III
6 Industrial Way West
Eatontown, New Jersey 07724
908-389-1182

DRUG PRODUCT NAME

Proprietary:	AMATINE
Nonproprietary/USAN:	Midodrine Hydrochloride
Code Name/#:	ST 1085
Chem.Type/Ther.Class:	Vasopresser

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: Idiopathic Orthostatic Hypotension

DOSAGE FORM: TABLET
STRENGTH 2.5 mg and 5.0 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: Rx

CHEMICAL NAME, CAS REGISTRY NUMBER, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

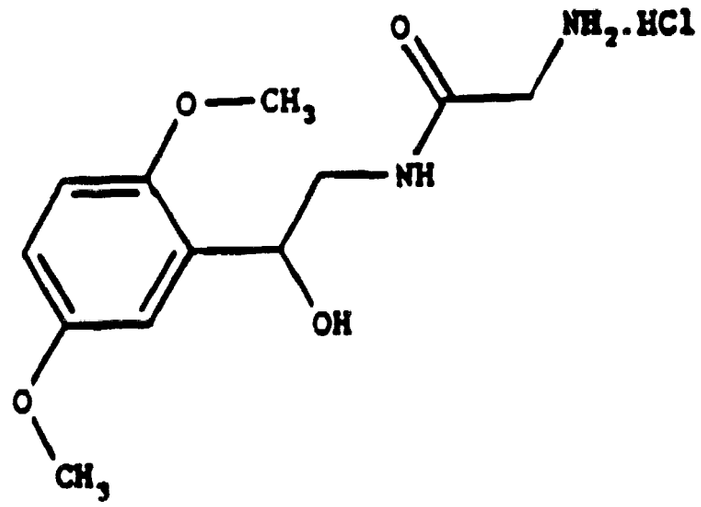
CHEMICAL NAME: Acetamide,2-amino-N-2[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-,monohydrochloride,(±)

CAS # : 3092-17-9

MOLECULAR FORMULA: $C_{12}H_{18}N_2O_4.HCl$

MOLECULAR WEIGHT: 290.74

STRUCTURAL FORMULA:



SUPPORTING DOCUMENTS:

Table I. List of IND's and DMF's

DOCUMENT #	SUBJECT	NAME OF COMPANY
IND	Midodrine	Roberts Laboratories

RELATED DOCUMENTS (if applicable): None

CONSULTS: None at present.

REMARKS/COMMENTS:

The amendment provides a reply to the Agency letter of February 13, 1990. The applicant has answered most of the comments described in this letter. The applicant made various changes and submitted new information. The application is still deficient in several areas which are commented in the review below and in the draft letter to Applicant Section. These deficient areas include closure for amber glass bottles, regulatory assay methods for the Midodrine HCl and impurities, Labeling, Environmental Assessment, DMF authorization letters and some other minor issues. The applicant has been requested to finalize between duplicate test methods and closures for bottles. At this stage it is quite early to request for EER and MV.

CONCLUSIONS & RECOMMENDATIONS:

NDA 19-815 is deficient for packaging, regulatory test methods, container/closure systems, Labeling and Environmental Assessment. Recommended Non-Approval. Draft Chemists portion of letter is attached.

cc:
Orig. NDA
HFD-110/Division File
~~HFD-110/Ram Mittal/date~~
~~HFD-110/CSO~~
HFD-102/CKumkumian [#1 only]
R/D Init by: RWolters/

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\19815\19815.002

DIVISION OF CARDIO-RENAL DRUG PRODUCT

SEP 28 94

Review of Chemistry, Manufacturing, and Control

NDA #: 19-815 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 26-SEP-94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT(S)	10-OCT-94	18-OCT-94	22-OCT-94

NAME & ADDRESS OF APPLICANT

Roberts Pharmaceutical Corporation
Meridian Center III
6 Industrial Way West
Eatontown, New Jersey 07724
908 389-1182

DRUG PRODUCT NAME

Proprietary:	AMATINE
Nonproprietary USAN:	Midodrine Hydrochloride
Code Name #:	ST 1085
Chem.Type Ther.Class:	Vasopressor

ANDA Suitability Petition/DESI/Patent Status: N.A

PHARMACOL.CATEGORY/INDICATION: Idiopathic Orthostatic Hypotension

DOSAGE FORM: TABLET
STRENGTH 2.5 mg and 5.0 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: **Rx**

CHEMICAL NAME, CAS REGISTRY NUMBER, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

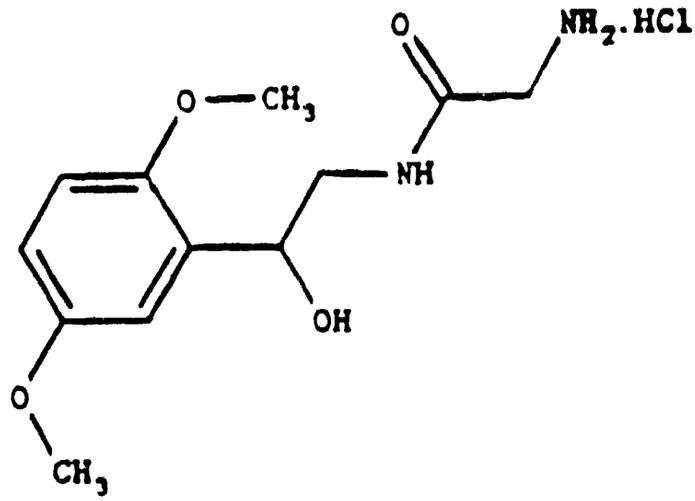
CHEMICAL NAME: Acetamide,2-amino-N-2[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-,monohydrochloride,(±)

CAS # : 3092-17-9

MOLECULAR FORMULA: $C_{12}H_{18}N_2O_4.HCl$

MOLECULAR WEIGHT: 290.74

STRUCTURAL FORMULA:



NDA 19-815 ROBERTS AMATINE

SUPPORTING DOCUMENTS:

Table I. List of IND's and DMF's

DOCUMENT #	SUBJECT	NAME OF COMPANY
IND	Midodrine	Roberts Laboratories

RELATED DOCUMENT (if applicable): None

CONSULTS: None at present.

REMARKS/COMMENTS:

This amendment provides a few of the many deficient items which were conveyed over the phone during the previous review and later addressed in Agency's letter of October 22, 1993. After submission of this amendment the applicant has called a few times and was informed that this amendment did not address various other deficiencies and they should respond to the above deficiency letter. In the last phone conversation between Ram Mittal and Dr. Harold Jacobson of Roberts Laboratories on Feb. 28, 1994, the applicant was made clear that this amendment did not address various other items and the applicant said that they will be replying to other deficiencies. The applicant was also informed that I will wait for their reply and till that time hold the review of this amendment. We are still waiting for the reply to Agency's letter of October 22,1993 which addressed various CMC deficiencies.

CONCLUSIONS & RECOMMENDATIONS:

NDA 19-815 remains deficient for all the CMC items of the deficiency letter of October 22, 1993.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO

Ramshalan D. Mittal Ph.D., Review Chemist
filename: **C:\NDA\19815\19815.003**

P/D Init by: PWolters 9/24/94

DIVISION OF CARDIO-RENAL DRUG PRODUCT

Review of Chemistry, Manufacturing, and Control

NDA #: 19-815 **CHEM.REVIEW #:** 4 **REVIEW DATE:** 09 DEC 94

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT(BC)	03 OCT 94	14 OCT-94	20-OCT-94
AMENDMENT(BC)	20-OCT-94	21-OCT-94	21-OCT-94
SPECIFCATION (FAX)	03 NOV-94	03 NOV 94	

NAME & ADDRESS OF APPLICANT

Roberts Pharmaceutical Corporation
Merdidian Center III
6 Industrial Way West
Eatontown, New Jersey 07724
908-389-1182

DRUG PRODUCT NAME

Proprietary:	AMATINE
Nonproprietary/USAN:	Midodrine Hydrochloride
Code Name/#:	ST 1085
Chem.Type/Ther.Class:	Vasopressor

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: Idiopathic Orthostatic Hypotension

DOSAGE FORM: TABLET
STRENGTH 2.5 mg and 5.0 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: Rx

CHEMICAL NAME, CAS REGISTRY NUMBER, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

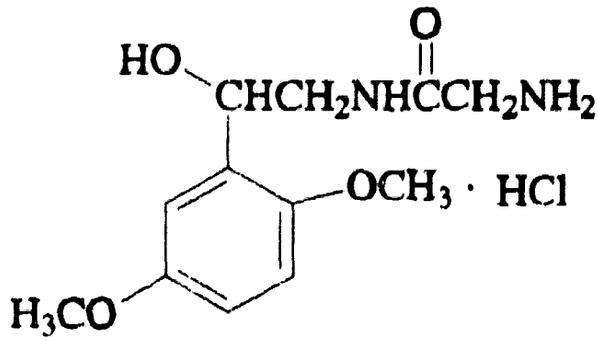
CHEMICAL NAME: Acetamide,2-amino-N-2[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-, mono-hydrochloride,(±)

CAS # : 3092-17-9

MOLECULAR FORMULA: $C_{12}H_{18}N_2O_4.HCl$

MOLECULAR WEIGHT: 290.74

STRUCTURAL FORMULA:



NDA 19-815 **ROBERTS** **AMATINE**

RELATED DOCUMENTS: (if applicable): None

CONSULTS: None at present.

REMARKS/COMMENTS:

There are minor some minor issues which remain to be answered and these are described in the comments and in the draft deficiency letter. The applicant needs to provide an EA in a proper format. For snap-on LDPE closures the tests were done by United States Testing Company, this facility should be included in the list of EER's.

CONCLUSIONS & RECOMMENDATIONS:

NDA 19-815 remains deficient for the CMC items included in the draft of the deficiency letter.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO

R/D Init by: RWolters/

Ramsharan D. Mittal Ph.D., Review Chemist
filename: **C:\NDA\19815\19815.004**

12-13-94

Table 8b

PROTOCOL C-85-047, STUDY II: PLEZIA

Table 7
Serum Fentanyl Concentration (ng/ml)

Patient Number+	Nominal Time (hours) 0	4	8	12	24	30	36	48
512 E								
513								
514								
515								
516 N								
522								
524								
525								
528								
529								
533								
534 E								
535								
536								
538								
569 N								
570								
571 N								
574 N								
576 E								
578 N								
579 N								
(Summary statistics exclude non-analyzable patients)								
N	16	16	16	14	13	13	12	9
Mean	0.06	0.64	1.15	1.31	1.52	1.47	1.01	0.63
SD	0.04	0.60	0.90	0.84	0.85	0.72	0.59	0 39
SE	0.01	0.15	0.22	0.22	0.24	0.20	0.17	0.13
Minimum								
Maximum								

+ Codes: E indicates TTS removed prior to 24 hours
N indicates non-analyzable patient

++ Values less than 0 1 ng/ml, the sensitivity of the assay, are reported as 0.05 ng/ml

* Values not included in summary statistics: patient had TTS removed early

a Value is the average of 0.4 ng/ml (3.0 hours) and 0.4 ng/ml (4.0 hours)

b Value is the average of 1.5 ng/ml (4.0 hours) and 2.4 ng/ml (5.7 hours)

h Slightly hemolyzed

H Hemolyzed

1.30/072

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Control

NDA #: **19-815** **CHEM.REVIEW #:** 5 **REVIEW DATE:** 11-MAY-95

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT(BC)	02-MAR-95	02-MAR-95	10-MAR-95

NAME & ADDRESS OF APPLICANT Roberts Pharmaceutical Corporation
Merdidian Center III
6 Industrial Way West
Eatontown, New Jersey 07724
908-389-1182

DRUG PRODUCT NAME

Proprietary:	PRO-AMATINE
Nonproprietary/USAN:	Midodrine Hydrochloride
Code Name/#:	ST 1085
Chem.Type/Ther.Class:	Vasopressor

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: Idiopathic Orthostatic Hypotension

DOSAGE FORM: TABLET
STRENGTH 2.5 mg and 5.0 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: **Rx**

CHEMICAL NAME, CAS REGISTRY NUMBER, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

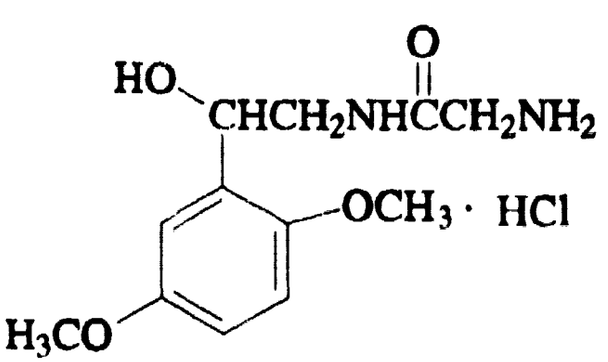
CHEMICAL NAME: Acetamide,2-amino-N-2[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-, mono-hydrochloride,(±)

CAS # : 3092-17-9

MOLECULAR FORMULA: $C_{12}H_{18}N_2O_4.HCl$

MOLECULAR WEIGHT: 290.74

STRUCTURAL FORMULA:



RELATED DOCUMENTS: (if applicable): None

CONSULTS: An EER was sent earlier and Methods Validation Request is being submitted.

REMARKS/COMMENTS:

EER is pending. In order to determine the expiration date, the applicant is being requested to resubmit the stability data. Details are covered below in the deficiency letter.

The labels have not been revised as yet. In one of the earlier ammnedments, applicant stated that as per their meeting with the Agency held on April 21, 1994, the suggestions of CMC deficiency letter of October 1993 will be incorporated in the revised labels.

CONCLUSIONS & RECOMMENDATIONS:

NDA 19-815 is not approvable as EER is pending and package insert has not been revised. The applicant requested an expiration date of 5 years. We are requesting additional information and at this stage an expiration date of three years is approvable.

The applicant should delete hyphen in proprietary name PRO-AMATINE.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO

R/D Init by: RWolters/

5/15/94

Ramsharan D. Mittal Ph.D., Review Chemist
filename: C:\NDA\19815\19815.005

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Control

NDA #: **19-815** **CHEM.REVIEW #:** 6 **REVIEW DATE:** 09-FEB-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT(BC)	03-AUG-95	07-AUG-95	10-AUG-95
AZ	22-SEP-95	25-SEP-95	04-NOV-95
AMENDMENT(BC)	28-NOV-95	06-DEC-95	11-DEC-96

NAME & ADDRESS OF APPLICANT Roberts Pharmaceutical Corporation
Merdidian Center III
6 Industrial Way West
Eatontown, New Jersey 07724
908-389-1182

DRUG PRODUCT NAME

Proprietary:	ProAmatine
Nonproprietary/USAN:	Midodrine Hydrochloride
Code Name/#:	ST 1085
Chem.Type/Ther.Class:	Vasopressor

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: Idiopathic Orthostatic Hypotension

DOSAGE FORM: TABLET
STRENGTH 2.5 mg and 5.0 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: **Rx**

CHEMICAL NAME, CAS REGISTRY NUMBER, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

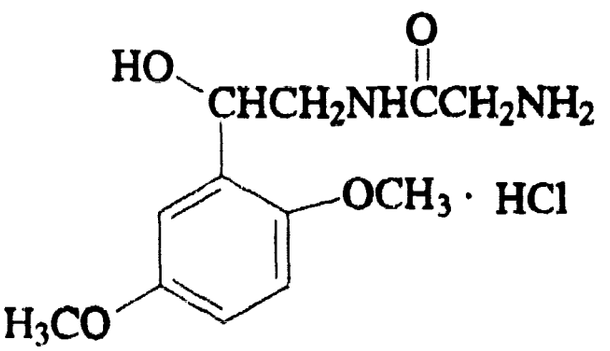
CHEMICAL NAME: Acetamide, 2-amino-N-2[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-, mono-hydrochloride, (±)

CAS # : 3092-17-9

MOLECULAR FORMULA: $C_{12}H_{18}N_2O_4.HCl$

MOLECULAR WEIGHT: 290.74

STRUCTURAL FORMULA:



RELATED DOCUMENTS: (if applicable): None.

CONSULTS: None.

REMARKS/COMMENTS:

The applicant has been issued a warning letter for significant deviations from Current Good Manufacturing Practices which is still in effect, but most of the issues are easily resolvable.

CONCLUSIONS & RECOMMENDATIONS:

From CMC standpoint, the NDA is approvable.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO

R/D Init by: RWolters/

Ramsharan D. Mittal Ph.D., Review Chemist
filename: **C:\NDA\19815\19815.006**

2/12/96

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Control

NDA #: **19-815** **CHEM.REVIEW #:** 7 **REVIEW DATE:** 20-FEB-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
NC	22-JUL-95	27-JUL-95	31-JUL-95
FAX	12-FEB-96		
MV (Philadelphia District)	30-OCT-95		
MV (DDA, St. Louis)	09-FEB-96	13-FEB-96	

NAME & ADDRESS OF APPLICANT

Roberts Pharmaceutical Corporation
Merdian Center III
6 Industrial Way West
Eatontown, New Jersey 07724
908-389-1182

DRUG PRODUCT NAME

Proprietary:	ProAmatine
Nonproprietary/USAN:	Midodrine Hydrochloride
Code Name/#:	ST 1085
Chem.Type/Ther.Class:	Vasopressor

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: Idiopathic Orthostatic Hypotension

DOSAGE FORM: TABLET
STRENGTH 2.5 mg and 5.0 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: **Rx**

CHEMICAL NAME, CAS REGISTRY NUMBER, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

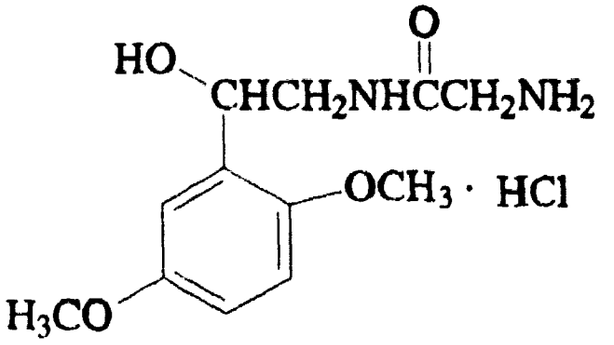
CHEMICAL NAME: Acetamide,2-amino-N-2[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-, mono-hydrochloride,(±)

CAS # : 3092-17-9

MOLECULAR FORMULA: $C_{12}H_{18}N_2O_4.HCl$

MOLECULAR WEIGHT: 290.74

STRUCTURAL FORMULA:



RELATED DOCUMENTS: (if applicable): None.

CONSULTS: None.

REMARKS/COMMENTS:

The applicant has been issued a warning letter for significant deviations from Current Good Manufacturing Practices which is still in effect, but most of the issues are easily resolvable.

This review evaluates the Method Validation reports from Division of Drug Analysis, St. Louis and Philadelphia District Laboratory. St. Louis Laboratory reported that IR's of the product were of poor quality and did not match the standard. There was no problem with the IR's recorded by Philadelphia Lab. This method is satisfactory. The TLC method for limit tests requires minor improvements and applicant is being sent a letter to modify TLC methods.

CONCLUSIONS & RECOMMENDATIONS:

From CMC standpoint, the NDA is approvable.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO

R/D Init by: RWolters/

Ramsharan D. Mittal Ph.D., Review Chemist
filename: **C:\NDA\19815\19815.007**

2/12/96

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Control

NDA #: 19-815 **CHEM.REVIEW #:** 8 **REVIEW DATE:** 12-JUN-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original Amendment	22-MAR-96	22-MAR-96	28-MAR-96
Original Amendment	11-APR-96	17-APR-96	23-APR-96

NAME & ADDRESS OF APPLICANT

Roberts Pharmaceutical Corporation
Merdian Center III
6 Industrial Way West
Eatontown, New Jersey 07724
908-389-1182

DRUG PRODUCT NAME

Proprietary:	ProAmatine
Nonproprietary/USAN:	Midodrine Hydrochloride
Code Name/#:	ST 1085
Chem.Type/Ther.Class:	Vasopressor

ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOL.CATEGORY/INDICATION: Idiopathic Orthostatic Hypotension

DOSAGE FORM: TABLET
STRENGTH 2.5 mg and 5.0 mg.
ROUTE OF ADMINISTRATION: ORAL
DISPENSED: **Rx**

CHEMICAL NAME, CAS REGISTRY NUMBER, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

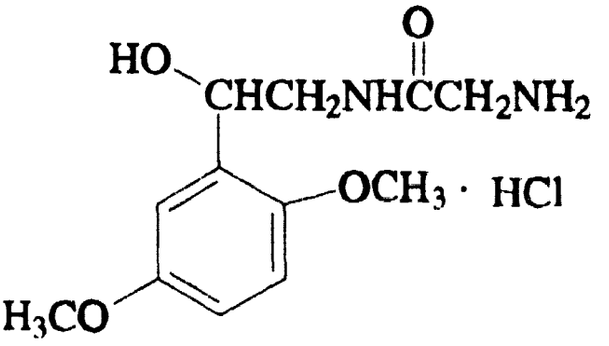
CHEMICAL NAME: Acetamide,2-amino-N-2[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]-, mono-hydrochloride,(±)

CAS # : 3092-17-9

MOLECULAR FORMULA: $C_{12}H_{18}N_2O_4.HCl$

MOLECULAR WEIGHT: 290.74

STRUCTURAL FORMULA:



RELATED DOCUMENTS: (if applicable): None.

CONSULTS: None.

REMARKS/COMMENTS:

The applicant was issued a Warning Letter for significant deviations from Current Good Manufacturing Practices. The applicant arraged a meeting with the compliance and CMC review team on February 6, 1996. As per compliance request the applicant provided revised validation protocol of 2 SOP's. The EER was approved on May 16, 1996, a copy of the EER was provided to Gary Buehler, CSO and also is attached at the end of this review.

CONCLUSIONS & RECOMMENDATIONS:

From CMC standpoint, the NDA is approvable.

cc:
Orig. NDA
HFD-110/Division File
HFD-110/Ram Mittal/date
HFD-110/CSO

R/D Init by: RWolters/

11/21/96

Ramsharan D. Mittal Ph.D., Review Chemist
filename: **C:\NDA\19815\19815.008**

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

PRO-AMATINE TABLETS

(midodrine hydrochloride)

NDA 19-815

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIORENAL DRUG PRODUCTS
(HFD-110)

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

PRO-AMATINE TABLETS

(midodrine hydrochloride)

NDA 19-815

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF CARDIORENAL DRUG PRODUCTS
(HFD-110)

FINDING OF NO SIGNIFICANT IMPACT

NDA 19-815

PRO-AMATINE TABLETS
(midodrine hydrochloride)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research carefully considered the potential environmental impact of this action and concluded that it will not have a significant effect on the quality of the human environment and that an environmental impact statement will not be prepared.

In support of their new drug application for Pro-Amatine (midodrine hydrochloride) Tablets, Roberts Pharmaceutical Corporation, Eatontown, NJ 07724-2274 prepared an abbreviated environmental assessment (attached) in accordance with 21 CFR 25.31a-(b)(3) which evaluates the potential environmental impacts of the manufacture, use and disposal of the drug product intended for the treatment of a rare disease.

Midodrine hydrochloride is a synthetic drug administered in tablets for treating idiopathic orthostatic hypotension. The drug substance and the drug product are manufactured at facilities of Hafslund Nycomed Pharma in Linz, Austria.

The finished drug product, Pro-Amatine (midodrine hydrochloride) Tablets will be used by patients in hospitals, clinics and their homes. Patients will excrete the drug and its metabolites in urine into the sewer system (POTW).

Significant environmental effects are not expected because the Maximum Expected Emitted Concentration (MEEC) of midodrine hydrochloride in the aquatic environment is much less than 1 part per billion. (< 1 part in 10^9)

Production waste is incinerated at the off-site facility operated by EBS in Vienna, Austria. Empty and partially empty packages resulting from hospital and clinic use will be disposed according to their policies and regulations. Empty and partially empty containers resulting from home use will be disposed in the municipal solid waste management system which includes landfill and incineration; insignificant quantities of unused drug may be disposed in the sewer system. Returned goods will be disposed by a contractor licensed by the EPA.

The Center for Drug Evaluation and Research concluded that the product can be manufactured, used and disposed without any significant adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

Nov 30, 1995 Florian Zielinski

DATE Prepared by Florian Zielinski, PhD, Review Chemist
Office of New Drug Chemistry I

DATE Concurrence by Robert J Wolters, PhD, Chemist
Office of New Drug Chemistry I

11/30/95

DATE Approved by Environmental Scientist
Center for Drug Evaluation and Research

Attachment: Environmental Assessment and Safety Data Sheet

Original: NDA 19-815
cc: HFD-110 Division File
HFD-110 Ram Mittal
HFD-110 FW Zielinski
HFD-110 CSO, Gary Buehler
HFD-004 FONSI File NDA # 19-815
HFD-004 Docket File
HFD-019 FOI COPY

File Name FWZ C:\...\wp60\...\curntwrk\fonsi815.V1 Oct 13, 1995

Attachment D

Pro-Amatine (Midodrine Hydrochloride) Tablets

Environmental Assessment

Attachment D

Environmental Assessment

Product Name: Pro-Amatine (midodrine hydrochloride) Tablets
(2.5 mg and 5.0 mg as base)
(Manufactured by Hafslund Nycomed in Linz, Austria)

1. Date: March 2, 1995

2. Name of Petitioner: Roberts Pharmaceutical Corporation

3. Address: 4 Industrial Way West
Eatontown, N.J. 07724

4. Description of the Proposed Action:

The drug substance, midodrine hydrochloride, and the drug product, Pro-Amatine Tablets, are manufactured at the facilities of Hafslund Nycomed Pharma (building 3/a/31s and 33) located at St. Peter Strasse 25, 4020, in Linz, Austria. These activities, to satisfy the Austrian market, have been on-going for about 10 years or more at this large industrial plant that manufactures numerous pharmaceutical products. The plant is located in an industrial area in the vicinity of plants manufacturing fertilizers, chemicals, iron, and steel.

The manufacture of the drug substance is described in DMF to which authorization to use has previously been granted to the FDA.

The drug product involves the raw materials to form tablets.

2.2 Investigators

The study was conducted at Emory University Hospital, 1364 Clifton Road, N.E., Atlanta, GA 30322. The study protocol was reviewed and approved by the Human Investigations Committee of Emory University. The principal investigators responsible for the overall conduct of the study were Richard Hotchkiss, M.D., Lars R. Newsome, M.D., C. Craig Moldenhauer, M.D., and C. C. Hug, Jr., M.D., Ph.D.. Curricula Vitae's for these individuals are included in a separate volume (Refer to table of contents for location of C.V.)

2.3 Subjects

2.3.1 Inclusion Criteria

Male and female patients between the ages of 21 and 70 years, providing informed consent and meeting the following criteria, were eligible for inclusion in the study:

a) ASA (American Society of Anesthesiologists) status I-III,

b) undergoing major elective surgery of the following type: thoracotomy, intra-abdominal or retroperitoneal exploration, laminectomy, or total hip or knee replacement.

2.3.2 Exclusion Criteria

Patients were excluded from the study for any of the following:

a) ASA status above III,

4. (Continued)

The following Austrian Authorities are involved with environmental protection:

- Bundesministerium/Umwelt (Federal Ministry/Environment)
- Amt der Oberosterreichischen Landesregierung
  (Office of the Upper Austrian Provincial Government)
- Wasserrechtsabteilung beim Amt der Oberosterreichischen Landesregierung
  (Department for Water Law of the Upper Austrian Provincial Government)
- Magistrat Linz, Amt für Technik und Umweltschutz
  (Municipal Council Linz, Office for Technic and Environmental Protection)

The regulations governing the protection of the environment are:

- Österr. Chemikaliengesetz (Austrian Chemical Law, Federal Law No. 326 of 1987)
- Österr. Abfallwirtschaftsgesetz-AWG (Austrian Waste Law, Federal Law No.325 dated June 26, 1990)
- Gewerbeordnung-GWO 1973 (Trade Regulations Federal Law No.50)
- Wasserrechtsgesetz 1959 (Water Law, current Federal Law 252/90 as of 01 07 1990)

Compliance with the technical standards and with the regulations is subject to periodical inspections (within 3 years) pursuant to § 338 of the Trade Authority, Municipal Council Linz, Office for Technic and Environmental Protection. Additionally the facilities are self-inspected at 5-year intervals pursuant to § 82 b of the Trade Regulations for complying with the authorities regulations. The plant and processes are approved by the local authorities prior to being put into operation.

At these sites, wastes from the manufacture of the drug substance and the drug product are controlled by Hafslund Nycomed Pharma AG Environmental, Safety & Security Department to meet all local and federal Austrian discharge levels as permitted for the site.

4. (Continued)

Drug Substance Production Sites

The drug substance is synthesized at our facilities in building 31a and 31s. Organic liquid wastes are divided into halogenated and non-halogenated streams. Both are disposed of by high temperature incineration at an off-site licensed hazardous waste disposal agency (i.e. EBS, Vienna). Aqueous waste streams are neutralized and cleaned in the physical waste water treatment plant and transferred to a biological pre-treatment system for waste water, prior to discharge to the public sewage plant in Asten, Upper Austria.

Hazardous waste, including sub-standard pharmaceutical raw materials and surplus chemicals are disposed of by high temperature incineration at an off-site licensed hazardous waste disposal company (i.e. EBS, Vienna). This procedure is performed according to Austrian Federal Law (No. 325 Waste Law (AWG) dated June 26, 1990) as required by the Hafslund Nycomed Pharma AG Environmental, Safety & Security department.

Drug Product Production Site

The Drug product is manufactured in building 33. All of the solid wastes associated with the drug product manufacturing process are treated by high temperature incineration at an off-site hazardous waste incinerator (i.e. EBS, Vienna). Dilute aqueous waste (i.e. from cleaning of equipment used in the manufacturing process) is neutralized before transfer to a biological pre-treatment system for waste water prior to discharge to the local public sewage plant in Asten, Upper Austria. Solid drug wastes associated with the packaging operations are disposed of by high temperature incineration in off-site licensed hazardous waste disposal facilities.

5. Identification of chemical substances that are the subject of the proposed action:

Midodrine Hydrochloride (ST 1085-HCl)
2-amino-N-[2-(2,5-dimethoxyphenyl)-2-
-hydroxyethyl]-acetamide hydrochloride
CAS Number 30902-17-9
M.W. 290.74
$C_{12}H_{18}N_2O_4 \cdot HCl$
White, non-volatile, crystalline powder, soluble in water (USP)
Additives: none Impurities: none

Silicon Dioxide, Colloidal (NF)
$Si O_2$
CAS Number 7631-86-9
M.W. 60.08
Non-volatile, water insoluble powder
Additives: none Impurities: none

Microcrystalline Cellulose (NF)
CAS Number 9004-34-6
Practically insoluble in water, acids, and most organic solvents; while powder; purified, partially depolymerized cellulose.
Additives: none Impurities: none

Starch (NF)
CAS Number 9005-25-8
Stored by plants as discrete granules in mature grains of corn, wheat, or potato
Additives: none Impurities: none

Talc (USP)
White, very fine, odorless, crystalline powder.
Insoluble in water, cold acids or alkalies

Magnesium Stearate (NF)
Octodecanoic acid, magnesium salt
CAS Number 557-04-0
M.W. 591.27
$C_{36}H_{70}Mg O_4$
Fine, white powder, faint odor.
Insoluble in water, alcohol, or ether
Additives: none Impurities: none

5. (Continued)

Purified Water (USP)

FD&C Yellow No. 6 Aluminum Lake
Aluminum salt of 1-p-sulfophenylazo -2-naphthol-6 sulfonic acid, absorbed onto a substratum of hydrated alumina.
Each lot is certified by the FDA and bears the certification lot number. The aluminum lake and the color from which it was originally produced conform to the purity specification of the FDA, UK, and EEC.

Substances listed below are used in the synthesis of drug substance:

5. (Continued)

5. (Continued)

6. Introduction of substances into the environment:

As explained in format item #4 above, wastes are handled in such a manner as to satisfy Austrian government requirements for this site. Organic liquid wastes and aqueous waste streams are handled in such a manner as to become innocuous when finally returned to the environment. Please see format item #4 above.

Format items 7 to 11 and 15 are not required for drugs that will be used infrequently (CFR 25.31a(b)(3)ii).

12. List of preparers:

Harold Jacobson, Ph.D.
Assistant Director, Regulatory Affairs
Roberts Pharmaceutical Corporation
4 Industrial Way West
Eatontown, N.J. 07724

Dr. H. K. Vorreither
Vice President
Pharmaceutical Production Concessionaire
Hafslund Nycomed Pharma
St. Peter Strasse 25
A-4021 Linz
Austria

Dr. Peter Seidel
Vice President
Environment, Safety, and Security
Hafslund Nycomed Pharma
St. Peter Strasse 25
A-4021 Linz
Austria

13. Certification:

The undersigned official certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm responsible for preparation of the environmental assessment.

Date: March 2, 1995
Signature of responsible official: _____
Drew Karlan

Title: Vice President
Worldwide Regulatory Affairs
Roberts Pharmaceutical Corporation
4 Industrial Way West
Eatontown, NJ 07724

14. References:
Not applicable other then those cited in format item #4 above.

Final Printed Labeling

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

Medical Officers Review

MEMORANDUM

JAN 16 [illegible]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 1/12/96

FROM: MARYANN GORDON, M.D.
PRIMARY MEDICAL REVIEWER, HFD-110

TO: RAYMOND LIPICKY, M.D.
DIVISION DIRECTOR, HFD-110

SUBJECT: MIDODRINE REVIEW, NDA#19,815

cc
ORIG:NDA#19,815
HFD-110
HFD-110/CSO
HFD-110/M. GORDON

CONCLUSIONS

CONCLUSIONS

This is a comprehensive review of the reports for the 3 most recently conducted double blind, placebo controlled trials: protocols 201, 318 and 320. The current NDA consists of 12 studies, mostly with a very small sample size and poorly conducted. These are all outlined in Appendix I. Neither an integrated summary of safety including all studies nor the annual safety report for 1995 has been submitted by the sponsor.

Midodrine is a sympathomimetic agonist being developed for the treatment of patients with orthostatic hypotension (OH) of neurogenic origin. Etiologies of OH for the study patients were originally Shy-Drager (multiple system atrophy) and Bradbury-Eggleston syndromes but the sponsor later expanded enrollment to include patients with OH secondary to diabetes mellitus and Parkinson's disease.

Current symptomatic treatment of OH includes increasing salt intake, body stockings and fludrocortisone (causing fluid retention). Numerous other drugs (at least 60) have been reported to be beneficial, to various degrees, but none are universally accepted. Kaufmann [1] states in a published article on neurally mediated syncope that non-pharmacologic interventions including reassurance and instructing patients how to avoid situations or triggers that can provoke an episode of OH "may be all that is needed."

One open label midodrine trial (20,762-12B) is ongoing. As of October, 1994, 695 patients have been enrolled, 171 (24.6%) have dropped out, and 56 (8.1%) have died. Over 13 months, there have been 15 reports of supine hypertension. Serious adverse events reported as of October, 1994 include, among others, congestive heart failure, cerebral ischemia/infarction (total of 4 reports), coma, myocardial infarction, and changes in mental status. Since there is no control group it is not possible to disassociate the use of midodrine with any of the serious events. It is well demonstrated that midodrine substantially increases supine (and sitting) blood pressure, so events such as stroke and heart failure for patients receiving midodrine are not unexpected.

Efficacy

A total of 250 patients were included in these 3 trials: 117 received only placebo, 110 received only midodrine, and 23 received both placebo and midodrine. The doses studied for most patients were 2.5, 10, and 20 mg and given 3 times a day 3 hours apart for the 2 studies that included multiple dosing. Only 1 of these studies (320) had a double blind treatment phase that was longer than 1 day.

All reviewed studies showed that midodrine, compared to placebo, can significantly raise standing blood pressure:

Study 320 showed that midodrine 10 mg given 3 times for 3 weeks, compared to placebo, raised standing blood pressure 1 hour after dosing.

Study 318 showed that midodrine 10 mg given 3 times 3 hours apart for 7 hours raised standing blood pressure, but only significantly more than placebo 1 hour after doses 2 and 3.

Study 201 showed that there is a dose response with single dose midodrine: 2.5 mg was not different from placebo, 10 mg was superior to placebo at 1 and 2 hours after dosing, and 20 mg was superior to placebo at 1 through 4 hours after dosing.

---

[1] Kaufmann, H., Neurally mediated syncope: pathogenesis, diagnosis, and treatment. Neurology 1995;45(5):S12-17.

There is no proof that raising standing blood pressure is an acceptable surrogate endpoint. Standing time, an endpoint that clearly can be categorized as a clinical benefit, was measured only in 1 study (318). This trial measured standing time 1 and 3 hours after each of the 3 doses for a total of 7 hours. The results showed that midodrine was numerically but not statistically better than placebo in prolonging standing time; however, there was a trend at 1 hour after the first dose. The lack of information about the effect of midodrine used chronically and at various doses and dosing regimens, compared to placebo, on standing time is a serious omission in this drug's development.

Studies 318 and 320 measured symptoms of OH.
Study 318 showed only a significant difference between midodrine and placebo 1 hour after the second dose for dizziness/lightheadedness/unsteadiness (DLU), and this was dependent upon what baseline was used. There were no differences for symptom dimming/blurring of vision (DBOV).
Study 320 showed a significant difference after 2 and 3 weeks of dosing with midodrine compared to placebo for DLU for study completers. There were no significant differences for the other symptoms at endpoint. The differences in mean scores were less than 1 point on a 10-point scale and it is likely that the elevated blood pressures and the unusual adverse events associated with midodrine (piloerection, pruritus, paresthesia) caused an unintentional unblinding of investigators who were instructed to assist the patient in completing the visual scale.

Safety
The number of drop outs in the midodrine group during the 3 week dosing study was more than 5 times the number of drop outs in the placebo group. It is quite surprising how well patients tolerated being on placebo for at least 3 weeks and how unwilling patients were to endure the troubling adverse events caused by midodrine.

Midodrine significantly raises supine (and sitting) blood pressure to levels identified by the Fifth Joint National Committee Report on Detection, Evaluation, and Treatment of High Blood Pressure (JNC) as Stage 2 hypertension and above. At the end of 3 weeks of dosing in study 320, the mean supine BP was 162/91 mm Hg for the midodrine group which was significantly higher than the mean for the placebo group (145/84).

For reference, the table below gives corresponding systolic and diastolic blood pressures for stages 1-4 hypertension as defined by the JNC Report.

Stages of hypertension as defined by JNC

Hypertension	Definition 1 (systolic/diastolic in mm Hg)	Definition 2 (systolic/diastolic in mm Hg)
Stage 1	140-159/<100	<160/90-99
Stage 2	160-179/<110	<180/100-109
Stage 3	180-209/<120	<210/110-119
Stage 4	systolic ≥210	diastolic ≥120

All 3 studies showed that it was not unusual for patients on midodrine to have systolic blood pressures of 200 mm Hg and above (stages 3-4 hypertension). Study 201, in which the effect of a single dose of midodrine was followed for 6 hours, showed that the 10 and 20 mg midodrine groups had a substantial number of patients with these elevated pressures while the placebo group had none. At 3 hours after dosing, 22% of patients in the 10 mg group and 45% of patients in the 20 mg group had supine systolic blood pressures above 200 mm Hg. Using the definition of "prolonged" hypertension as supine SBP ≥ 200 mm Hg for at least 2 consecutive readings, the percents of patients who fell into this category were 17% and 41% in 10 and 20 mg dose groups, respectively. Midodrine increased sitting systolic and diastolic BP 1 hour after dosing at all double blind visits. The increase provoked by midodrine on sitting blood pressure was as much as 20 mm Hg systolic and 10 mm Hg diastolic. Reviewing 24-hour BP profiles of patients taking midodrine chronically (including various doses and various dosing regimens) is necessary in understanding the extent of the risk of this adverse event.

Other adverse events well associated with the use of midodrine and reported in the 3 week study include paresthesia (18.3% midodrine vs. 4.5% placebo), piloerection (13.4% midodrine vs. 0% placebo), dysuria (including increased urinary frequency, impaired urination, 13.4% midodrine vs. 0% placebo), and supine hypertension (6.1% midodrine vs. 0% placebo).

Laboratory values obtained during double blind treatment (and not 2 weeks after as in study 320) are not available so the impact of midodrine on hematology and blood chemistries is unknown.

Risks/Benefits

Clearly, a drug that would be beneficial in the treatment of OH is one that, compared to placebo, can prolong standing time and allow patients to carry out their daily activities of living. The lack of adequate information about the ability of midodrine to do this along with the risks associated with the substantial increase in supine (and sitting) blood pressure cause this reviewer to conclude that the mostly unexplored benefits of midodrine do not outweigh its real risks, thus making midodrine not approvable. This conclusion, in a way, is supported by the many patients who actually took the drug. In the only study of reasonable size and duration (320), the remarkable difference in drop out rates (5 times compared to the placebo group) leads one to conclude that patients with OH seem to tolerate being on placebo very well (at least for 3 weeks) and that they themselves have decided that midodrine's "benefits" do not out weigh the discomfort of its adverse events.

STUDY 320

Study 20,762-320C

SYNOPSIS 2

SUMMARY 3

PROTOCOL 4
- Dates of protocol and amendments 4
- Study design 4
- Number of subjects planned 4
- Study drug/dosing instructions 4
- Notable inclusions 4
- Notable exclusions 4
- Primary objective 4
- Blood pressure measurements 4
- Symptom questionnaire 5
- Global questionnaire 5
- Concomitant treatment 5
- Statistical procedures 5
- Amendments 5

RESULTS 6
- Patient disposition 6
- Demographics 6
- 1 minute standing systolic blood pressure 7
- Symptoms 8
- Global assessments 9

SAFETY 10
- Drop outs 10
- Adverse events 12
- Concomitant illnesses 13
- Supine blood pressure 14
- Sitting blood pressure 16
- Laboratory values 16

Study 320

NDA#19,815
M Gordon, MD

The first finding was that the trial was sensitive to the amount of fentanyl delivered by the system, as there was a graded and predictable fall in the amount of rescue medication used with increasing blood levels of fentanyl. The analgesic effects of the system became apparent when the patients achieved blood levels above 0.5 ng/ml, but maximal analgesia was reached about 1.5 ng/ml for the group as a whole.

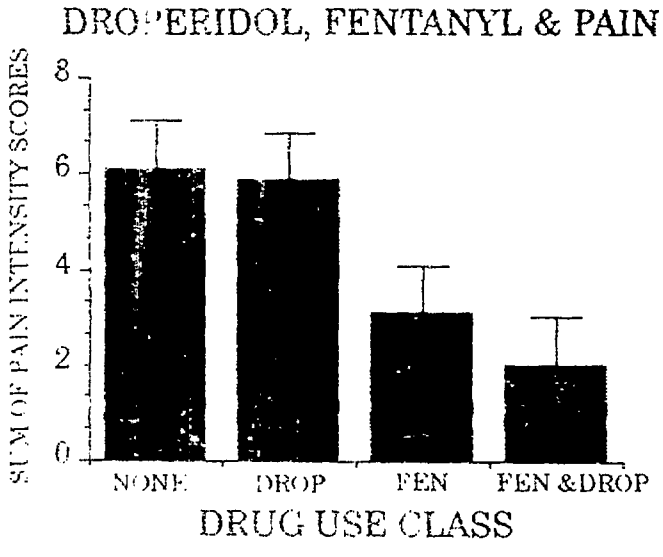
The second finding was that there was a probable interaction with droperidol. This interaction with droperidol is speculative, as the drug was prescribed on a prn basis for nausea during the postoperative period and not given in an orderly fashion. As shown , the patients who received droperidol for nausea had no greater blood levels of fentanyl than those who did not, and droperidol use was not related to fentanyl blood levels. When the four possible drug combinations were related to pain scores and meperidine use, the combination of fentanyl and droperidol was more effective than fentanyl alone in relieving pain and much more effective than droperidol alone.

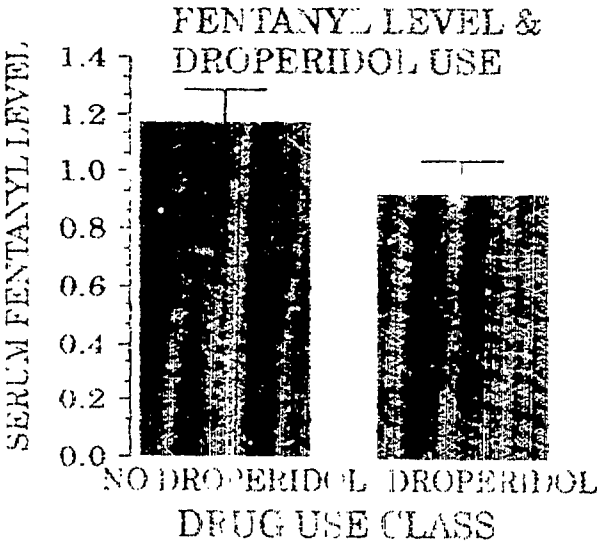
Although post-hoc and not statistically significant due to multiplicity, there was a clear and consistent falling trend in both pain scores and use of rescue meperidine in the order Placebo = Droperidol > Fentanyl TTS > Fentanyl & Droperidol.

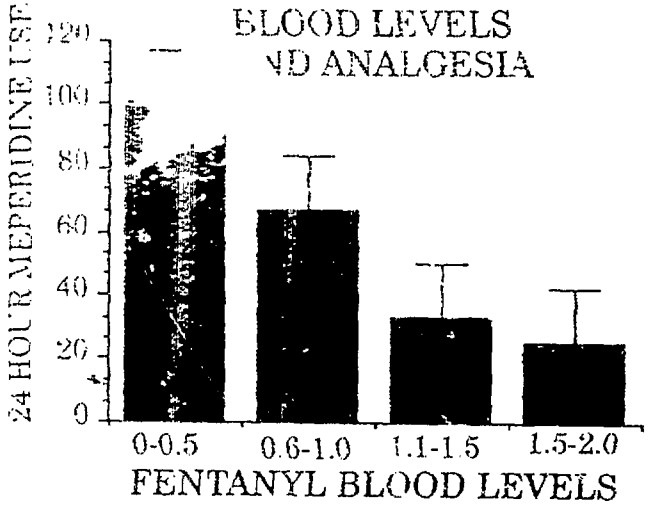
Conclusion

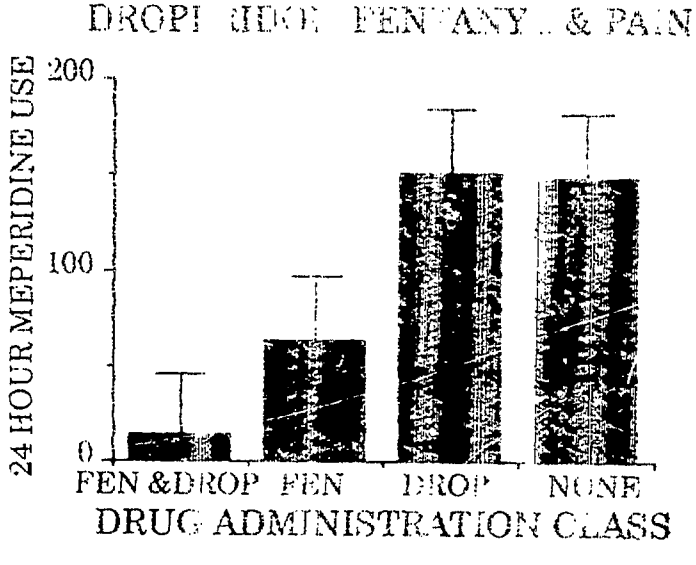
This study cannot be considered to <u>prove</u> a superior analgetic effect for TTS fentanyl, due to the failure of randomization, significant bias from unbalanced genders in the study groups, confounding by other medications and a significant number of patients who failed to achieve analgesic blood levels. The trial is not <u>negative</u>, since it showed better analgesia for TTS fentanyl, but must be considered to be only supportive due to the aforementioned bias and confounding.

The major finding of the study is that preoperative use of a benzodiazepine combined with postoperative use of the neurolept anti-emetic Droperidol may make the system more effective in relieving pain and may reduce the frequency of subjective adverse effects. Investigation of an orderly sequence of premedication, system application, and use of synergistic medication may be appropriate to develop a clinically sound strategy for the use of this product in postoperative pain.


DROPERIDOL, FENTANYL & PAIN
SUM OF PAIN INTENSITY SCORES
8
6
4
2
0
NONE
DROP
FEN
FEN &DROP
DRUG USE CLASS


FENTANYL LEVEL &
DROPERIDOL USE
SERUM FENTANYL LEVEL
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
NO DROPERIDOL
DROPERIDOL
DRUG USE CLASS


BLOOD LEVELS
ND ANALGESIA
24 HOUR MEPERIDINE USE
120
100
80
60
40
20
0
0-0.5
0.6-1.0
1.1-1.5
1.5-2.0
FENTANYL BLOOD LEVELS


DROPERIDOL FENTANYL & PAIN
24 HOUR MEPERIDINE USE
200
100
0
FEN &DROP
FEN
DROP
NONE
DRUG ADMINISTRATION CLASS

SYNOPSIS

Title	A randomized, double blind, multicenter study comparing midodrine 10 mg vs. placebo in patients with neurogenic orthostatic hypotension
Date of protocol/revisions	November 21, 1991, March 26, 1992, July 2, 1992, July 5, 1994
Date of final medical/statistical report	February, 1995/December, 1994
Number of patients randomized	170 patients were randomized (88 received placebo, 82 received midodrine).
Study design	Double blind, randomized, parallel group, placebo controlled, multicenter. Double blind phase was 3 weeks.
Dose and dosing interval	1 week: single blind placebo run in 3 weeks: double blind study drug (10 mg tid or placebo) 2 weeks: single blind placebo run out
Primary objective (amended July 5, 1994)	Standing systolic blood pressure [1 minute after rising, 1 hour after dose] and symptoms of dizziness/lightheadedness/unsteadiness (DLU)
Other endpoints	Standing diastolic blood pressure, other symptoms of orthostatic hypotension, supine blood pressure, global assessments
Notable inclusions	Diagnosis of moderate to severe orthostatic hypotension associated with autonomic dysfunction, fall in systolic BP ≥ 15 mm Hg upon rising, with symptoms DLU of 5 or less on 10 point scale.
Notable exclusions	Pre-existing sustained supine hypertension (>180/110 mm Hg); need for disallowed concomitant medications
Volumes of NDA reviewed	Protocol and case report forms vol 16.1 (SN 022) received 7-19-95; statistical report serial no. 0186 received 3-16-95; medical report dated 2-95; CRFs of drop outs serial no. 033 dated 12-21-95

SUMMARY

This was a multicenter, randomized, placebo controlled, parallel group. Study periods included 1 week single blind placebo run in, 3 week double blind treatment phase, and 2 week placebo run out. There were 170 patients randomized: 88 to placebo and 82 to midodrine 10 mg.

Midodrine, compared to placebo, significantly raised 1 minute standing blood pressure at all double blind visits 1 hour after dosing. There was no attempt made by the sponsor to show if midodrine also raises blood pressure at the end of the 3 hour dosing interval. The evidence that midodrine raises blood pressure is irrefutable. However, it is the relevance of this effect that remains unclear.

More than 5 times the number of midodrine patients dropped out of the study, mainly for adverse events, compared to placebo. Considering the significant effect of midodrine on BP, one would have expected more placebo patients to have dropped out. This unanticipated finding of how well patients tolerated being on placebo for at least 3 weeks casts doubts on the use of standing systolic BP as an endpoint for evaluating drugs for patients with orthostatic hypotension. Patients are concluding on their own, so it seems, that the benefits of midodrine do not out weigh the nuisance of the drug's adverse events.

Regarding the symptoms scores, patients on midodrine had significantly higher mean scores of improvement in symptoms of DLU compared to placebo at the last 2 double blind visits. The differences in mean scores were less than 1 point on a 10-point scale (a scale of unknown validity) and those patients who could not tolerate midodrine were excluded. In addition, it is likely that the elevated blood pressures and the unusual adverse events associated with midodrine (piloerection, pruritus, paresthesia) caused an unintentional unblinding of investigators. This further confounds the reliability of the scores because the investigators were instructed by the protocol to assist the patient in describing the severity or frequency of the symptoms of orthostatic hypotension.

At the end of double blind treatment, midodrine could not be differentiated from placebo in other symptoms of orthostatic hypotension.

The patient and investigator global assessment scores were significantly higher (i.e., improved) for patients on midodrine compared to patients on placebo. The validity of the rather crude scale, as with the symptom scale, is unknown and the results only included patients who could tolerate midodrine.

Along with increasing standing blood pressure, midodrine increases supine and sitting blood pressure. While patients with orthostatic hypotension tend to have supine hypertension, there were significant differences in BP between midodrine and placebo patients that were as much as 16 mm Hg systolic and 8 mm Hg diastolic. Mean supine blood pressures in the midodrine group were as high as 162/91 mm Hg with the corresponding mean for the placebo patients being 145/84 mm Hg. It is unknown what the mean supine (and sitting) blood pressures were during the entire 9 hour dosing period and throughout the night. Understanding the effect of midodrine on supine/sitting blood pressure measured throughout 24 hours is essential in assessing its risks.

In conclusion, it is difficult to accept standing blood pressure as a surrogate endpoint

demonstrating clinical effect. Clearly, a drug that would be beneficial in the treatment of orthostatic hypotension is one that, compared to placebo, can prolong standing time and allow patients to carry out their daily activities of living. The lack of this information along with the substantial increase in supine (and sitting) blood pressure of unknown duration prohibits this reviewer from concluding that the (mostly unexplored) benefits of midodrine outweigh its real risks.

Protocol

Dates of protocol and amendments: original protocol: November 21, 1991. Amendment A: March 26, 1992. Amendment B: July 2, 1992. Amendment C: July 5, 1994. Sample size estimate and primary endpoints changed with this amendment.

Study design: Multicenter, randomized, placebo controlled, parallel group. Study periods included 1 week (visit 1) single blind, placebo run in; 3 week (visits 2, 3 and 4) double blind treatment phase, 2 week (visit 5) placebo run out.

Number of subjects planned: originally 98 patients were planned. This was increased to 130 patients with amendment C (dated July 5, 1994).

Study drug/dosing instructions: 10 mg (2 5-mg tablets) three times daily (30 mg total daily dose). First dose taken upon rising, second dose taken mid-day, third dose taken late afternoon but not after 6:00 PM. Actual time of each dose appeared to be at the discretion of the patient. Dosing interval was to be at least 3 hours apart. On the day of clinic visit, the patient was instructed not to take a dose of study medication less than 3 hours before coming to clinic (the time of last dose was recorded). There was no stipulation about what time of day the clinic visit should occur (AM or PM) and there was no attempt to keep the time of clinic visits constant for each patient to account for diurnal variation. There were instructions that the patients were not to eat, ingest caffeine, or smoke within 2, 3 and 4 hours prior to the office visit, respectively. The time of the last occurrence of each of these activities were recorded).

Notable inclusions: patient must have had a diagnosis of moderate to severe orthostatic hypotension (OH) associated with autonomic dysfunction; had a fall in systolic blood pressure with supine to standing drop of $\geq$ 15 mm Hg; report symptoms of DLU with a severity of 5 or less on a 10 point symptom scale (1: always —>10: never).

Notable exclusions: pre-existing sustained supine hypertension > 180/110 mm Hg; concomitant administration of sympathomimetic of alpha receptor agonist or antagonist, or any drug with significant smooth muscle relaxant or constrictive properties.

There was no mention about patients being treatment previously with midodrine

Primary objective: evaluate efficacy of midodrine compared to placebo based on the ability of midodrine to elevate standing SBP and improve major symptoms of OH (limited to DLU in amendment c). Standing time was not included in the endpoints and was not collected in the case report forms.

Blood pressure measurements: made pre and 1 hour post dosing with standard

sphygmomanometer or automatic BP device. Supine BP was measured after the patient was supine for 3 minutes. Standing BP was measured after patient was standing for 1 min. Tilt table: angle must be 70 degrees or greater and the angle was to be kept constant (a place to record the angle could not be located in CRF) from visit to visit. Sitting BP was measured after the patient had been sitting for 1 minute. Sequence: supine (after 3 minutes), standing (after 1 minute), sitting (supine for 3 minutes followed by sitting for 1 minute). There was no stipulation about whether the dose given at the clinic was to be the first, second, or third dose of the day. There was a requirement that 3 hours had to lapse between the dose taken prior to the clinic visit.

Symptom questionnaire: all visits, "the investigator, in conjunction with the patient, will describe the severity or frequency of the symptoms of orthostatic hypotension using a visual scale" (1: always --->10: never). The case record form instructed the reader to "circle the number that corresponds to the severity or frequency of the patient's symptoms for the past week."

Global questionnaire: visit 5 (after 3 weeks on double blind drug) and visit 6 (after 2 weeks single blind placebo). Patient and investigator gave a global assessment of improvement in patient's symptoms of orthostatic hypotension using a 5 point scale (1: no improvement, 5: excellent improvement).

Concomitant treatment: allowed but to be kept constant: fludrocorotisone, high salt diet, Jobst garments;
disallowed: sympathomimetics, alpha-agonists, alpha-antagonists.

Laboratory values: drawn at screen (visit 1) and 2 weeks after the end of double blind period (visit 6).

Statistical procedures: sample size was estimated based on the symptom score DLU. With amendment C, the sample size for each group was increased from 49 to 65 patients in order to be able to detect the difference in improvement rates of 25% of drug over placebo. This size was to allow the detection of a difference in mean scores of 1.2 units.
-the primary efficacy variables with amendment C were: symptoms DLU and standing systolic blood pressure (change in predose to 1 hour post dose pressures). -the secondary efficacy variables were symptom energy level and standing diastolic blood pressure.
-the tertiary efficacy variables were symptom dimming and blurring of vision (DBOV), symptom fainting, supine systolic and diastolic blood pressures, global assessments by investigator and patient.
For all planned efficacy evaluations, the statistical significance level was to be taken as alpha = 0.05, two-tailed.
The original protocol identified the primary endpoints as standing systolic blood pressure and symptoms of DLU, DBOV, fainting and energy level.

Amendments:
A (March 26, 1992): tilt table, if used, must have an angle of 70 degrees or greater and the angle must be kept constant from visit to visit. Prohibition of eating was changed from 1 to 2 hours, ingesting caffeinated food or beverages for 3 hours and smoking for 4 hours were added.
B (July 2, 1992) added: At visit 6, if the investigator judges that the patient has deteriorated

since the double-blind phase, the investigator should circle none on the improvement scale and check the box indicating deterioration.
Ç (July 5, 1995): change in total sample size from 98 to 130 patients. Primary efficacy variables changed to symptom of DLU and standing systolic blood pressure. Other symptoms including DBOV, fainting and energy level, and other blood pressures recordings became secondary and tertiary variables.

RESULTS

24 investigative sites were involved in screening and randomizing patients. Three centers contributed 48% (82/170) of the patients.

Patient disposition:
--192 patients were screened at Visit 1; 22 were not eligible for randomization;
--170 were randomized at Visit 2 : 82 received midodrine, 88 received placebo;
--25 (14.7%) discontinued double blind treatment (21 on midodrine and 4 on placebo).

Demographics: of the 170 patients randomized; demographics are only available for 162 because the sponsor excluded 8 patients from the efficacy analyses.

Demographics

	placebo	midodrine	total
No of patients randomized	88	82	170
No.included in sponsor's analyses	83	79	162
No. of males	41	40	81
No. Of females	42	39	81
Mean age	59.2	60.1	
Etiologies			
Shy-Drager	24	16	40
Bradbury- Eggleston	22	15	37
Diabetes	13	24	37
Other	15	14	29
Parkinson's	9	10	19

The sponsor excluded a total of 8 patients (5 midodrine and 3 placebo) from their efficacy analyses. Of the remaining patients, the number of males and females were evenly split and the mean age was 60 years. The majority of patients (70%) had either Shy-Drager, Bradbury-

Eggleston, or diabetes is the etiology of their hypotension

Most patients (85.7%) were white.
The treatment groups were balanced at baseline.

Efficacy: these intent-to-treat analyses were performed by Dr. Kooros Mahjoob. All p values are 2-tailed.

The majority of patients (69-80%) had morning clinic visits. Depending on the visit, 35-48% of patients had a minimum of 14 hours between the last dose taken and the dose during the clinic visit.

1 minute standing systolic blood pressure: mean values before and 1 hour after dosing at each double blind visit, and change from baseline (pre dose at each visit) minus placebo effect are shown in the table below. Visit 2 was the first day and Visit 5 was the last day (after approximately 21 days) of double blind medication.

Standing systolic BP (mm Hg)

	n	Placebo	n	Midodrine	Midodrine: change from baseline minus placebo
Visit 2-pre dose; day of randomization	82	97	78	97	
Visit 2-post dose; effect of first dose	82	102	78	118	17**
Visit 3-pre dose; after 1 week of dosing	78	98	62	93	
Visit 3-post dose;	78	101	61	113	16**
Visit 4-pre dose; effect of 2 weeks of dosing	74	97	55	95	
Visit 4-post dose	75	102	58	116	16**
Visit 5-pre dose; effect of 3 weeks of dosing	73	99	55	98	
Visit 5-post dose	72	102	54	115	14**

** $p < 0.01$

Midodrine significantly raised 1 minute standing systolic BP compared to placebo 1 hour after the dose at each visit during double blind treatment. It is unknown if midodrine is effective at the end of the dosing interval (3 hours) and if the second and third doses of the day are

effective.

The size of the BP increase seen after the last dose of midodrine on Visit 5 was similar to the increase seen after the first dose on Visit 1. These data, therefore, indicate that there is no loss of effect of blood pressure with chronic dosing with at least a 3 hour interlude between dosing.

Those study patients who completed the double blind period underwent a 2 week placebo washout (visit 6). The mean change from baseline for standing systolic blood pressure 1 hour after dosing with placebo was 2 and 3 mm Hg, for the midodrine and placebo patients, respectively.

The question of the adequacy of the 1-minute standing BP as a surrogate endpoint must be addressed. It is of interest that there were far fewer patients remaining on midodrine compared to those remaining on placebo after 3 weeks of double blind dosing. Looking at the above table, one can see that 82 placebo patients at Visit 2 and 73 at Visit 5 had their 1 minute standing BP recorded. This compares to 78 midodrine patients at Visit 2 and only 55 at Visit 5. Considering the significant effect of midodrine on BP, one would anticipate that placebo patients would drop out of the study more frequently than the midodrine patients. The unexpected finding of how well patients tolerated being on placebo for 3 weeks, in addition to the 2 week placebo wash out at the end of the study, casts doubts on the use of standing systolic BP as a valuable efficacy endpoint for evaluating drugs for patients with OH.

Symptoms: were broken into 4 groups: 1). DLU 2). DBOV 3). "how often do you feel like you were going to faint," 4). "energy level." At visit 1 (screening) and 2 (baseline), patients had to have a score of 5 or less (moderately severe) for the symptom of DLU in order to qualify for the study. The responses to the other 3 symptoms were not used as inclusion/exclusion criteria.

Symptoms were evaluated at every visit using a visual rating scale shown below. The words in parentheses refer to questions of energy level.

1	2	3	4	5	6	7	8	9	10
Always (none)	Often (low level)			sometimes (moderate level)			rarely (high level)		Never (very high level)

There were no instructions in the protocol about the sequence of recording of symptoms in relation to the recording of blood pressure and adverse events. This raises the possibility that the substantial increase in blood pressure and the unique adverse events (piloerection, for example) caused by midodrine led to unintentional unblinding of the investigators to study drug and, as a result, influenced the recording of symptoms. It was stated in the protocol that the investigator was to assist the patient in describing the severity or frequency of symptoms (Protocol section V. C. page 6).

symptom--DLU: mean scores for each treatment group and means scores for midodrine minus mean scores for placebo at each double blind visit are shown in the table below.

Symptoms of DLU

	n	Placebo	n	Midodrine	Midodrine minus placebo
Visit 2 (baseline)	82	3.4	78	3.3	-0.1
Visit 3	77	4.1	63	4.4	0.3
Visit 4	76	4.4	60	5.1	0.7*
Visit 5 (end of double blind)	75	4.7	56	5.3	0.6*

* P≤0.02 for midodrine compared to placebo

The mean scores for midodrine were significantly better compared to placebo at visits 4 and 5. However, the differences between groups were less than 1 point on a 10 point scale and the scores included only those patients who could tolerate study drug.

symptom--fainting: the only significant differences between midodrine and placebo for this variable occurred at visit 3 (p= 0.03) and visit 4 (p=0.05). There was no significant difference in mean scores between midodrine and placebo at visit 5.

symptom--DBOV and energy level: there were no significant differences between midodrine and placebo at any visit.

Global assessments: the patient and investigator were to give a global assessment of the patient's improvement in symptomatology at the end of the double blind visits (Visit 5) and at the end of the 2 week washout (Visit 6). The instructions in the case record form were to "describe the patient's overall symptom improvement" for both the investigator and the patient using the following scale

none		moderate		excellent
1	2	3	4	5

The validity of this scale is unknown.

Global assessment scores at end of double blind (Visit 5)

Global assessment	n	placebo	n	midodrine	midodrine minus placebo
investigator	75	2.0	55	2.8	0.8**
patient	75	2.2	55	2.7	0.5**

** $p \leq 0.01$

Both assessment scores were significantly higher for the midodrine patients compared to the placebo patients. These scores, however, do not take into account the patients who were unable to tolerate midodrine. And, as was cited above for symptoms, the substantial increase in blood pressure and the unique adverse events (piloerection, for example) caused by midodrine could have resulted in unintentional unblinding of the investigators to study drug and, as a result, influenced the recording of global assessments.

SAFETY

Serious safety: there were no reported deaths during this study.

Drop outs: of the 82 patients randomized to midodrine, 25 patients (21 midodrine and 4 placebo) dropped out of the study.

The randomized patients who dropped out and the reasons are displayed below. All midodrine drop outs are in the first table and all placebo drop outs are in the second table.

Midodrine patients who discontinued

Reasons for discontinuation	Last visit	Patient number
Fainted	2	06-084-070
Urinary retention	4	18-163-130+
Painful paresthesia, chills	2	11-122-097+
Increase in supine bp, lethargy, unsteadiness at visit 4	5#	04-077-062+
Pain, testicular/penile constriction	2	16-197-156+
upine hypertension	3	12-169-134
Dysuria, leg cramps, paresthesia	2	03-094-075
Tingling pain, blotches	2	09-299-241+
Urinary urgency	2	06-188-149
hypotension	3	25-295-238+
Supine hypertension, urinary retention	2	10-132-105+
Retinal vein occlusion	2	10-135-096+
Supine hypertension, scalp tingling, itching, piloerection	2	14-147-116+
Implantation of permanent pacemaker	2	22-211-166
Pruritus, piloerection	2	13-140-111+
Generalized tingling	2	18-060-055
Neck rash	2	22-212-162
No show	4	18-116-094
On disallowed concomitant med	4	06-086-068
Refusal	3	22-213-058
Refusal	3	18-204-054

+Agreed to enter open label midodrine study
#refused to take last dose of study medication at Visit 5

Of the 82 randomized midodrine patients, 21 (25.6%) dropped out; 13 did not return after visit 2 (first day of dosing) mainly because of adverse events. There were 4 drop outs at visit 3, 3 at visit 4, and 1 at visit 5.

Placebo patients who discontinued

Reasons for discontinuation	Last visit	Patient number
Refusal: felt drug was not helping	5+	02-030-024
hepatitis	4	1-013-013
Refusal	3	18-165-131
Noncompliance (no show)	2	18-061-056

+Did not take last dose of study medication

It is surprising that only 4 (4.5%) placebo patients dropped out of the study.

One placebo patient (02-034-028) was classified by the sponsor as a drop out although the patient completed all double blind visits; he did not return for visit 6. This patient is not included in the above table.

Adverse events: the sponsor classified events as either adverse events or concomitant illnesses. The list of adverse events that were reported more than 1 time is shown in the table below. Adverse events reported once by midodrine patients were asthenia, headache, vasodilation, flatulence, leg cramps, increased confusion, dizziness, dry mouth, insomnia, nervousness, somnolence, erythema multiforme, dry skin, and visual field defect. Patients could report more than 1 event.

Adverse events

	placebo n=88		midodrine n=82	
event	# of reports	% of patients	# of reports	% of patients
Total number of reports	22		76	
paresthesia^	4	4.5	15	18.3
piloerection	0	0	11	13.4
dysuria+	0	0	11	13.4
pruritus$	2	2.3	10	12.2
supine hypertension^^	0	0	5	6.1
chills	0	0	4	4.9
pain#	0	0	3	3.7
rash	1	1.1	2	2.4

^includes hyperesthesia and scalp paresthesia
+includes dysuria (1), increased urinary frequency (2), impaired urination (1), urinary retention (5), urinary urgency (2)
$includes scalp pruritus
^^includes supine hypertension increase
#Includes abdominal pain and pain increase

The midodrine group reported over 3 times the number of adverse events compared to the placebo group (76 vs. 22). The majority of events were paresthesia, piloerection, problems with urination, pruritus, and supine hypertension. Of these events, only paresthesia and pruritus were reported by the placebo patients.

With the exception of supine hypertension, none of the reported adverse events appeared to be serious or of concern although they did cause a rather large number of patients to choose not to continue treatment.

Concomitant illnesses
The table below shows the number of concomitant illnesses reported by at least 2 midodrine patients during the double blind treatment period. The ones reported by only 1 midodrine patient include: pain, cerebral ischemia, diarrhea, flatulence, hallucinations, supine hypertension, somnolence, increased tremor, laryngismus, pharyngitis, scalp pruritus, jaw surgery.

Concomitant illnesses

	placebo n=88	midodrine n=82
event	# of reports	# of reports
headache	1	2
infection	0	3
Accidental injury	1	2
syncope	0	3
nausea/vomiting	0	4
dizziness	1	2
UTI	4	2

The table below adds selected adverse events and concomitant illnesses to derived the total number of reported events.

Combined events

	placebo n=88	midodrine n=82
event	# of reports	# of reports
dysuria	4	13
pruritus	2	11
Supine hypertension	0	6
pain	0	4

The following events are strongly associated with the use of midodrine: supine hypertension, pruritus, dysuria, chills, piloerection, and paresthesia.

Supine blood pressure: supine and sitting blood pressures were also collected at each double blind visit. The mean supine blood pressures for both treatment groups are shown below.

Supine systolic/diastolic blood pressure (mm Hg)

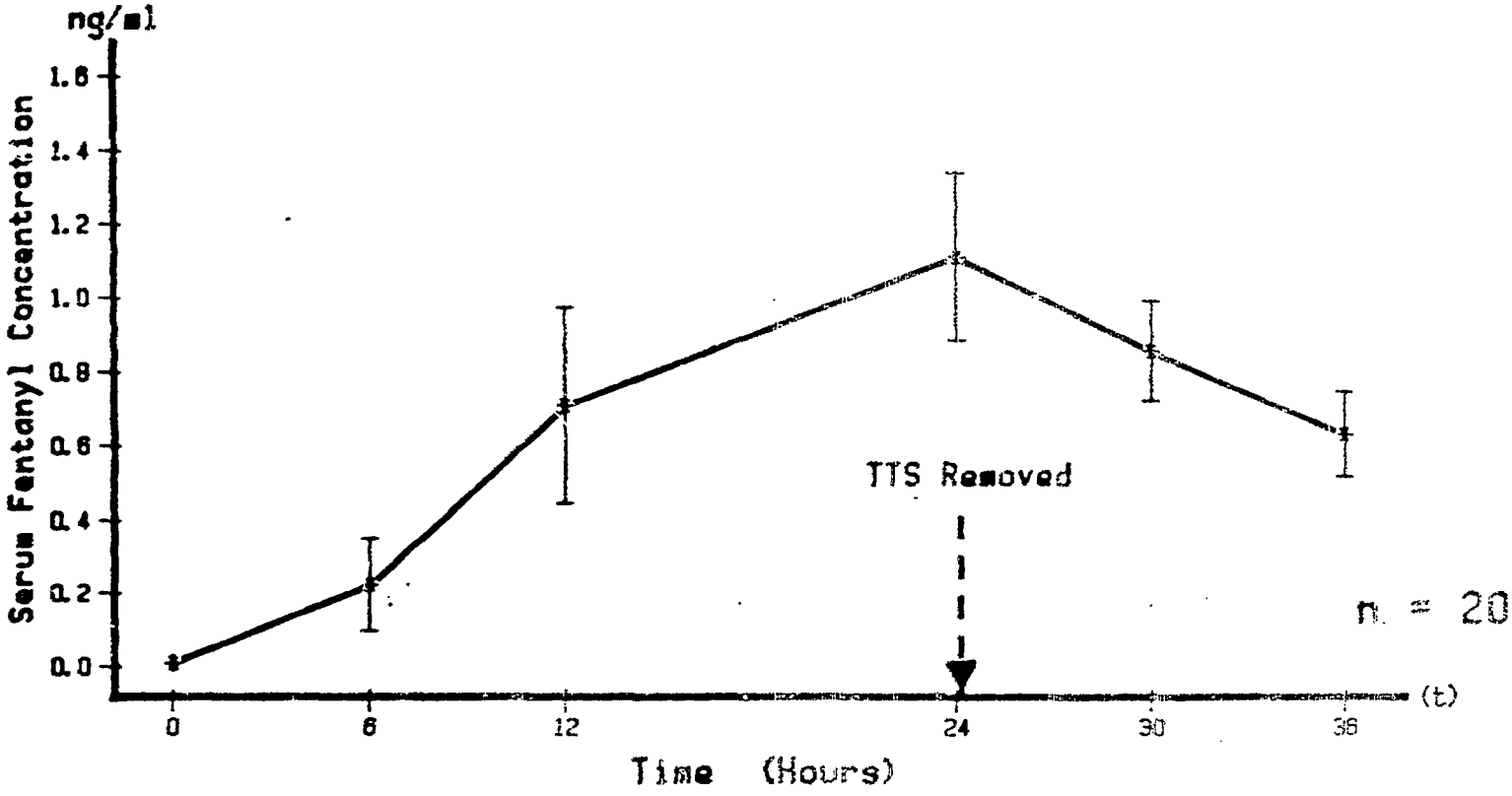
	n	Placebo	n	Midodrine	Midodrine: change from baseline minus placebo
Visit 2-pre dose; day of randomization	82	145/84	78	145/83	
Visit 2-post dose; effect of first dose	82	145/83	78	161/90	16**/8**
Visit 3-pre dose; after 1 week of dosing	78	142/82	63	146/84	
Visit 3-post dose;	78	145/84	62	164/92	15**/6**
Visit 4-pre dose; effect of 2 weeks of dosing	75	143/82	58	151/85	
Visit 4-post dose	75	146/85	59	168/94	15**/7**
Visit 5-pre dose; effect of 3 weeks of dosing	74	143/84	56	150/86	
Visit 5-post dose	73	145/84	55	162/91	10**/5**

**$p \leq 0.01$

There were statistically significant increases in supine systolic and diastolic blood pressure in the midodrine group compared to the placebo group and the increases (placebo subtracted) were as much as 16/8 mm Hg. Since the sponsor did not collect 12- or 24-hour blood pressure profiles, one cannot assume that supine (and probably sitting) blood pressures did not remain excessively elevated throughout the double blind treatment period.

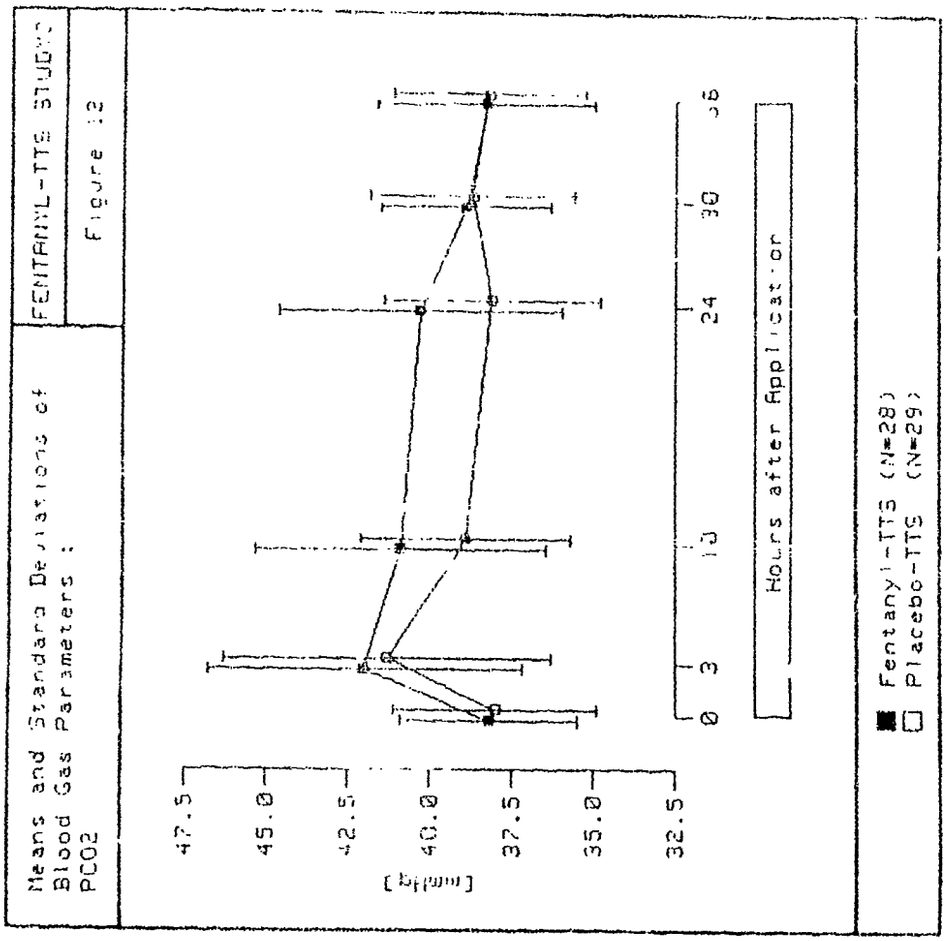
Mean (95% Confidence Interval) Serum Fentanyl Concentration

at Time from TTS Application



at Time 0 and 36 (h) n = 19

CONTINUED


FENTANYL-TTS STUDIES
Figure 12
Means and Standard Deviations of Blood Gas Parameters : PCO2
47.5
45.0
42.5
40.0
37.5
35.0
32.5
[mmHg]
0
3
12
24
30
36
Hours after Application
Fentanyl-TTS (N=28)
Placebo-TTS (N=29)

Sitting blood pressure

The following table displays the mean sitting systolic and diastolic BP readings for the 2 treatment groups. Only patients with pre and post baseline data per visit are included. No statistics were performed on the differences between the placebo and midodrine groups.

Sitting systolic/diastolic blood pressure (mm Hg)

	n	Placebo	n	Midodrine	Midodrine: change from baseline minus placebo
Visit 2-pre dose; day of randomization	87/86	122/77	82/81	122/75	
Visit 2-post dose; effect of first dose		124/79		144/87	20/10
Visit 3-pre dose; after 1 week of dosing	86/86	120/75	68/66	124/78	
Visit 3-post dose;		125/79		146/87	17/5
Visit 4-pre dose; effect of 2 weeks of dosing	85/83	121/78	65/64	124/76	
Visit 4-post dose		128/82		148/89	17/9
Visit 5-pre dose; effect of 3 weeks of dosing	80/78	123/77	61/60	127/79	
Visit 5-post dose		130/79		142/86	8/5

from fax sent 1-4-96

Midodrine increased sitting systolic and diastolic BP 1 hour after dosing at all double blind visits. The increase was as much as 20 mm Hg systolic and 10 mm Hg diastolic.

Laboratory values: were drawn at screen before patients entered the trial (visit 1) and at end of the 2 week post study placebo washout out phase (visit 6). The sponsor did not obtain laboratory values while patients were taking study drug. Mean values for selected laboratory parameters are listed in the table below.

Mean laboratory values

	midodrine		placebo	
parameter	Before study start	2 weeks after end of double blind	Before study start	2 weeks after end of double blind
Hematology g/dl	13.45	13.31	13.42	13.37
Hematocrit %	41.26	40.86	41.43	41.00
WBC thou/cmm	6.56	6.5	6.41	6.35
Platelets thou/cmm	252.34	252.45	250.38	244.0
SGOT IU/l	17.78	17.08	22.22	21.55
SGPT IU/l	14.86	14.49	20.82	19.07
BUN mg/dl	20.37	19.65	17.59	18.24
S. Creatinine mg/dl	1.24	1.22	1.11	1.14

Pre and post laboratory means were similar for midodrine and placebo groups. Again, laboratory values were not collected while patients were actually taking midodrine.

Regarding adverse/concomitant events, there was one report of hypokalemia (midodrine), one report of jaundice (placebo), one report of both hyperglycemia and hypoglycemia (placebo). There is no evidence that midodrine has a large adverse effect any laboratory parameter although laboratory values obtained while patients were on midodrine would be more informative.

STUDY 318

STUDY 20,762-318

Synopsis 1

Summary 3

Protocol 4
- Protocol objectives 4
- Inclusions/exclusions 4
- Sample size 4
- Procedures 5
- Major amendments 5
- Statistical considerations 5

RESULTS 5
- Demographics 5
- Drop outs 6
- 1-minute standing systolic/diastolic BP 6
- 3-minute standing systolic/diastolic blood pressure: 7
- Standing time 7
- Symptoms 9

SAFETY 10
- Drops outs 11
- Adverse events 11
- concomitant illnesses 12
- supine blood pressure 12
- Laboratory values 14

Synopsis

Title	A double blind comparison of midodrine and placebo in midodrine responder patients suffering from severe orthostatic hypotension due to autonomic dysfunction
Date of protocol/revisions	February 20, 1991/March 25, 1991/March 26, 1991
Date of final medical/statistical report/additional information	October, 1992/August, 1995/June, 1995
Number/type of subjects enrolled into double blind Day 3	63 patients were randomized and 58 received double blind drug (29 received placebo, 28 received to midodrine and 1 received unknown drug).
Study design	Double blind, randomized, parallel group, placebo controlled, multicenter. Study was 3 days duration
Dose and dosing interval	Day 1: no study drug Day 2: single blind midodrine 10 mg bid (6 hours apart) Day 3: placebo or midodrine 10 mg tid (3 hours apart)
Primary objective (as written in statistical procedures, protocol page 23)	Standing systolic blood pressure [not further specified] and symptoms lightheadedness, dizziness, or unsteadiness, (DLU) dimming or blurring of vision (DBOV)
Other endpoints	Standing diastolic blood pressure Supine blood pressure
Notable inclusions	Diagnosis of severe orthostatic hypotension associated with autonomic dysfunction; treated with midodrine for at least 2 weeks prior to entering the study and have the ability to stand while taking midodrine.
Notable exclusions	Pre-existing sustained supine hypertension (>180/110 mm Hg); ability to stand > 15 minutes without symptoms in between doses of midodrine
Volumes of NDA reviewed	Protocol and case report forms vol 16.1 (SN 022) received 7-19-95; statistical report serial no. 027 received 9-12-95; medical report serial no. 028 and vols 8.1, 8.2

Summary
This was a double blind, randomized, placebo controlled trial evaluating the effect of 10 mg midodrine (given 3 times, 3 hours apart for 1 day--total dose 30 mg) compared to placebo on blood pressure, symptoms of orthostatic hypotension (OH), and standing time in patients who had previously responded to midodrine. The total double blind evaluation of patients was 7 hours. All 58 patients treated with double blind medication had received single blind 10 mg midodrine bid the day *before* the double blind period.

The primary objective, change in standing systolic blood pressure, was measured at 1 and 3 minutes after rising and at hour 0, 3, 4, 6 and 7 hours after drug intake. The protocol did not pre-specify which BP recording was to be used to show statistical superiority of midodrine over placebo. There were no adjustments for multiple comparisons in the sponsor's statistical report.

The study evaluated symptoms of orthostatic hypotension using a crude scale where patients checked a number on a line demarcated by numbers from 1 (extreme) to 10 (none). The sequence of study procedures with blood pressure measured prior to symptom assessment and the coordinator/investigator actively assisted the patient in symptom assessment lead one to question the validity, reliability and objectivity of this measurement.

There were 64 patients who were randomized and received at least 1 dose of open label midodrine. Etiologies of OH were primarily Shy-Drager (34%), idiopathic OH (23%), and Parkinson's disease (11%). Six randomized patients did not meet entry criteria for Day 3 and did not received study drug.

Midodrine was numerically but not usually statistically superior to placebo in raising 1 minute and 3 minute standing BP and prolonging standing time during the one day of double blind dosing.

Midodrine improved symptoms of dizziness/unsteadiness/lightheadedness (DLU) compared to placebo but this was rarely statistically significant. The effect of midodrine on symptoms of dimming and blurring of vision (DBOV) was not different from placebo.

Patients on midodrine reported the adverse events usually associated with this agent, tingling/pruritus/piloerection/chills, while patients on placebo reported no events.

With the exception of baseline values, mean supine BP was always higher in the midodrine group compared to placebo and often met the JNC definition of stage 2 hypertension. Mean supine BP 1 hour after the third dose of study drug was 176/95 for the midodrine group and 146/85 for the placebo group. Individual systolic BP for the midodrine group were up to, and even greater than, 210 mm Hg (stage 4 hypertension).

In conclusion, this trial of very short duration measured the effect of 3 doses of midodrine 10 mg given 3 hours apart over a total of 7 hours demonstrated that midodrine raises standing systolic blood pressure in a population that was shown to respond to midodrine. Symptoms of OH were measured with a scale of unknown validity and with the active participation of the study coordinator. The significance of this is unclear. The most clinically relevant endpoint, standing time, was unable to differentiate midodrine from placebo although the mean changes from baseline were numerically greater for midodrine compared to placebo. Midodrine is associated with unique adverse events of piloerection, chills, pruritus. Few patients found these events intolerable for the 2 days of dosing. However, the elevation in supine systolic blood pressure was striking with mean SBP at the end the 7 hours nearly 30 mm Hg higher than the mean for the placebo group. Individual SBP in the midodrine group had readings greater than 210 mm Hg. This reviewer concludes that this 7 hour study showed a poor benefit to risk ratio for midodrine.

Protocol

This was a 5-center study: J. Gilden, North Chicago, Il (n=36); H. Kaufmann, New York (n=15); B. Hiner, Marshfield, WI (n=2); J. Jankovic, Houston TX (n=7); D. Robertson, Nashville, TN (n=10).

Protocol objectives: Primary: standing systolic BP and symptoms DLU and (DBOV)). Secondary: standing diastolic and supine systolic and diastolic BP.

Inclusions/exclusions

Notable inclusions: patients who were:
--diagnosed with severe OH associated with autonomic dysfunction,
--treated with midodrine for a minimum of 2 weeks prior to start of study,
--able to stand while receiving midodrine.

Additional eligibility criteria for Days 2 and 3 pre-dose measurements include
--supine to standing systolic blood pressure fall of ≥ 15 mm Hg;
--symptom score of 5 or less on at least on of the symptoms of hypotension;
--unable to stand motionless and unassisted for more than 15 minutes.

For Day 2 (single blind midodrine treatment) only: 1 hour after receiving first dose of midodrine there must be a 10 mm Hg increase in standing (or sitting) systolic BP and the score for qualifying symptom must increase 1 point.

Notable exclusions: patients who have 1) a history of being able to stand for a period of > 15 minutes without symptoms when midodrine is withdrawn (e.g., between doses), 2) pre-existing sustained supine hypertension > 180/110 mm Hg.

Sample size: There were no power calculations in the protocol. Protocol stated that 12-30 patients would be studied (page 3).

Procedures
Day 1: screening and washout period. Midodrine was to have been discontinued at least 15 hours prior to entry. Supine and 1 and 3 minute standing BP and sitting BP were recorded. The symptom evaluation for DLU and DBOV was completed. Standing time was recorded. A limit of 15 minutes was included which was later disregarded and a limit of 5 minutes was used to identify analyzable patients. All measurements were repeated again after 6 hours. No drug was administered.

Day 2: all patients were evaluated for orthostatic drop in systolic BP of ≥ 15 mm Hg and symptom score of 5 (moderate) or less for at least one of the symptoms, and able to stand motionless and without significant symptoms for less than 15 min. All qualified patients received *open label* midodrine 10 mg at hour 0 and 10 mg at hour 6. Randomization to double blind drug occurred on this day.

Day 3: all patients who had an orthostatic drop in SBP of ≥ 15 mm Hg and a symptom score of 5 or less for at least one of the symptoms and could stand unassisted and motionless for less than 15 minutes were randomized to double blind midodrine 10 mg or placebo. Fifteen hours were to have lapsed between the last dose of Day 2 and the first dose of Day 3. Doses on Day 3 were given at hours 0, 3 and 6. BP, symptoms, and standing time were measured at hours 0, 1, 3, 4, 6, and 7. Standing time was not measured (after the pre-dose measurement) for patients whose standing times were > 5 minutes.

The sequence of study procedures as written in the protocol was in the following order: blood pressure, pulse, symptoms and standing time. In addition, the protocol states that "The patient, with the **active** assistance of the coordinator, will complete a symptom evaluation . . . ."

Major amendments to the protocol included change in eligibility requirements: improvement in symptoms while on midodrine Day 2, 1 hour after first midodrine dose and Day 3, 1 hour after first double blind dose went from 2 points to 1. Twenty patients were enrolled under old criterion of 2 points and 50 under the new criterion of 1 point.

Statistical considerations: baseline was defined as measurements recorded Day 3, immediately before dose #1. Endpoint was not pre-specified in the protocol.

RESULTS

All efficacy data in this review are derived from the statistical report from Roberts dated August, 1995, and from Dr. Kooros Mahjoob's statistical review. All analyses are intent-to-treat and all p values are 2-tailed. Only efficacy data from Day 3 are evaluated. Safety information also include data from the medical report from Roberts dated October, 1992.)

Demographics: 70 patients enrolled on Day 1 (washout period). The mean age was 61.8 years. The etiologies of OH included idiopathic orthostatic hypotension (22.9%), Shy-Drager (34.3%), Parkinson's (11.4%), diabetes (24.3%), other (7.1%).

Drop outs Day 1: 70 patients entered on Day 1, 2 patients dropped; on Day 2, 64 patients were randomized and received open label midodrine. Six patients dropped before the start of double blind dosing on Day 3. A total of 58 patients were dosed on Day 3 (29 received placebo and 28 received to midodrine and 1 received unknown drug).

Standing blood pressure

This sponsor collected and analyzed both 1-minute and 3-minute standing BP without pre-specifying which one would be the primary endpoint. The emphasis of this review is on the 1-minute systolic BP although the results of the 3-minute systolic BP were also inspected.

For the purposes of this review, changes from baseline values were calculated 2 ways: a). Baselines were the values recorded immediately before each dose (i.e., values recorded at Hours 0, 3, and 6); and b) baseline was only the Hour 0 value (this was pre-specified in the protocol).

1-minute standing systolic/diastolic BP: table below shows the mean BP values before and after each dose by treatment group.

Mean standing BP (mm Hg)

		systolic		diastolic	
Hour since #1 dose	Dose #	Mido (n)	Placebo (n)	Mido (n)	Placebo (n)
0	Pre dose #1	75 (25)	75 (27)	52 (21)	51 (23)
1	Post dose#1	93 (27)	85 (27)	65 (24)	59 (22)
3	Pre dose #2	93 (27)	81 (27)	66 (23)	60 (22)
4	Post dose#2	97 (27)	80 (27)	65 (25)	55 (21)
6	Pre dose #3	93 (26)	84 (25)	66 (20)	57 (23)
7	Post dose#3	107 (27)	88 (26)	71 (25)	60 (23)

(all patients with data)

At baseline (hour 0), the mean BP was similar between treatment groups. At all time points after baseline, the mean blood pressures in the midodrine group were higher than the mean pressures in the placebo group.

The changes from baseline (when baseline was the BP recorded immediately before each dose) at 1 hour after the dose are shown in the table below. Only patients with both pre and post baseline data are included.

Mean change from baseline for systolic/diastolic BP (mm Hg)

Dose #	midodrine	placebo	placebo subtracted
1	18/12	10/7	8/4
2	4/-1	0/-4	5/3
3	16/10	7/6	9^/4

^ p=0.09

The differences between treatment groups always favored midodrine but none reached statistical significance. There was a trend toward significance with dose #3.

The mean changes in BP using the Hour 0 reading as the only baseline are shown in the table below. Dose #2 was given at hour 3 and dose #3 was given at hour 6.

Mean change in from baseline for systolic/diastolic BP (mm Hg)

time after 1st dose	midodrine	placebo	placebo subtracted
Hour 1	18/12	10/7	8/4
Hour 3	19/14	7/8	12^/6
Hour 4	23/12	6/4	17**/9^
Hour 6	20/14	7/6	12^/8^
Hour 7	31/19	13/11	18*/7

** p=0.01
*p=0.02
^ p values between 0.08 and 0.06

Midodrine was numerically better than placebo at all time points and the differences were significant at hours 4 (1 hour after dose #2) and 7 (1 hour after dose #3). There was a trend toward significance for some of the other values.

3-minute standing systolic/diastolic blood pressure: tables showing these data are in Dr. Mahjoob's statistical review. The differences between midodrine and placebo in 3-minute blood pressure elevation were not statistically significant at any time point when using the 3 baselines in the analysis except diastolic BP after dose #3 (p=0.04). When hour 0 is used as the only baseline, midodrine significantly raises blood pressure more than placebo at hours 2, 4 and 7. Midodrine was numerically superior to placebo at all time points except Hour 3.

Standing time: unlike increases in blood pressure, increases in standing time is an indisputable clinical benefit. The table below shows mean standing time for all patients with post baseline data by treatment group. The numbers of patients with data are shown in parentheses. The protocol stated that "patients will be asked to stand motionless for a maximum of 15 minutes until the onset of herald symptoms that indicate the onset of syncope." In addition, the protocol instructed investigators that standing times will not be measured in patients who stand longer than 5 minutes before the first dose on Day 3.

Mean standing times (sec)

	midodrine (n=28)	placebo (n=29)
Pre dose #1	87.9 (27)	83.2 (28)
Post dose #1	176.3 (27)	97.6 (26)
Pre dose #2	135.8 (26)	107.6 (26)
Post dose #2	181.3 (27)	92.7 (27)
Pre dose #3	142.7 (27)	104.4 (28)
Post dose #3	211.2 (27)	120.6 (27)

(All patients with data)

At all time points, midodrine had higher mean standing times compared to placebo.

The changes from baseline (when baseline was the standing time recorded immediately before each dose) at 1 hour after the dose are shown in the table below. All patients with pre and post baseline data are included.

Mean change (sec) from baseline

	midodrine	placebo	placebo subtracted
Dose #1	88.4	24	64.4^
Dose #2	24.3	-8.7	33
Dose #3	68.4	23.4	45

^p=0.09

The differences in standing time between midodrine and placebo were not statistically significant, although the effect with Dose #3 was trending toward significance.

The table below shows mean changes in standing blood pressure using the Hour 0 reading as the only baseline. Dose #2 is given at hour 3 and dose #3 is given at hour 6.

Mean change from baseline (hour 0) for standing time (sec)

time after 1st dose	midodrine	placebo	placebo subtracted
Hour 1	88.4	24.0	64.4^
Hour 3	45.8	24.5	21.3
Hour 4	93.4	19.0	74.4*
Hour 6	54.9	21.2	33.7
Hour 7	123.3	46.9	76.4^

*p=0.02
^ p=0.09

With this evaluation, midodrine was statistically superior to placebo in prolonging standing time at hour 4 (1 hour after dose #2 was taken) and there was a trend toward superiority at hours 1 and 7. Three hours after each dose, there was less of a difference between drug and placebo although midodrine was always numerically better.

Conclusions: midodrine 10 mg given 3 times 3 hours apart was usually numerically but not always statistically superior to placebo in raising systolic BP and prolonging standing time. The greatest effect on BP and standing time was seen one hour after each dose and the effect tended to dissipate after subsequent doses.

Symptoms: the symptom evaluation consisted of the following instructions as stated in the case record forms: "check the one box under the number that most accurately describes the severity of the symptoms that you feel upon standing for this evaluation."

1. Feelings of dizziness/lightheadedness/unsteadiness (DLU)

ex-treme				moderate					none
1	2	3	4	5	6	7	8	9	10
()	()	()	()	()	()	()	()	()	()

2. Same instructions and scoring system were given for symptoms of dimming/blurring of vision (DBOV)

Symptom score #1 for DLU: mean change from baseline.

The table below shows mean symptom score for all patients with post baseline data. The lower the score the less improvement in symptoms as reported by the patient.

Mean symptom score

	midodrine (n=28)	placebo (n=29)
Pre dose #1	4.0 (28)	3.7 (29)
Post dose #1	5.8 (28)	4.7 (29)
Pre dose #2	6.4 (27)	5.5 (29)
Post dose #2	7.0 (28)	5.4 (29)
Pre dose #3	6.2 (28)	5.6 (29)
Post dose #3	7.2 (29)	6.1 (29)

(all patients with data)

At all time points, midodrine had higher mean symptom scores compared to placebo.

The changes from baseline for each of the 3 doses by treatment group are shown in the table below. Only patients with pre and post baseline data are included.

Mean change from baseline

	midodrine	placebo	placebo subtracted
Dose #1	2.0	1.3	0.7
Dose #2	0.4	-0.4	0.8*
Dose #3	1.3	0.7	0.6

*p=0.03

While the differences between drug and placebo in symptom score for DLU favored midodrine, they were all less than 1 point. Only the difference for dose #2 was significant.

The table below evaluated mean changes in symptom score using the Hour 0 reading as the only

baseline. Dose #2 is given at hour 3 and dose #3 is given at hour 6.

Mean change from baseline (hour 0) for symptom score DLU

time after 1st dose	midodrine	placebo	placebo subtracted
Hour 1	1.9	1.0	0.9
Hour 3	2.3	1.7	0.6
Hour 4	2.9	1.6	1.3^
Hour 6	2.1	1.8	0.3
Hour 7	3.1	2.3	0.8

(all patients with data)
^ p=0.08

None of the differences in scores between midodrine and placebo were statistically significant. The hour 4 difference (1 hour after dose #2) was trending toward significance.

Symptom score 2 (dimming/blurring of vision).

There were no significant differences between midodrine and placebo in mean score of DBOV at any timepoint and this was true regardless of what baselines were used. The differences between scores for midodrine and placebo were small and at times, placebo was numerically better than midodrine. These results are available in Dr. Mahjoob's statistical report.

SAFETY

Drops outs: there were 5 randomized patients who received at least one dose of midodrine on Day 2 and dropped out of the study. These patients are discussed in the table below.

Drop outs

Patient number	Amount midodrine dispensed	Reasons for dropping
Drops outs Day 2		
1-24-24	4 tablets	Gastroparesis; failed to meet entry criteria; later re-entered
02-09-09	2 tablets	Worsening ascites; failed to meet entry criteria
05-07-05	2 tablets	failed to meet entry criteria
03-02-02	2 tablets	failed to meet entry criteria (also had abdominal discomfort)
Drops outs Day 3		
03-01-01	4 tablets	Did not meet eligibility requirements

Although the sponsor stated that these patients were dropped from the study because they failed to meet entry criteria, 3 of these patients also reported adverse events.

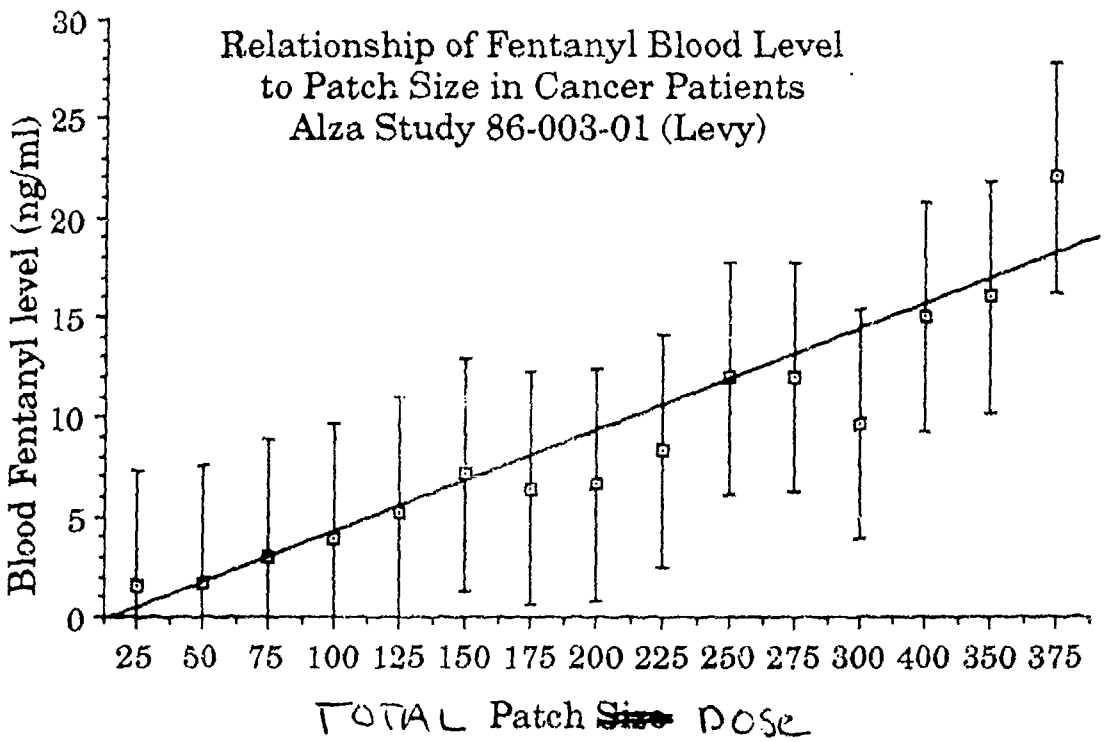
Adverse events: the table below lists the adverse events reported during this study on Days 2 (open label midodrine) or 3 (double blind).

Adverse Events
Upper body tingling
Goose flesh
Tingling scalp
Itching scalp
Piloerection, cold
Cold sensation
Elevated blood pressure
Flushing
Pyrosis
Urinary urgency
Pressure in head

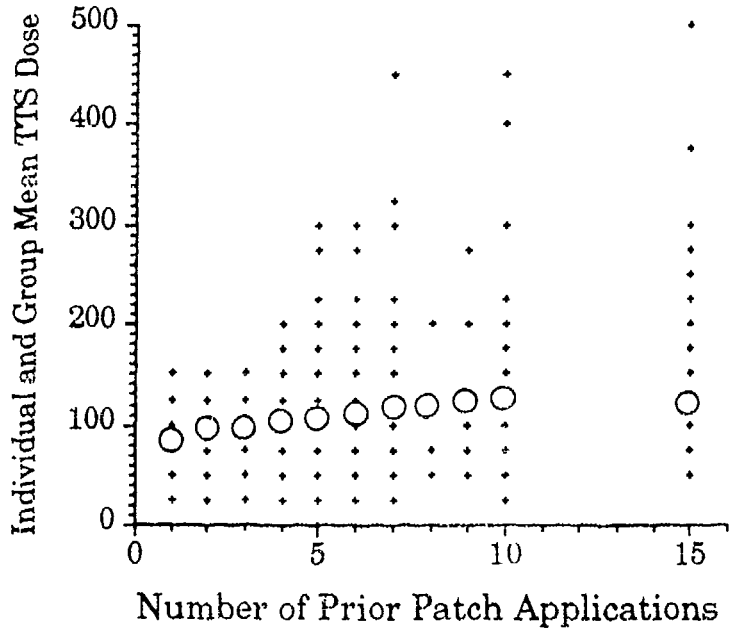
All 11 events were reported by patients receiving midodrine and included tingling/pruritus/piloerection/chills as well as elevated blood pressure, flushing, pyrosis, urinary urgency, pressure in head. All events with the exception of elevated blood pressure were reported on Day 2.

concomitant illnesses: these events were designated by the investigator as concomitant illnesses if they were considered to be unrelated to study medication. Only events reported by randomized patients are included in the following table and events are reported by one patient unless noted.

Concomitant illnesses
Hypoglycemic episode
Low blood sugar
Headache upon standing
Heart burn
Syncope (2 patients)
Extra insulin dose/gastroparesis
Increased ascites
UTI
Elevated blood and urine glucose
Abdominal discomfort
Confusion


Relationship of Fentanyl Blood Level
to Patch Size in Cancer Patients
Alza Study 86-003-01 (Levy)
Blood Fentanyl level (ng/ml)
0
5
10
15
20
25
30
25 50 75 100 125 150 175 200 225 250 275 300 400 350 375
TOTAL Patch ~~Size~~ DOSE

Time Trend in Total TTS Dose for the Combined Chronic Cancer Pain Studies



It is unclear if these events occurred on Day 2 (open label midodrine) or Day 3 (on double blind drug). It seems reasonable to count these as concomitant illnesses.

supine blood pressure: the dramatic effect that midodrine has on supine blood pressure is a safety concern. The table below shows the mean blood pressure values before and after each dose by treatment group.

Mean supine blood pressure (mm Hg)

	systolic		diastolic	
	midodrine (n=28)	placebo (n=29)	midodrine (n=28)	placebo (n=29)
Pre dose #1	131	129	77	73
Post dose #1	150	139	86	79
Pre dose #2	158	139	91	81
Post dose #2	163	136	89	77
Pre dose #3	166	141	90	80
Post dose #3	176	146	95	85

(all patients with data)

Mean supine BP was always higher in the midodrine group compared to placebo and often met the JNC definition of stage 2 hypertension. Mean supine systolic/diastolic BP for the placebo group, on the other hand, was not above 146/85 mm Hg.

Regarding individual recordings, there were numerous recording above 180 mm Hg (stage 3 hypertension) with some ≥ 210 mm Hg (stage 4 hypertension). (From figure A.7 of Dr. Mahjoob's report.)

Supine BP in this trial was analyzed in the same manner as standing BP: a) using 3 baselines (hour 0, 3, and 6), and b) using 1 baseline (hour 0).

The changes from baseline for each of the 3 doses by treatment group are shown in the table below. Only patients with pre and post baseline data are included.

Mean change from baseline for supine systolic/diastolic BP (mm Hg)

	midodrine	placebo	placebo subtracted
Dose #1	20/10	10/6	9/4
Dose #2	4/-2	-3/-4	8/2
Dose #3	10/5	5/6	5/-1

Midodrine raised supine systolic and diastolic BP more than placebo with 1 exception, but these increases were not statistically significant.

The table below evaluated mean changes in supine systolic blood pressure using the Hour 0

reading as the only baseline. Dose #2 is given at hour 3 and dose #3 is given at hour 6.

Mean change from baseline (hour 0) for supine systolic BP (mm Hg)

time after 1st dose	midodrine	placebo	placebo subtracted
Hour 1	17.5	10.2	7.3
Hour 3	27.8	10.3	17.4*
Hour 4	32.2	7.1	25.1***
Hour 6	35	11.7	23.3***
Hour 7	45	16.6	28.5***

*p<0.02
***p≤0.001

Unlike the previous analysis that used multiple baselines, there were (highly) statistically significant differences between treatment groups on supine systolic blood pressure blood at all time point except 1 hour after the first dose. Diastolic BP (not shown) was only significantly different (or nearly so) at hours 4 and 6.

Laboratory values: these were only drawn at screen.

STUDY 201

Study 20,762-201

Synopsis 2

Protocol 4
- Amendments 4
- Primary objective 4
- Study design 4
- Doses studied 4
- Number and type of subjects 4
- Global assessments 4
- Symptoms 5
- Statistics 5

Results 5
- Patient disposition 5
- Demographics 5
- Symptoms 7

Safety 8
- Drop outs for adverse events 9
- Adverse events 9
- Supine blood pressure 9

SYNOPSIS

Title	A Double-Blind, Randomized Dose Response Study of Midodrine in Patients with Neurogenic Orthostatic Hypotension
Date of protocol/amendments	July 13, 1992/September 7, 1993
Date of final study report	7/25/95 (NDA submission serial number 024)
Number/type of subjects	25 patients randomized, 23 patients completed study doses/Neurogenic orthostatic hypotension. Sample size determination was not discussed in protocol.
Study design	Randomized, double blind, cross over
Dose/Dosing interval	0, 2.5, 10, and 20 mg/single dose (3 patients received 5 mg instead of 20 mg)
Primary objective	Standing systolic blood pressure, not further specified. The measurement 1 hour post dose was selected post hoc.
Notable inclusions	-Supine to standing drop in SBP $\geq$ 15 mm Hg -exhibit dizziness/lightheadness/ unsteadiness
Notable exclusions	-Pre-existing sustained supine hypertension (>180/110 mm Hg) -need for concomitant medications that would interfere with interpretation of efficacy results; -have one of the disallowed diseases
Primary objective	Standing systolic blood pressure

Summary

There were 25 patients who were randomized and 23 patients who completed this double blind cross over study comparing single midodrine doses (2.5, 10, and 20 mg) to placebo. Patients were selected based on 1.) a diagnosis of moderate to severe orthostatic hypotension associated with autonomic dysfunction, 2.) a drop in SBP of at least 15 mm Hg upon rising from a supine position and 3.) symptoms of orthostatic hypotension. Two patients dropped out of the trial after taking the 20 mg dose.

The primary efficacy endpoint was standing SBP measure [after 1 minute upon rising--added post hoc]. The mid and high dose groups significantly increased standing SBP compared to placebo for about 4 hours after dosing. Both mid and high doses were significantly different from the low dose at selected time points; there was a significant difference between mid and high doses ($p=0.03$) at hour 2.

There was no evaluation of midodrine on the drop of BP upon rising even though patients were selected on this basis, and, most importantly, there was no demonstration that patients on midodrine could maintain the upright position longer than patients on placebo. Although it may be intuitive, there is no evidence that an increase in standing systolic blood pressure has been demonstrated to be of clinical benefit to the patient with orthostatic hypotension.

Global assessments were to be completed by both patient and investigator 1 hour after each dose of study drug using a crude visual scale ranging from 1 (designated as none) to 5 (designated as excellent). The 10 and 20 mg dose groups had significantly higher (i.e., improved) mean scores compared to placebo. However, the validity of the scale and what the results mean are unknown. It is unclear from the protocol how the responses on the scale were obtained (what questions were asked, if any) and if unintentional unblinding of the study medication occurred because global assessments were recorded after blood pressure measurements.

Two patients dropped out of the study after taking midodrine 20 mg. Reported adverse events were mainly paresthesia, pruritus, and piloerection.

The higher doses of midodrine caused a substantial number of patients to have supine SBP $\geq$ 200 mm Hg, which, depending on the corresponding DBP, is stage 3 or 4 hypertension according to the Fifth JNC . . . On High Blood Pressure, and it is of interest that patients qualified for the SHEP study with SBP > 160 mm Hg . The high dose midodrine group had 45%, the mid dose had 22% and the placebo group had 0% of patients with SBP $\geq$ 200 mm Hg. It was also demonstrated that this midodrine-provoked elevation in supine SBP was long lasting. Using the definition of "prolonged" hypertension as supine SBP $\geq$ 200 mm Hg for at least 2 consecutive reading, the percents of patients in the low, mid and high dose midodrine groups fulfilling this criterion were 4%, 17%, and 41%, respectively.

In conclusion, while the clinical benefits of long term use of midodrine remain mostly elusive, the risks, related to grossly elevated supine systolic blood pressure as shown in this study, are clear.

Protocol

Amendments
6 amendments made Sept 7, 1993 and included elimination of 5 mg dose and substitution of 20 mg dose. Reduced number of blood draws per study segment from 8 to 7. Reduced number of evaluations from 8 to 6 hours per day. Blood pressure recording at 15 minutes after drug intake was changed to optional. Three patients from center #1 (0101, 0102, and 0103) were studied under the original protocol and were included in the analyses for 0, 2.5 mg and 10 mg treatment groups.

Primary objective:
to assess the dose response to midodrine by measuring standing systolic blood pressure. Blood pressure was to be measured 1 minute after rising (using tilt table) and then optionally for 15 minutes. The primary objective was changed, post hoc, to standing BP 1 minute after rising 1 hour after drug intake.
Secondary objective:
to gain information on blood levels of midodrine and the active metabolite.

Study design:
randomized, double-blind, four-way complete crossover. The study was 6 days in duration. Day 1 is pretreatment, Day 2-5 is dosing period, Day 6 is post treatment period. Each dose was taken once by all patients and the sequence of doses was determined at randomization

Doses studied:
all patients were to receive single doses of 0, 2.5, 10 and 20 mg. Tablet strengths included 2.5 mg and 5 mg. The dosing sequence was randomly assigned. Meals were standardized and the timing was as follows: breakfast at least 2 hours prior to dosing, lunch immediately after the hour 5 measurements.

Number and type of subjects:
Patients with neurogenic orthostatic hypotension. Each patient must exhibit a supine to standing systolic blood pressure fall of $\geq$ 15 mm Hg and a major symptom of orthostatic hypotension (dizziness/lightheadedness/unsteadiness) or other presyncopal symptoms. Notable exclusion was "pre-existing sustained supine blood pressure greater than 180/110 mm Hg." There was no discussion of sample size in the protocol.

Global assessments:
overall symptom improvement to be completed by both patient and investigator involved a crude visual scale of 1 (none) to 5 (excellent) made at hour 1 after dosing for days 2-5. The first 3 patients from center 1 had their assessment at 8 hours post dose.

The scale appears as such:

Describe the patient's overall symptom improvement

1_____	2_____	3_____	4_____	5
none		moderate		excellent

The validity of this quite crude scale is unknown. There are no instructions in the protocol about how this scale was to be present to patients (i.e., what questions were asked to which the patients were to respond).

Safety was assessed by adverse events, especially the occurrence of supine hypertension defined by the sponsor as supine SBP $\geq$ 200 mm Hg

Saline replacement:
administration of normal saline iv injection was allowed for each day that blood draws are made. Time of administration and amount were to be at the discretion of the investigator. All patients at both centers received volume replacement (NDA submission 024).

Dropouts were replaced and their substitutes were given the same treatment sequence.

Blood draws for midodrine and desglymidodrine levels were to be performed at 0, 15 and 30 minutes and 1, 2, 4, and 6 hours after dosing.

Symptoms:
Day 1: standing (at 1 minute and optionally every minute for up to 15 min) blood pressure measurements at Hours 0, 1, 2, 3, 4, 5, and 6 hours after dose. Supine blood pressure measurements at Hour 0 and then every 30 minutes for 6 hours.

Day 2-5: qualified patients were randomized to a particular dosing sequence and included doses of 0, 2.5, 5, and 10 mg (protocol amendment changed doses to 0, 2.5, 10, and 20 mg).

Statistics: if baseline BP measurements were not obtained from a patient, the average of the remaining baselines was used. If BP was not obtained at other time point evaluations, the patient's baseline was used.

RESULTS:

Patient disposition: 25 patients from 2 study sites were enrolled, 2 dropped out after receiving the 20 mg dose and were excluded from the analyses. Therefore, there were 23 patients who completed the study and took 1 dose of placebo and 3 doses of midodrine.

Patients missing from blood pressure and global score tables

placebo	Midodrine 2.5	Midodrine 10	Midodrine 20
105, 201	105	105, 201	101, 102, 103

Therefore, the efficacy analyses should include the 23 completed patients and the safety analyses should include all 25 randomized patients.

Demographics:

age, sex, race
Of the 25 patients, there were 14 females (56%), the mean age was 62 years (range 38-78), mean height and weight were 66 inches and 153 pounds, respectively.

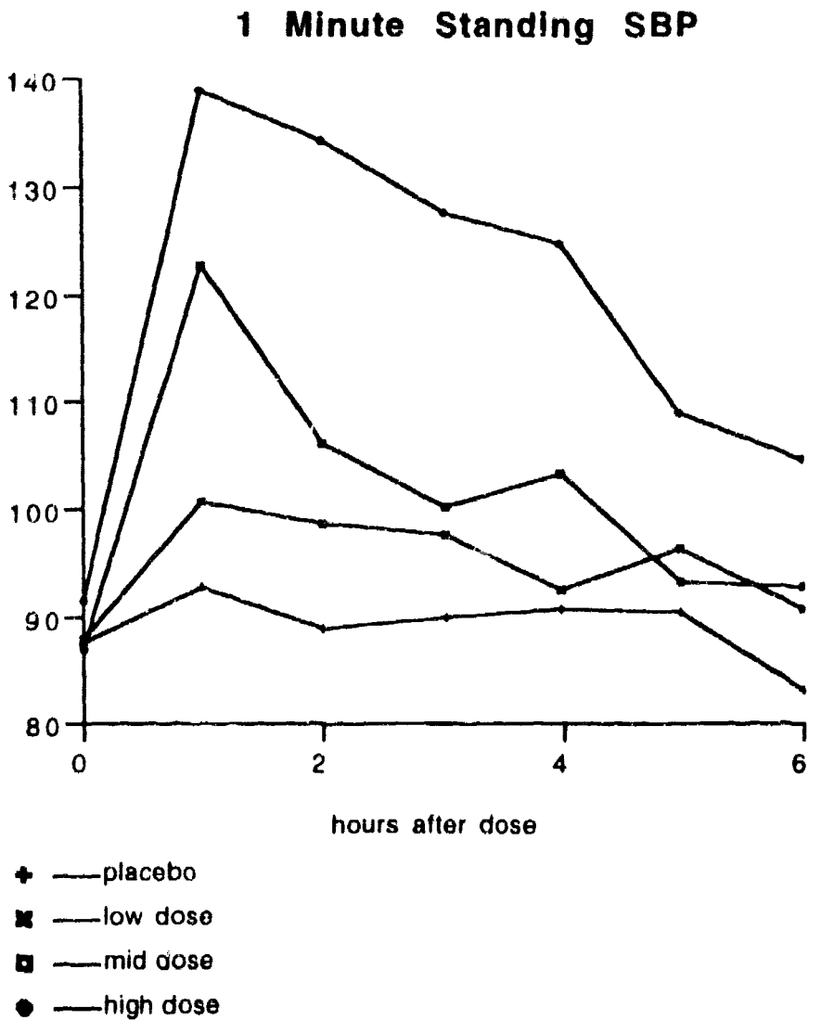
Etiology
There were 14 patients (56%) with Bradbury-Eggleston (IOH), 7 patients (28%) with Shy-Drager, 2 with diabetes, and 1 each with Parkinson's and Giullian-Barre syndrome.

Efficacy
1 minute standing blood pressure. The table below shows standing systolic blood pressure for all patients by treatment group.

Mean standing systolic blood pressure (mm Hg)

		Midodrine		
Time	Placebo n=23	Mido 2.5 mg n=24	Mido 10 mg n=23	Mido 20 mg n=22
Hour 0	88	88	87	92
Hour 1	93	101	123**	139**
Hour 2	89	99	106**	135**
Hour 3	90	98	100	128**
Hour 4	91	93	103	125**
Hour 5	91	96	93	109
Hour 6	83	91	93	105

**P<0.01 for drug vs. Placebo



The standing SBP was similar at hour 0 for the different treatment groups. Both of the mid and high doses significantly increased SBP compared to placebo for about 4 hours after dosing. Both mid and high doses were significantly different from the low dose at selected time points; there was a significant differences between mid and high doses (p=0.03) at hour 2.

Symptoms

The sponsor chose to evaluate patient well being by investigator and patient "global evaluations" of overall symptom improvements. These evaluations were performed 1 hour after dose on each treatment day. A score of 1 is "none," or no improvement, and a score of 5 is "excellent," or excellent improvement. Data from patient #105 are excluded from the 20 mg group.

Mean Score

		Midodrine		
Global assessment by:	Placebo n=23	Mido 2.5 mg n=24	Mido 10 mg n=23	Mido 20^ mg n=21
investigator	1.9	2.0	2.9*	3.3*
patient	2.0	2.3	3.0*	3.3*

* p< 0.5 for the comparison of drug and placebo
^excludes patient 201

There is a significant difference between higher doses of midodrine and placebo in the mean scores for both investigator and patient assessments. There is concordance between the investigator and patient scores.

The table below identifies the number of patients per score category (investigator/patients responses).

Category of Global Score-Number of patients
Investigator response/patient response

		Midodrine		
score	Placebo n=23	Mido 2.5 mg n=24	Mido 10 mg n=23	Mido 20 mg n=21^
1(none)	9/9	7/8	2/2	2/2
2	8/7	10/3	4/4	1/2
3	5/5	6/10	11/9	10/9
4*	1/1	1/3	6/7	5/4
5* (excellent)	0/1	0/0	0/1	3/4

* p<0.05 using Cochran-Mantel-Haenszel procedure for the 10 and 20 mg midodrine groups vs. placebo
^excludes patient 201

There were significantly more patients with higher scores in the mid and high dose midodrine groups compared to the placebo and low dose midodrine groups.

Conclusion: it is impossible to judge what this "symptom" score is measuring. The sponsor stated that blood pressure measurements were recorded before the global assessments (submission serial number 024, received July 28, 1995). Therefore, it is probable that the elevation of blood pressure seen in the midodrine group could have resulted in unintentional unblinding of the investigator/patient to the study drug.

SAFETY (not all 25 patients per dose group were evaluated)

Drop outs for adverse events
There were 2 patients who dropped out of the study after the 20 mg dose, one patient (#0201) for excessive hypertension (supine BP 2 hours after the 20 mg dose was 266/110 mm Hg) and one patient (0105) for acute confusional state.

Adverse events
No adverse events were reported when patients were receiving placebo and 5 mg dose (taken by 3 patients). Surprisingly, only 1 patient out of 9 at center 1 reported an event. On the other hand, all but 2 patients from center 2 reported at least one event. The events consisted primarily of paresthesia, piloerection and pruritus and there was a dose response: patients on low dose reported the fewest events and patients on high dose reported the most events. While only 2 patients had supine hypertension listed as an adverse event, at hour 3, there were 10 patients in the high dose group who had supine SBP ≥ 200 mm Hg.

The 2.5 mg group had single reports of
headache, dry mouth, abnormal thinking, piloerection, paresthesia, scalp paresthesia and scalp pruritus.

The 10 mg group had
3 reports of paresthesia, 4 reports of scalp paresthesia, 2 reports of piloerection, 1 report of pruritus and 1 report of scalp pruritus.

The 20 mg group had
2 reports of supine hypertension, 2 reports of paresthesia, 4 reports of scalp paresthesia, 2 reports of piloerection, and 3 reports of pruritus.

Supine blood pressure
The number of patients with supine SBP ≥ 200 mm Hg (clinically significant hypertension) recorded between 0 and 6 hours after drug intake was as follows.

Number of patients with supine SBP ≥ 200 mm Hg

		Midodrine		
Hours after drug intake	Placebo n=23	Mido 2.5 mg n=24	Mido 10 mg n=23	Mido 20 mg n=22^
Hour 0	0	0	0	1
Hour 0.5	0	1	3	3
Hour 1	0	2	2	6
Hour 1.5	0	0	3	9
Hour 2	0	2	5	9
Hour 2.5	0	0	4	8
Hour 3	0	0	5	10
Hour 3.5	0	0	3	6
Hour 4	0	0	3	5
Hour 4.5	0	0	1	6
Hour 5	0	0	2	5
Hour 5.5	0	0	0	3
Hour 6	0	0	0	4

^Includes patient 201

Unlike the placebo group which had no patient with supine SBP ≥ 200 mm Hg, the higher doses of midodrine had a substantial number of patients with these elevated pressures. The mid and high dose groups had 22% (5/23) and 45% (10/20) of patients with elevated blood pressure 3 hours after the dose, respectively.

The elevation in supine SBP is long lasting. Using the definition of "prolonged" hypertension as supine SBP ≥ 200 mm Hg for at least 2 consecutive readings, the percents of patients who fell into this category were 4%, 17%, and 41% in low, mid and high dose groups, respectively.

APPENDIX I

remain constant. Serious adverse events (requiring medical evaluation or dosage adjustment) occurred at a rate of 8-10 per 100 patient-months, and had occurred in about half the patients by the end of the study.

The investigators & sponsor did not feel that any of the serious adverse events were directly related to the TTS Fentanyl, but review of the case report forms revealed a number of probable associations (in many cases the evaluating physician removed the system or adjusted the dose as the therapeutic intervention).

Patient 202- Hospitalized on day 46 for confusion, slurred speech & poor memory. System removed.

Patient 203- Hospitalized day 8 agitation, confusion, hallucinations. System removed.

Patient 205- Nausea, dizziness, mental confusion, fall at home, urinary retention. TTS continued.

Patient 209- Dose increased day 40, one day episode of emesis, dyspnea, weakness. TTS continued.

Patient 214- Mild confusion and disorientation during a period when TTS dose increased rapidly from 100-300 μg/hr. TTS continued.

Patient 215- Somnolence, woozy, shaky, unsteady gait, dizzy when TTS increased to 100. TTS reduced to 50.

Patient 218- Dysphoria, "weird spaced-out feeling" when TTS increased to 450 μg/hr. TTS reduced.

Patient 302- Increased sleepiness when dose increased to 300 μg/hr. TTS reduced.

Patient 315- Nausea & vomiting when TTS increased to 75. TTS removed.

These patients represent 9 of 54 for a total serious adverse reaction rate of 15-20%. No patient suffered any permanent injury or death attributable to TTS fentanyl, none suffered respiratory depression or was treated with naloxone, and all skin reactions resolved with system removal.

Laboratory screening data was available for most individuals during the period of TTS application, but much of it was abnormal due to prior disease. Scatter-plots of this data revealed no consistent trend signifying medication induced abnormalities.

Pharmacologic Performance

No pharmacokinetic or pharmacodynamic data were collected.

Additional Analyses

This study used two methods of predicting analgesic demand, predicted demand based on the patient's reported use of analgesics, and actual 24 hours usage rates of oral morphine while under observation. The enclosed scatterplots show the predicted v. actual morphine demand, and the relationship of TTS dose to observed morphine use at the initial application of the TTS and after one week. Since TTS dose was set by the observed use of morphine in the stabilization period in the protocol, there should be a strong relationship between that two, and this is, in fact, observed. After a week in which the dose is adjusted to best analgesia, the doses of TTS are higher, with the relationship 300 mg/24 h oral morphine (50 mg/24 hour parenteral morphine) = 100 μg/hr TTS fentanyl. This probably represents a more accurate reflection of the analgetic relationship.

Conclusion

This study establishes the acceptability of TTS Fentanyl for pain control by cancer patients and suggests that that ratio of oral morphine to TTS Fentanyl for conversion to TTS fentanyl lies between 75-125 μg/hr TTS fentanyl per 360 mg/24 h oral morphine demand. The study revealed no unexpected clinical or laboratory hazards of the drug, a serious adverse events rate (mostly opioid side effects on the CNS) of 10 per 100 patient months, and a rate of dose increase of approximately 50% per month of therapy.

All midodrine studies#

						# patients midodrine+ /comparator
1 (Tarazi)	titration/ DB cross over	ephedrine	7.5-30	tid q 8 hrs	up to 10 days	R=A=8/7
1A	titration/ DB cross over	ephedrine	7.5-30	tid q 8 hrs	up to 10 days	R=22, A=8/8
2A Yahr	DB cross over	placebo	7.5-30	tid q 5 hrs	up to 32 days	R=7, A=6/6
3 Vinik	titration/ DB cross over	dihydroergotamine	7.5-30	tid q 5 hrs	up to 9 days	R=A=9/9
4	open label		7.5-30	tid q 5 hrs	up to 3 yrs	E=74, A=64
5	open label		7.5-30	tid q 8 hrs	up to 5 yrs	A=34
10	DB, placebo control, parallel groups	placebo	7.5-40	3-6x/day q 4-q 8 hrs	8-19 days	R=A=7
11/11A	DB, placebo control, parallel groups	placebo	7.5, 15, 30	tid q 4 hr	4 weeks	R=A=74/23
12	open label		7.5-40	tid-qid q 3-q 6 hrs	up to several years	E=695 as of 10-94
201	DB, placebo controlled, cross over	placebo	2.5, 10, 20	once	3 days	R=25, A=23
318	SB, DB, placebo controlled, parallel groups	placebo	20 single blind, 30 double blind	bid, q 6 hrs tid q 3 hrs	1 day 7 hrs	R=A=28/29
320	DB, placebo controlled, parallel groups	placebo	30	tid q 4 hrs	3 weeks	R=A=82/88

DB=double blind, SB= single blind, R=randomized, A= analyzed

numbers for studies 318 and 320 have been verified from SAS data sets and can be assumed to be correct. The other numbers have be obtained from the sponsor and have not been verified.

PHILADELPHIA HEART INSTITUTE

DEC 2 1992

Presbyterian Medical Center
39th and Market Streets
Philadelphia, PA 19104

Telephone
215 662 9022

November 29, 1992

Raymond Lipicky, M.D.
Director, Cardio Renal Drugs Division
Food and Drug Administration HFN 110
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 19-815 Midodrine (Roberts Pharmaceuticals)

Dear Doctor Lipicky:

Enclosed please find my review of the study in responders of midodrine conducted by Roberts Labs. You will note that in this highly selected mixed population that the 10 mg dose level of midodrine does show pharmacologic effects on blood pressure and 1 of the 2 symptom category studied by a very unsophisticated questionnaire. Limitations include a mixed sample of patients including even some with mitral prolapse, only one rather large dose level studied (10 mg-sponsor recommends starting at 2.5 mg), and a pre required set of responders during single blind (open to the investigator) who then during only 1 day of treatment had to show the same response compared to placebo.

I think it is obvious that with these criteria that midodrine is not inert but this study I think is at best only supportive and thus does not clearly change the drug's regulatory status. This is of course perhaps more a policy decision rather than strict "science" and will require an overall response from you. Please let me know if I can help in any way. Best regards.

Sincerely,

Joel Morganorth, M.D.

JM:encl

MEDICAL REVIEW OFFICER'S EVALUATION

PRODUCT: MIDODRINE HCL (AMATINE®)

NDA#: 19-815

SPONSOR: ROBERTS PHARMACEUTICAL
DREW KARLAN 908-3891182

PROTOCOL: 20,762-318
DOUBLE BLIND COMPARISON OF MIDODRINE AND PLACEBO IN MIDODRINE RESPONDER PATIENTS SUFFERING FROM SEVERE ORTHOSTATIC HYPOTENSION DUE TO AUTONOMIC DYSFUNCTION

TYPE: MULTICENTER (N=5) SINGLE TO DOUBLE BLIND PLACEBO CONTROLLED 3 DAY INPATIENT STUDY

DRUG: 2 MIDODRINE 5 MG TABLETS GIVEN AS 10 MG BID ON DAY 2 AND 10 MG TID ON DAY 3

TIME PERIOD: 4/23/91-9/23/92

OBJECTIVE: TO IMPROVE STANDING SYSTOLIC BLOOD PRESSURE AND SYMPTOMS OF SEVERE ORTHOSTATIC BLOOD PRESSURE

STUDY DESIGN:

The study was conducted at 5 centers in patients who are over 17 years of age, males and non-pregnancy potential females, who had been on and responded to Midodrine for at least 2 weeks for severe orthostatic hypotension. Patients with supine bllod pressure over 180/110 mm Hg, able to stand for over 14 minutes without symptoms, on concomitant sympathomimetic or alpha receptor agonists/antagonists, or who had pheochromocytoma, severe cardiac disease, acute nephritis/chronic renal failure, thyrotoxicosis, uncontrolled diabetes, or a history of CVA or coagulopathies were excluded.

STUDY DESIGN CONTINUED

Day 1 was entry into hospital for washout of midodrine, all caffeine and smoking prohibited

Day 2 required the patient to show orthostasis with symptoms and response to midodrine and evaluation of duration of action of midodrine, 10 mg Midodrine given 2 hrs after breakfast and a second 10 mg dose 6 hours later. 15 hrs will elapse before first dose on day 3. Eligibility pre-dose 1 was a supine to standing BP fall of over 14 mm Hg (but not less than 70 as initially required) and a symptom score of 5 or less in 1 of the 2 symptom categories; elligible patient after the first dose are tested at hrs: 1,3,4 and 6. BP taken every 30 minutes though. To go on patients had to have at 1 hr post dose an increase in systolic BP of >9 mmHg and an increase in the symptom score by at least 1 point (an amendment allowed this 1 vs the initial protocol which requires a 2 point rise).

Day 3 eligibility by symptom demonstration and randomization to placebo or midodrine given as 2 tablets 2 hrs after breakfast and 2 more tablets in 3 hours and again in another 3 hours; Predose 1 if standing occurs for <6 minutes then this parameter is measured throught the day if between 5-15 then not measured again. To continue into day 3 the patient has to have eligibility criteria remet as on day 2. Post dose 1 and 2 the endpoints are measured at 1 and 3 hours and only 1 hour after dose #3. (page 2b,2c show the study procedures)

Efficacy endpoints were the standing 1 and 3 minuted systolic BP and effect on symptom class dizziness felt more common than visual change in these patients. Secondary endpoints were standing diastolic and supine BPs and supportive were standing time and sitting BPs.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPENDIX A

MIDODRINE STUDY #26.722-318
STUDY SCHEDULE DAY 1

DAY 1	UPON ADMISSION	6 HOURS AFTER ADMISSION
Medical History	X	
Physical Exam	X	
Laboratory Tests	X	
Review of Inclusion & Exclusion Criteria	X	
Record Time Of Last Midodrine Dose	X	
Supine, Sitting and Standing Blood Pressure and Pulse	X	X
Symptom Evaluation	X	X
Standing Time	X	X

APPENDIX A (CONTINUED)

MIDODRINE STUDY #26,722-318
STUDY SCHEDULE DAY 2 AND DAY 3

DAY 2	HOUR															
	-2	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0
osing *		X												X		
eal **	X							X								
ipine BP & Pulse		X	X	X	X	X	X	X	X	X	X	X	X	X		X
tting/Standing BP & Pulse		X		X				X		X				X		X
mptom Evaluation		X		X				X		X				X		X
Time		X		X				X		X				X		X
igibility Evaluation		X		X												

DAY 3	HOUR															
	-2	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0
sing *		X						X						X		
al **	X							X								
pine BP & Pulse		X		X				X		X				X		X
ting/Standing BP & Pulse		X		X				X		X				X		X
mptom Evaluation		X		X				X		X				X		X
nding Time		X		X				X		X				X		X
gibility Evaluation	*	X														

g is to immediately follow any evaluations made at that time point (i.e BP, pulse, standing time, etc.)

are to immediately follow the dose at that time point.
naded area for meals is the time during which diabetic patients may have a snack if absolutely necessary

2C

STUDY DESIGN -CONTINUED

Blood pressure: measured by cuff at first clear sound = systolic and Phase V absense = diastolic (nonaudible diastole or <40mmHg = not detectable (ND)). Supine = 3 minutes prone , standing obtained at 1 and 3 minutes , sitting = after 1 minute from supine. Order of pressure measurements: supine then standing then return to supine and do sitting. Meal times were to be kept constant and standing time to symptoms measured with over 15 minutes without symptoms = ineligibility. Concomitant medications such as fludrocortisone and high salt diet (as well as Jobst stockings) were allowed. A 10 point symptom evaluation for dizziness /lightheadedness /unsteadiness and dimming/blurring of vision was obtained by the coordinator and patient filling out a form:

SYMPTOM SCALES

CHECK THE ONE BOX UNDER THE NUMBER THAT MOST ACCURATELY DESCRIBES THE SEVERITY OF THE SYMPTOMS THAT YOU FEEL UPON STANDING FOR THIS EVALUATION.

1. Feelings of dizziness/lightheadedness/unsteadiness

Extreme 1 2 3 4 5 6 7 8 9 10 None

[ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

Severe Moderate Slight

2. Dimming/blurring of vision

Extreme 1 2 3 4 5 6 7 8 9 10 None

[ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ] [ ]

Severe Moderate Slight

3

3

STATISTICAL ANALYSIS:

Data from day 2 were subjected to ANOVA comparing each time point with hour 0. On day 3, systolic BP and standing time were analyzed by ANCOVA with hour 0 as the covariate. One hour after each dose (hours 1,4,7) were compared for midodrine vs placebo and only in patients evaluated at those hours with complete datasets.

RESULTS

There were 70 patients enrolled but only 54 eligible for day 2 and 53 for day 3 of study for efficacy and 53 and 52 respectively for symptoms at the 5 centers.

LIST OF INVESTIGATORS PARTICIPATING IN MIDODRINE STUDY NO. 20,762-318

CENTER NO.	INVESTIGATOR NAME	INSTITUTION	NO. PTS.
1	Gilden, J.	Univ. of Health Sciences/ Chicago Medical School Diabetes & Endocrine Sections 3333 Green Bay Rd. (111E) North Chicago, IL 60064	36
2	Kaufmann, H.	Mt. Sinai Medical Center Annenburg Building Dept. of Neurology One Gustav Levy Place New York, NY 10029	15
3	Hiner, B.	Marshfield Clinic Neurology Department 1000 N. Oak Avenue Marshfield, WI 54449-5777	2
4	Jankovic, J.	Baylor College of Medicine Movement Disorder Clinic 6550 Fannin Houston, TX 77030-2707	7
5	Robertson, D.	Vanderbilt University Clinical Research Center Medical Center North Nashville, TN 37232-2195	10
TOTAL			70

RESULTS - CONT

Reasons for the drop from 70 to 53 evaluable patients is : 2 for concomitant event during day 1, symptoms not sevre enough (4); no blood pressure response(6), no symptom response (1) and other (3) or 14 during day 2 and on day 3 1 patient with not severe enough symptoms.

The demography of the patients on day 3 are:

PATIENT DISTRIBUTION
FOR PATIENTS IN DOUBLE-BLIND PHASE (EFFICACY ANALYSIS)

	RANDOMIZED		
TOTAL	10 mg MIDODRINE	PLACEBO	TOTAL
NO. PATIENTS	27	26	53*
NO. MEN	19	14	33 (62%)
NO. WOMEN	8	12	20 (38%)
MEAN (RANGE) AGE (YRS)	58.6 (17-78)	63.9 (20-81)	61 (17-81)
DIAGNOSTIC GROUPS			
ION (BRADBURY-EGGLESTON)	5	8	13
SHY-DRAGER	13	9	22
PARKINSON'S	2	1	3
DIABETES	7	5	12
OTHER	0	3	3

*) Patients eligible for and included in efficacy analysis

5

RESULTS - CONT

Of the 53, 13 (25%) had Bradbury Eggleston Syndrome, 22 (42%) ShyDrager, 3 (6%) Parkinsonism, 12 (23%) diabetes. Of the last 3 , 2 had mitral prolapse and 1 just orthostatic hypotension.

DAY 2 RESULTS

Pre dose BP response on day showed that the mean standing systolic was 79/55 at 1 and 77/55 at 3 minutes with a supine-standing fall of 53/23 and 57/23 mm Hg respectively in 54 eligible responding patients.

Duration of action was defined by 0.5 hr BP measurements in the supine position after the first dose for 6 hours compared to the "0" hour value. Figure 1 (see end of report) shows that the blood pressure rose from 132 mmHg at baseline to 155 at 1 hour and 166 at 3 hours then fell either because the drug's effect waned or food was taken at this time. Blood pressure rose again to 154 at 6 hours before the next dose. Standing BP at hours 0,1,3,4,6 and 7 with doses at 0 and 6 hours given. At 1 minute the systolic BP increased from 80-105 and remained elevated for 3 hours (Figure 2) as did the 3 minute values (Figure 3). Symptom results showed that for the dizzy category 49 of 53 had a score of 5 or more severe (a lower number) at baseline and the score went from 3.7 to 6.1 at 1 hour and began to decrease at 3 hours (Figure 4). Only 18 of 53 had a visual abnormality and a similar effect was seen as shown in figure 5. The standing time (time to the symtom of suggested syncope) is shown in Figure 6 and again is similar to the other symtoms with the observed change lasting for 3 hours before starting to suggest a decrease in effect. No effect on pulse rate was seen of note.

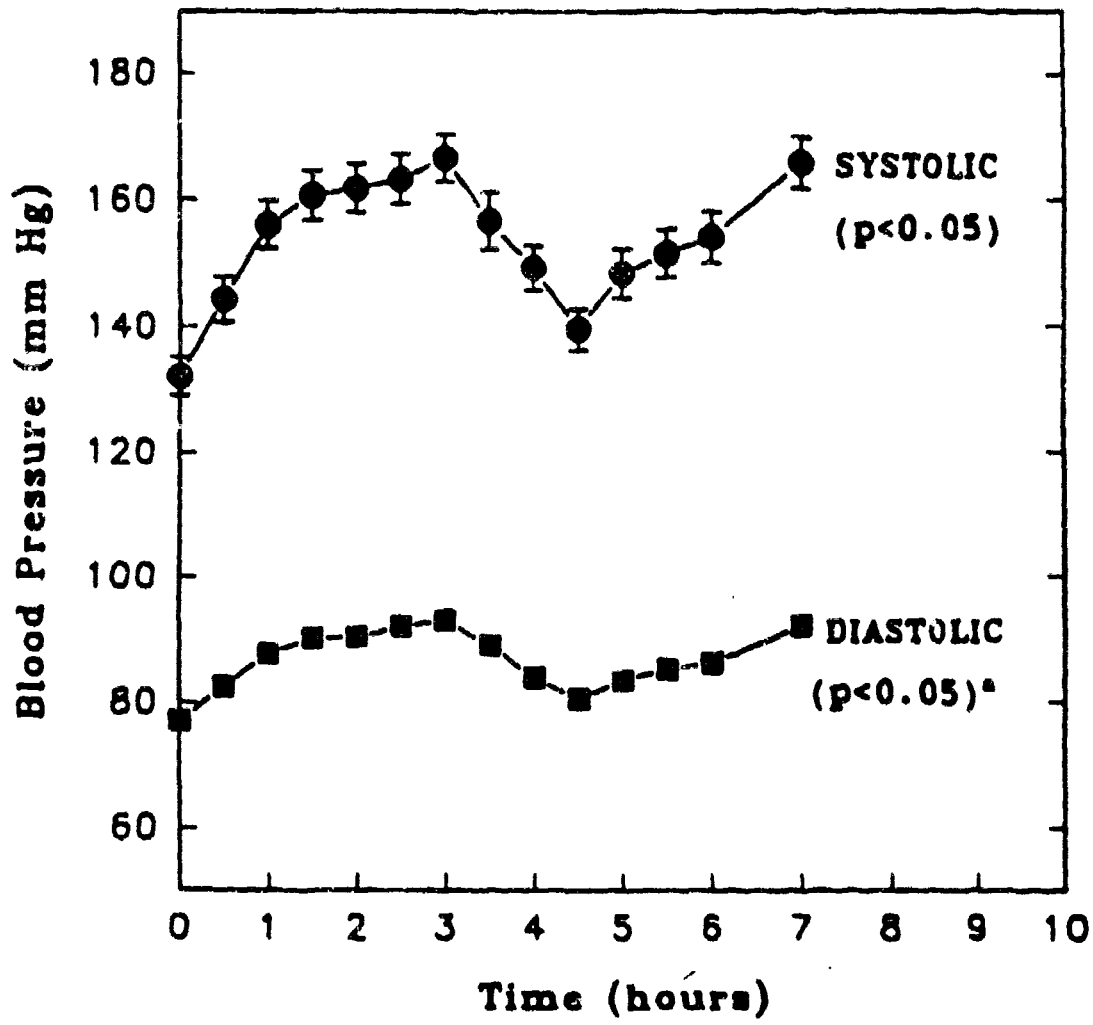
DAY 3 RESULTS

The results for the 10 mg Midodrine dose vs placebo for the key parameters is:

standing systolic BP 1 min (p=.02) 3 min (p=.02) dizzy symptoms (p=.03) and visual symptoms (p=.55). Standing diastolic (p=.03), supine systolic (p=.001) and diastolic (p=.02). Standing time (p=.07), sitting systolic (p=.004),diastolic (p=.005). These comparisons are based on comparing hours 1,4,7 as adjusted for hour 0 (the peak 1 hour effect) in those with complete data sets. Figures 7-12 show these results.

FIGURE 1

DURATION OF ACTION OF MIDODRINE
SUPINE BLOOD PRESSURE
DAY 2

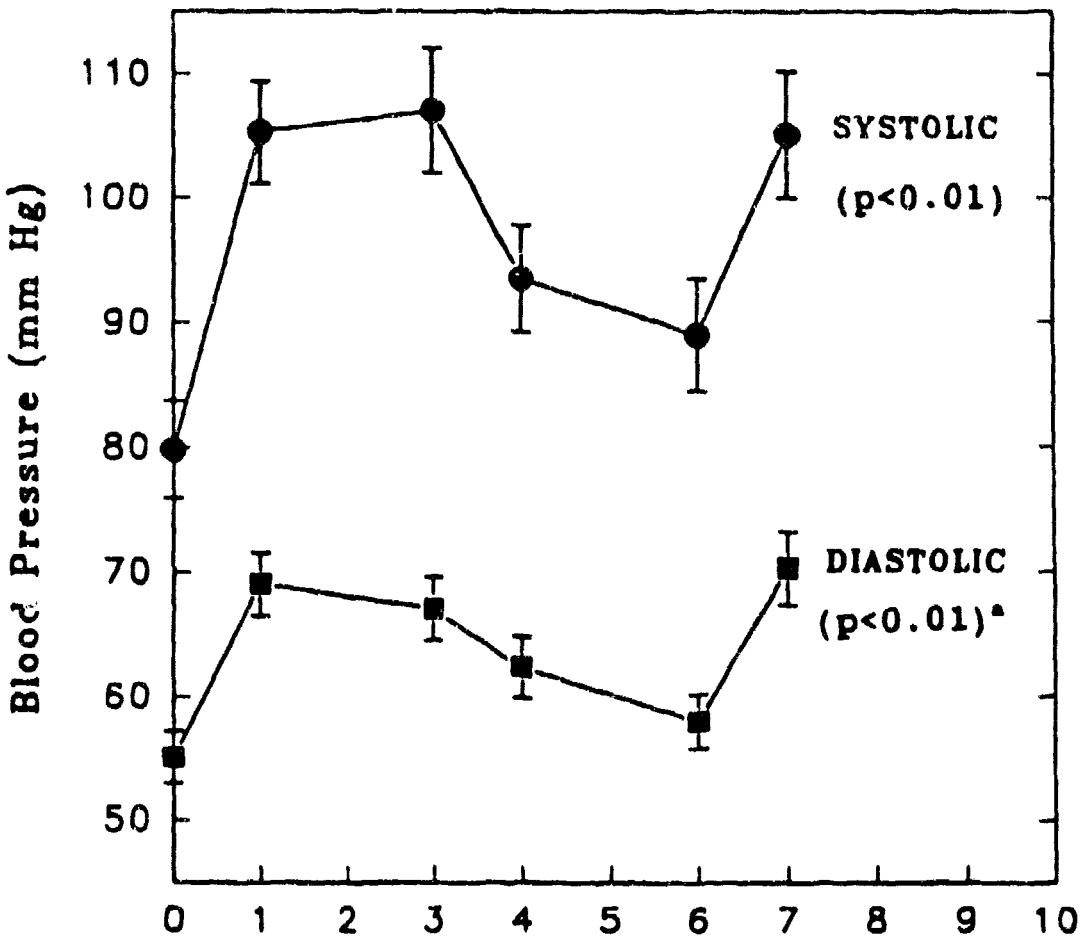


(n = 51). These patients provided complete data sets at Hours 0, 1, 3, 4, 6 and 7. Values represent the means ± S.E. S.E. for diastolic BP is contained within the data point. A dose of 10 mg midodrine was given at Hours 0 and 6; a meal at Hour 3. Significance vs. Hour 0: p<0.05 for all data points; a) excluding Hour 4.5.

7

FIGURE 2

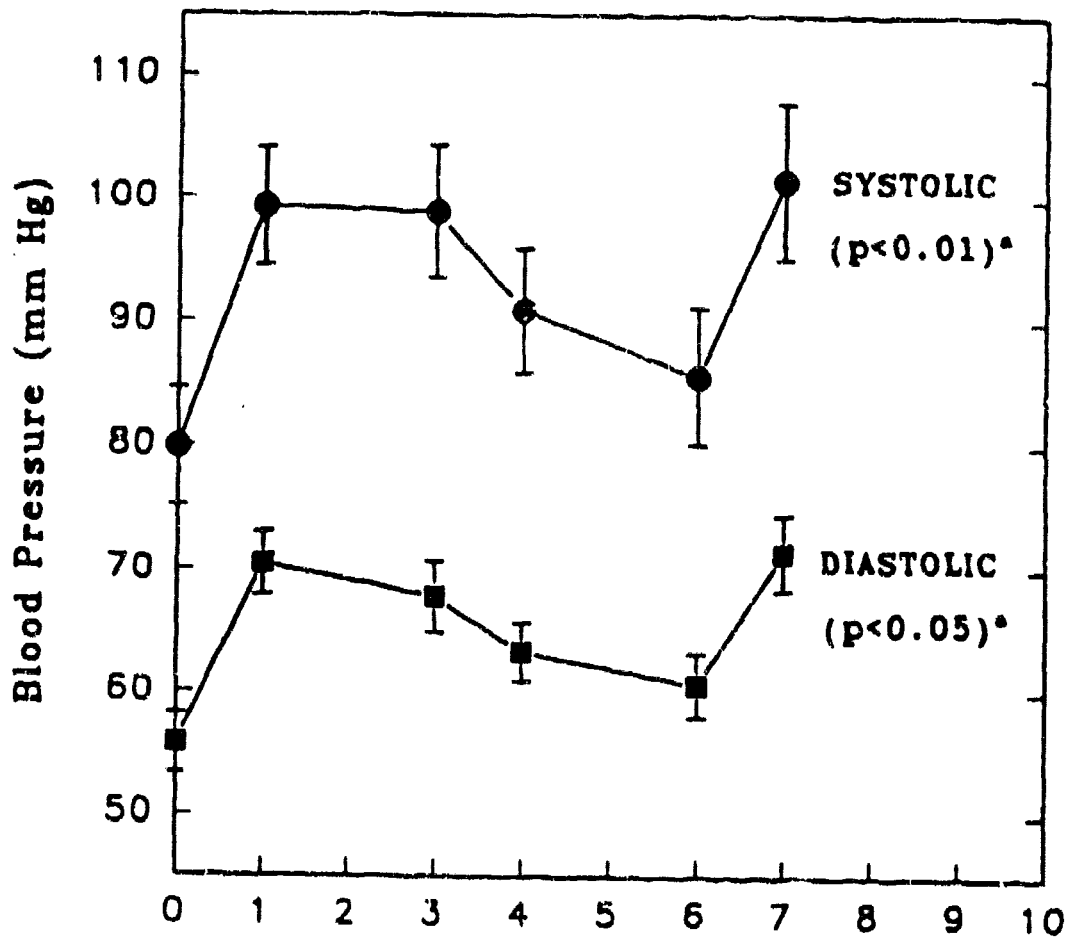
EFFECT OF MIDODRINE ON
1 MINUTE STANDING BLOOD PRESSURE
DAY 2



(n = 42 for systolic and 34 for diastolic). These patients provided complete data sets at Hours 0, 1, 3, 4, 6 and 7. Values represent the means ± S.E. A dose of 10 mg midodrine was given at Hours 0 and 6; a meal at Hour 3. Significance vs. Hour 0: $p<0.01$ for all data points; a) excluding Hour 6.

FIGURE 3

EFFECT OF MIDODRINE ON
3 MINUTE STANDING BLOOD PRESSURE
DAY 2



(n = 33 for systolic and 22 for diastolic). These patients provided complete data sets at Hours 0, 1, 3, 4, 6 and 7. Values represent the means ± S.E. A dose of 10 mg midodrine was given at Hours 0 and 6; a meal at Hour 3. Significance vs. Hour 0: $p<0.05$ for all diastolic data points; $p<0.01$ for all systolic data points; a) excluding Hour 6.

Medical Officer Review
NDA #: 19,813
Alza Corporation

TTS Fentanyl

(Transdermal Therapeutic System)

Volume 2 - Pharmacokinetics & Pharmacodynamics

Executive Summary

This amendment was requested of the sponsor by HFD-007 in May 1990 in order to address concerns about the pharmacokinetic performance of the TTS system and to clarify the pharmacodynamics of fentanyl at blood levels between 0-5 ng/mL. The submission consists of a mixture of material from the open literature and new data from the sponsor. It shows that while the manufacturing controls and in-vitro performance of the TTS system are acceptable, there is a large variation in the blood level of the drug supplied by the system in clinical trials and that not all of this variation is due to individual variation in clearance. The data provided support a Ctox for opioid-naive postoperative patients of 3.0 ng/ml (2.0 ng/ml for patients with one or more respiratory risk factors such as chest surgery, concomitant administration of CNS depressants, poor ASA status, lung disease), and a MEC of 0.6 ng/ml.

Blood levels for patients wearing the TTS 50 system (50μg/hr) will be below the Minimum Effective Concentration (0.6 ng/ml) for 15%, hit the target zone (0.6-2.0 ng/ml) for 83% of the patients, be toxic (2.0-2.99) for 2% of vulnerables, but will not exceed 3.0 ng/ml. Of the three systems tested in clinical trials it is both safe and effective.

The 75 & 100 μg/hr systems both provide too much fentanyl (3% and 11% above 3.0 ng/ml) for unrestricted postoperative use and the sponsor has been advised that approval will depend on the adequacy of the labeling in identifying postoperative patients who should and should not be prescribed the larger systems, and the adequacy of carton/package/system warnings.

All systems (25,50,75,100) are reliable enough so that they will not dose-dump (Cmax < 5 ng/ml) and should not be toxic for opioid-tolerant individuals in the cancer pain indication.

Submitted: 5/16/90
Reviewed: 5/31/90 to 6/6/90
Curtis Wright MD,MPH

WRITTEN CWIV - 6/6/90
PEER REVIEWED RD- 6/18/90
SPONSOR'S COMMENTS MS -6/19/90

General Comments Regarding the PK-PD Amendment

One of the factors which has prolonged the review process for TTS fentanyl was a nearly universal concern about safety on the part of the regulatory staff who reviewed the original submission. This discomfort was due, in part, to the novelty of transdermal administration of a potent opioid, but was also the result of concerns about the pharmacokinetic reliability of this method of delivery of fentanyl. As a direct result, the sponsor was asked to examine the pharmacokinetics of the TTS systems in detail and to develop additional pharmacodynamic information about the pharmacodynamics of fentanyl in the 0-5 ng/ml range delivered by the system. This amendment is their response to this request.

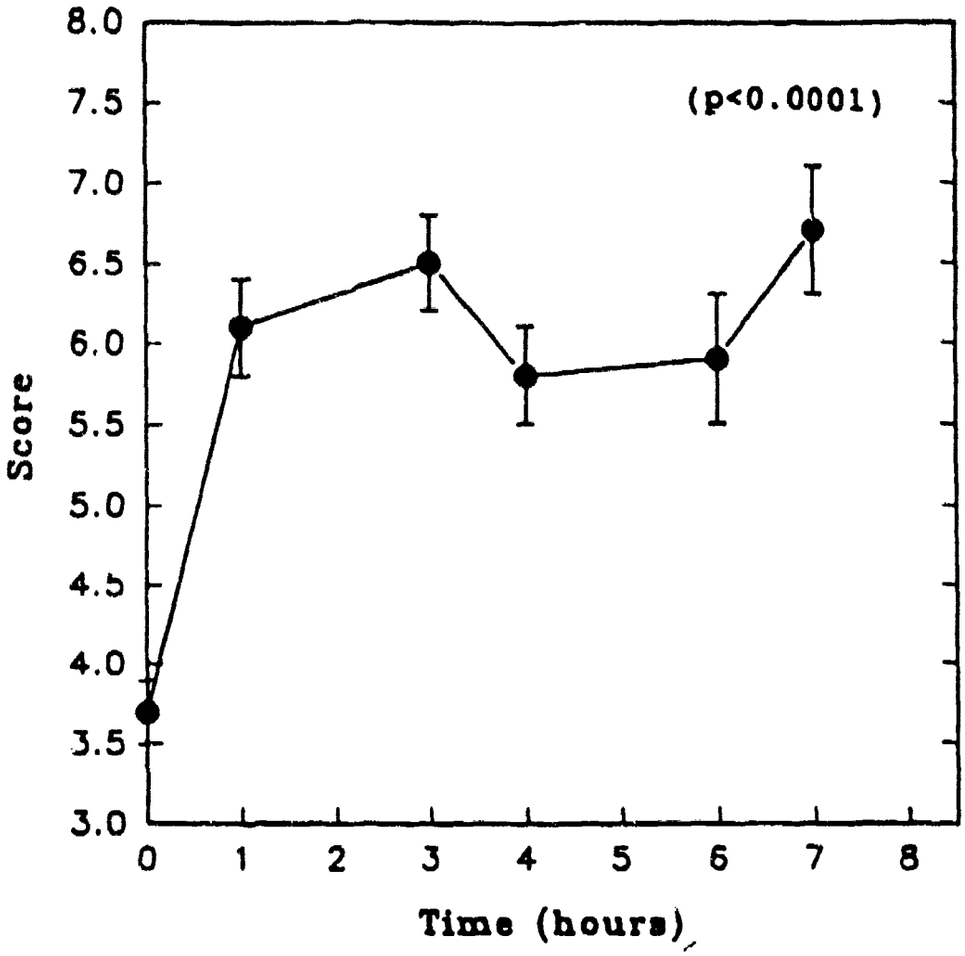
Overview of the Amendment & Review

The submission consists of a series of discussions of the performance of the TTS system and a combination of new and old data which defines the system and evaluates the probable causes of variation in its pharmacokinetic performance.

Main	Topics	Review Page	Orig. page
System Variables	Rate Limiting Membrane	3	3
	Ethanol Flux	4	3
Skin Variables	Skin Site	5	8
	Skin Temperature	8	9
	Blood Flow	8	10
Pharmacokinetics	Dose Proportionality	9	14
	Body Weight Effects	23	
	Average Blood Level Profiles	10	
	Skin-Depot Effects	11	
	Repeated Dosing	11	23
	Liver/Renal disease	12	26
	Obesity	12	27
	Elderly	12	28
TTS System Modeling	Pharmacokinetic Model	12	31
	Physio-chemical Model	13	35
TTS Variability	Release Rate	14	38
	Skin Permeability	15	38
	Clearance	16	39
Pharmacodynamics	Cardiovascular	16	41
	Ventilatory	16	41
	Analgesic	17	42
	Hysteresis	20	46
	Adverse Effects	21	48
Reviewer's conclusions		21	

FIGURE 4

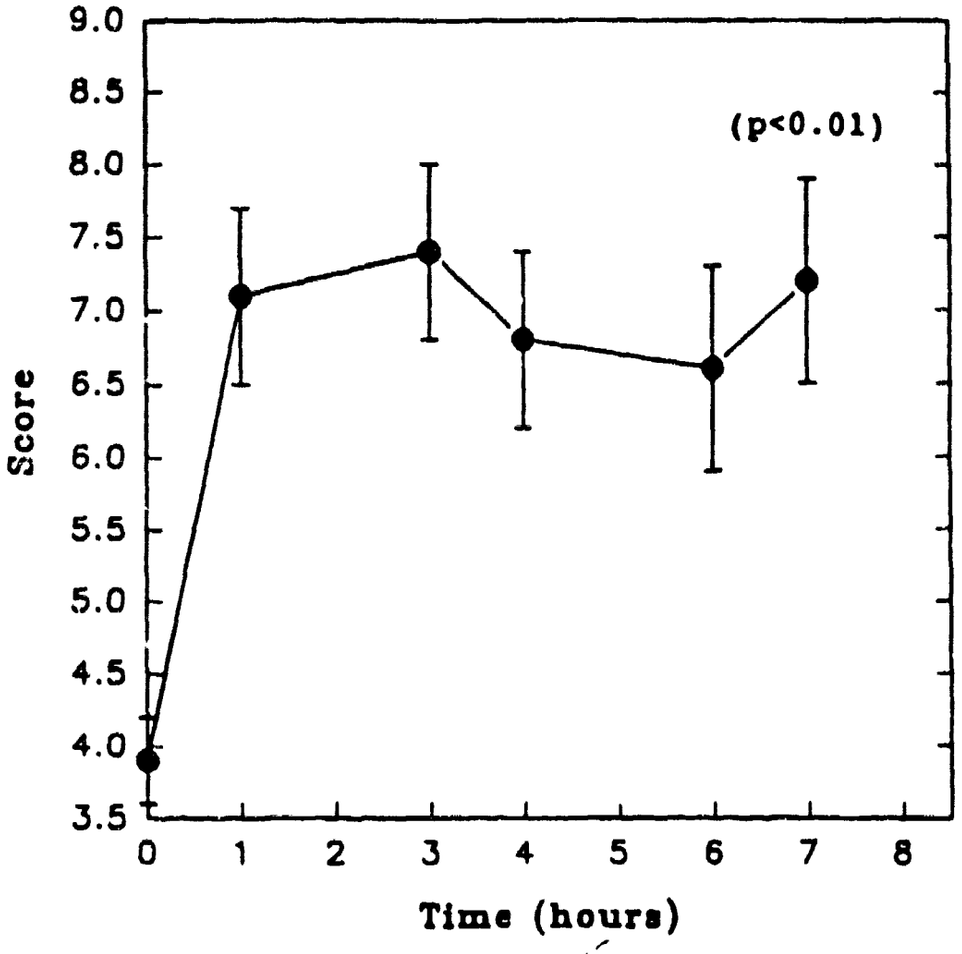
EFFECT OF MIDODRINE ON
THE KEY SYMPTOM OF ORTHOSTATIC HYPOTENSION
SYMPTOM 1
DIZZINESS/LIGHTHEADEDNESS/UNSTEADINESS
DAY 2



(n = 49). These patients provided complete data sets at Hours 0, 1, 3, 4, 6 and 7 and reported the symptom with a score of 5 or more severe. Values represent the means ± S.E. A dose of 10 mg midodrine was given at Hours 0 and 6; a meal at Hour 3. Significance vs. Hour 0: $p<0.0001$ for all data points. A score of 1 was most severe, a score of 10 indicated that the patient did not have the symptom.

FIGURE 5

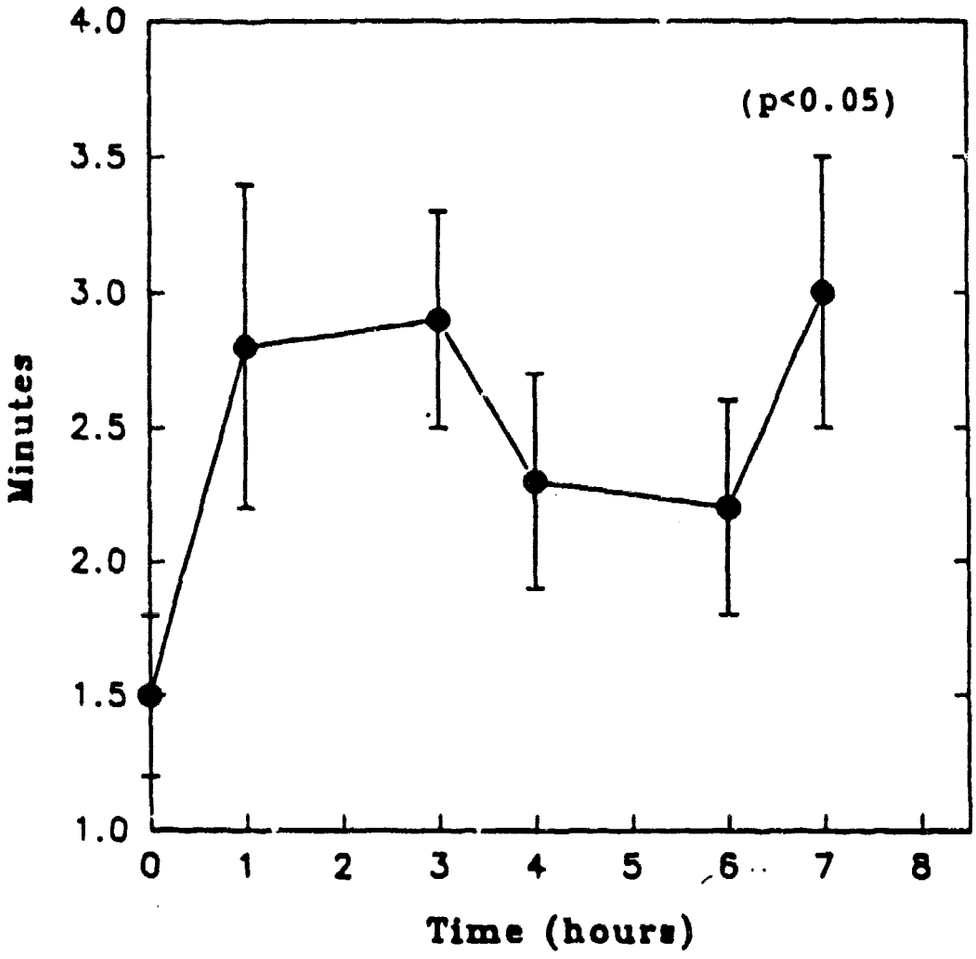
EFFECT OF MIDODRINE ON
A SYMPTOM OF ORTHOSTATIC HYPOTENSION
SYMPTOM 2
DIMMING/BLURRING OF VISION
DAY 2



(n = 18). These patients provided complete data sets at Hours 0, 1, 3, 4, 6 and 7 and reported the symptom with a score of 5 or more severe. Values represent the means ± S.E. A dose of 10 mg midodrine was given at Hours 0 and 6; a meal at Hour 3. Significance vs. Hour 0: $p<0.01$ for all data points. A score of 1 was most severe, a score of 10 indicated that the patient did not have the symptom.

FIGURE 6

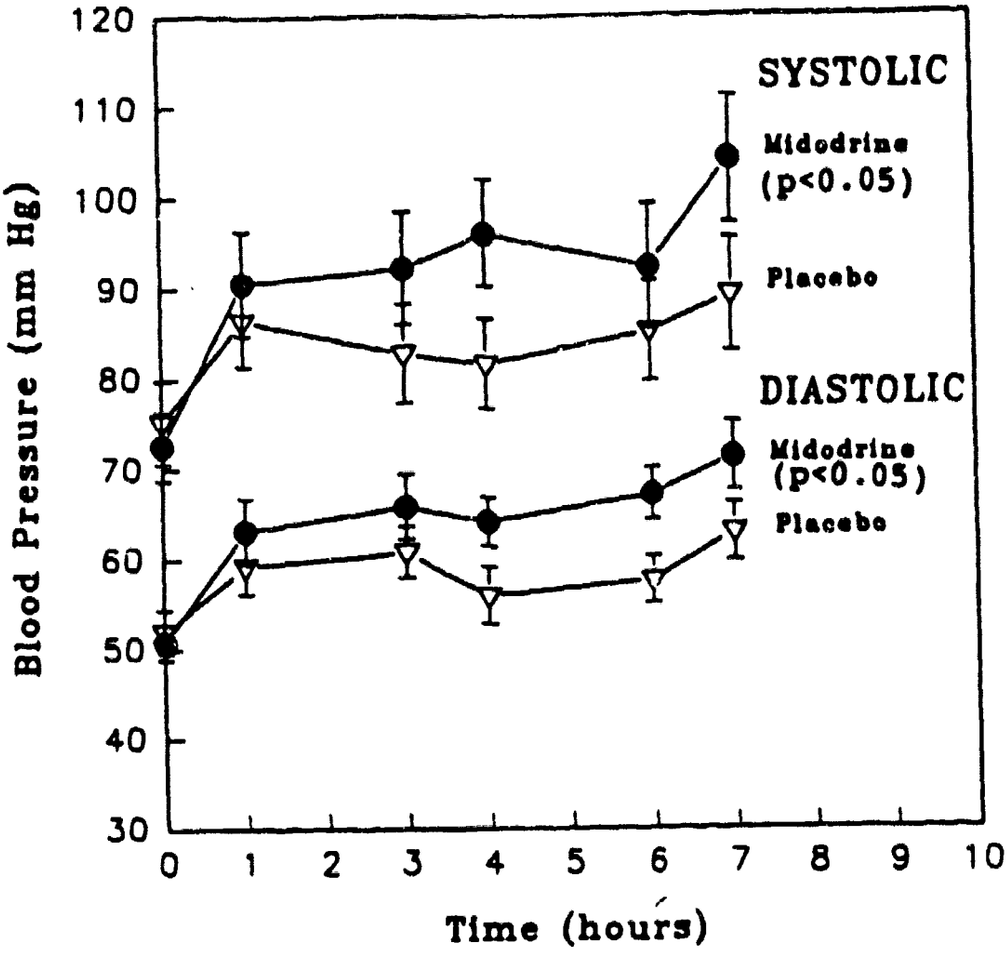
EFFECT OF MIDODRINE ON STANDING TIME DAY 2



(n = 49). These patients provided complete data sets at Hours 0, 1, 3, 4, 6 and 7. Values represent the means ± S.E. A dose of 10 mg midodrine was given at Hours 0 and 6; a meal at Hour 3. Significance vs. Hour 0: $p<0.05$ for all data points.

FIGURE 7

EFFECT OF MIDODRINE AND PLACEBO ON
1 MINUTE STANDING BLOOD PRESSURE
DAY 3



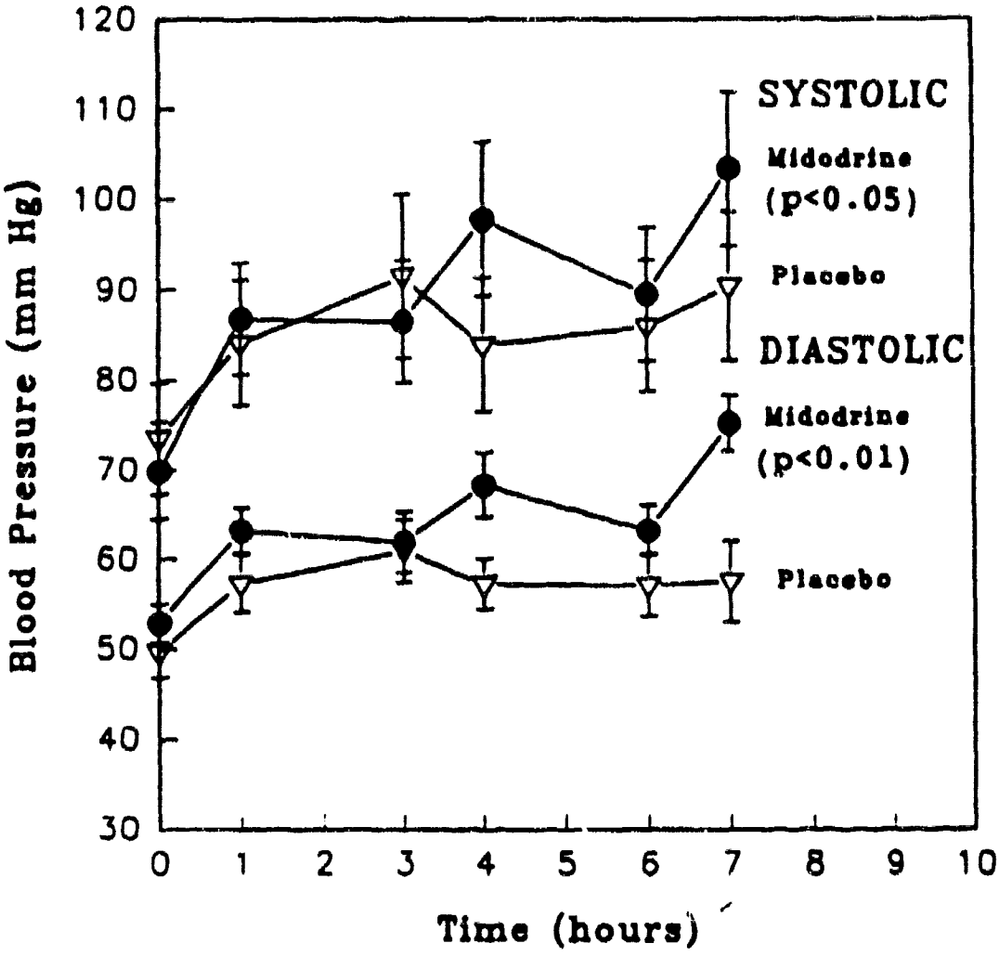
(n = 24 midodrine, 24 placebo for systolic; 20 midodrine, 18 placebo for diastolic). These patients provided complete data sets at Hours 0, 1, 4 and 7. Values represent the means ± S.E. Doses were given at Hours 0, 3 and 6; a meal at Hour 3. ANCOVA Midodrine vs. Placebo, Hours 1, 4 and 7 (adjusted for Hour 0). Significance: ($p<0.05$) for both systolic and diastolic BP.

0070

13

FIGURE 8

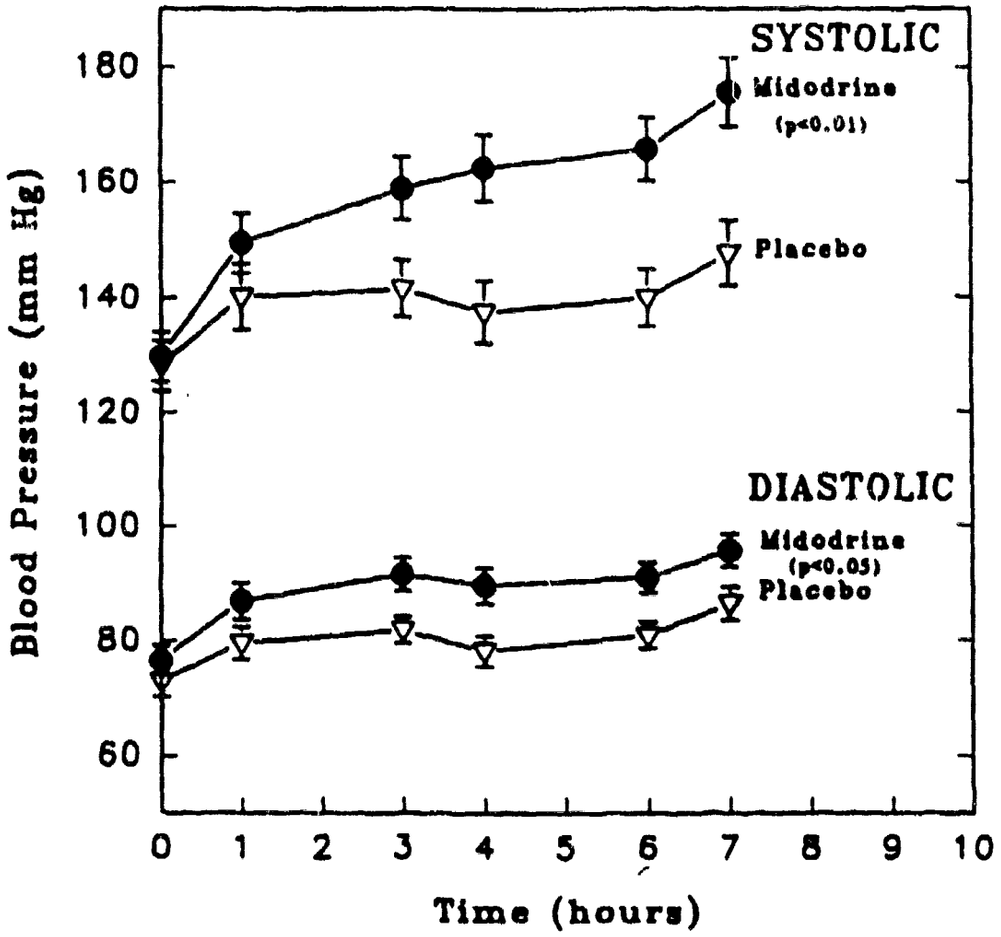
EFFECT OF MIDODRINE AND PLACEBO ON
3 MINUTE STANDING BLOOD PRESSURE
DAY 3



(n = 17 midodrine, 17 placebo for systolic; 13 midodrine and 15 placebo for diastolic). These patients provided complete data sets at Hours 0, 1, 4 and 7. Values represent the means ± S.E. Doses were given at Hours 0, 3 and 6; a meal at Hour 3. ANCOVA Midodrine vs. Placebo, Hours 1, 4 and 7 (adjusted for Hour 0). Significance: ($p<0.05$) for systolic BP and ($p<0.01$) for diastolic BP.

FIGURE 9

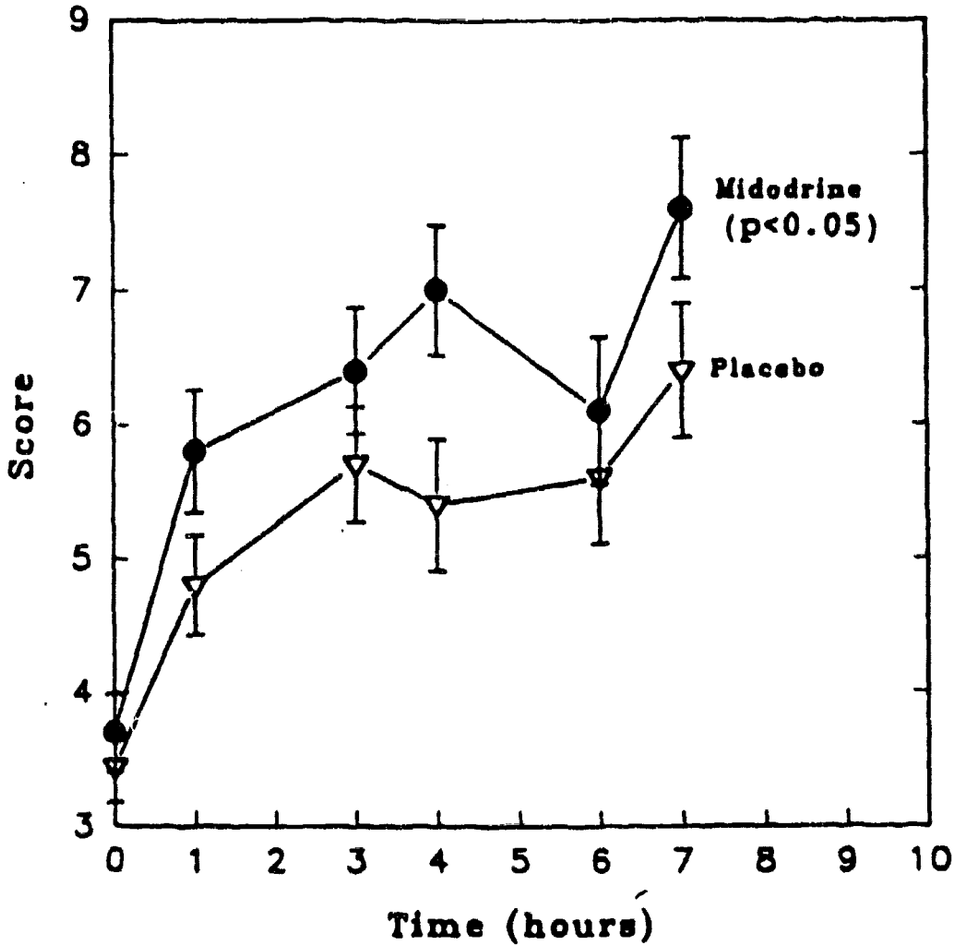
EFFECT OF MIDODRINE AND PLACEBO ON SUPINE BLOOD PRESSURE DAY 3



(n = 27 midodrine, 26 placebo). These patients provided complete data sets at Hours 0, 1, 4 and 7. Values represent the means ± S.E. Doses were given at Hours 0, 3 and 6; a meal at Hour 3. ANCOVA Midodrine vs. Placebo, Hours 1, 4 and 7 (adjusted for Hour 0). significance: ($p<0.01$) for systolic and ($p<0.05$) for dinstolic BP.

FIGURE 10

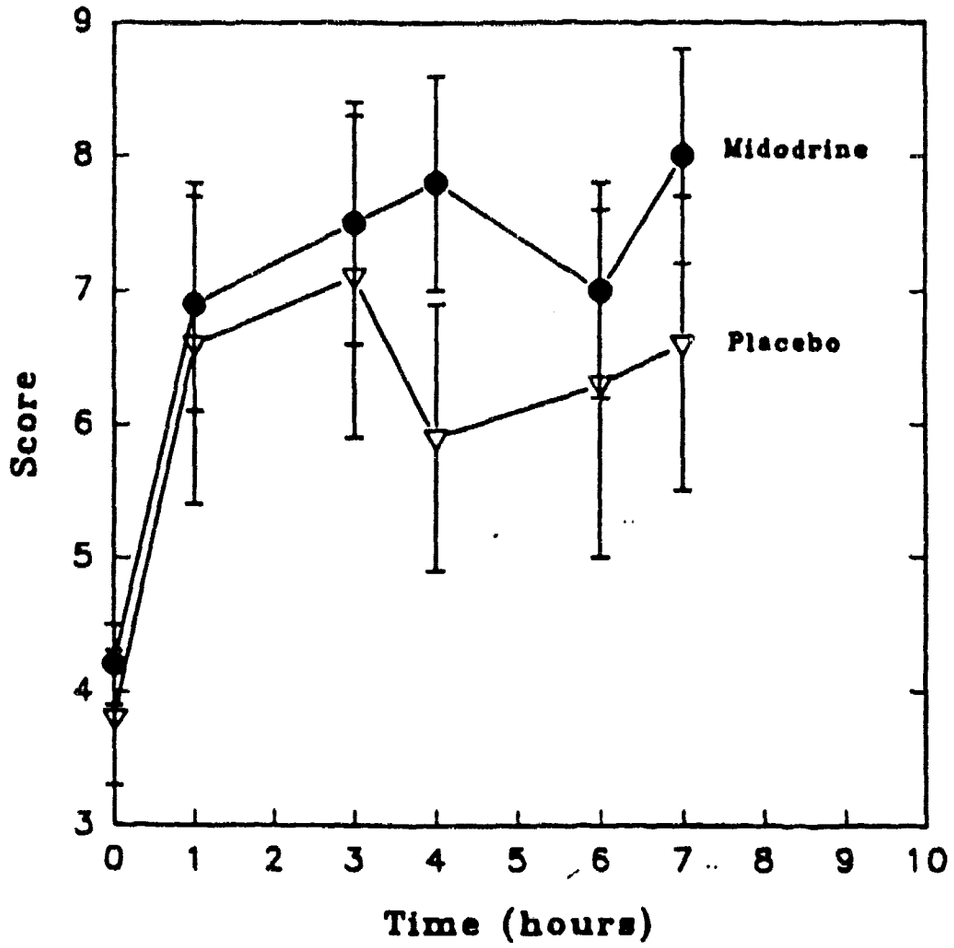
EFFECT OF MIDODRINE AND PLACEBO ON
THE KEY SYMPTOM OF ORTHOSTATIC HYPOTENSION
SYMPTOM 1
DIZZINESS/LIGHTHEADEDNESS/UNSTEADINESS
DAY 3



(n = 24 midodrine, 25 placebo). These patients provided complete data sets at Hours 0, 1, 4 and 7. Values represent the means ± S.E. Doses were given at Hours 0, 3 and 6; a meal at Hour 3. ANCOVA Midodrine vs. Placebo, Hours 1, 4 and 7 (adjusted for Hour 0). Significance: (p<0.05).

FIGURE 11

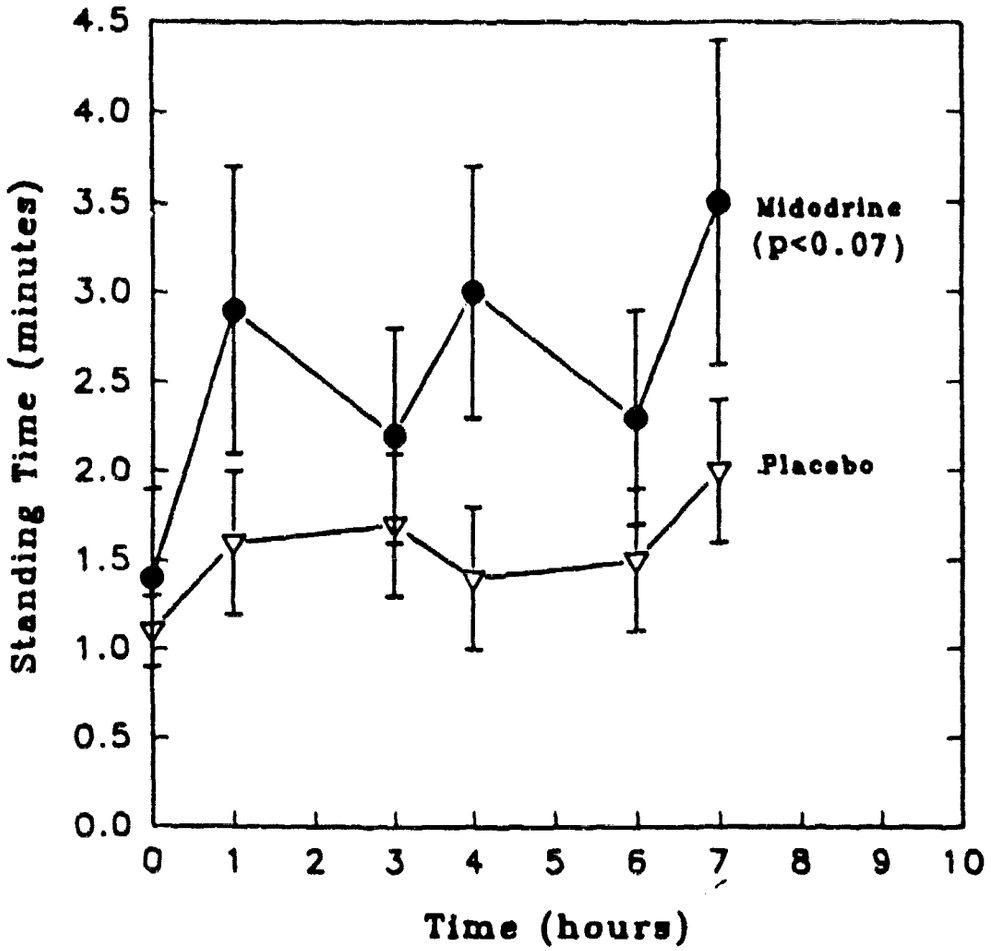
EFFECT OF MIDODRINE AND PLACEBO ON
A SYMPTOM OF ORTHOSTATIC HYPOTENSION
SYMPTOM 2
DIMMING/BLURRING OF VISION
DAY 3



(n = 12 midodrine, 8 placebo). These patients provided complete data sets at Hours 0, 1, 4 and 7. Values represent the means ± S.E. Doses were given at Hours 0, 3 and 6; a meal at Hour 3. ANCOVA Midodrine vs. Placebo, Hours 1, 4 and 7 (adjusted for Hour 0).

FIGURE 12

EFFECT OF MIDODRINE AND PLACEBO ON
STANDING TIME
DAY 3



(n = 26 midodrine, 24 placebo). These patients provided complete data sets at Hours 0, 1, 4 and 7. Values represent the means ± S.E. Doses were given at Hours 0, 3 and 6; a meal at Hour 3. ANCOVA Midodrine vs. Placebo, Hours 1, 4 and 7 (adjusted for Hour 0). Significance: (p<0.07).

0075

18

SAFETY

There were 10 on day 2 and 1 on day 3 adverse effects related to midodrine of 64 patients dosed with the drug. None of the placebo patients on day 3 had an adverse effect. The effects noted were considered tolerable and are listed in this table and what was considered concomitant events in the next table (note 2 syncopes):

TREATMENT-RELATED SIDE EFFECTS

REACTION	INCIDENCE N (%)	
	PLACEBO (N=29)	MIDODRINE (N=64)
Tingling/Pruritus/Piloerection/Chills	0 (0%)	6 (9.4%)
Elevated Blood Pressure	0 (0%)	1 (1.6%)
Flushing	0 (0%)	1 (1.6%)
Pyrosis	0 (0%)	1 (1.6%)
Urinary Urgency	0 (0%)	1 (1.6%)
Pressure in Head *	0 (0%)	1 (1.6%)
TOTAL	0	11

70 patients enrolled, 64 patients treated with midodrine on Day 2, 11 ADR's reported for 10 patients (15.6% reporting ≥ 1 ADR) *) ADR reported on Day 3, all other ADR's reported on Day 2. All reports were considered by investigator as either possibly, probably or definitely related to drug.

APPENDIX TABLE F3
CONCOMITANT EVENTS

PATIENT NUMBER	CONCOMITANT EVENT	ETIOLOGY OF EVENT
1-01-01	Hypoglycemic Episode	Missed Bedtime Snack
1-04-04	Low Blood Sugar	Change in Meal Times
1-06-06	Headache upon standing	Low BP on Standing
1-10-00	Severe nausea & vomiting	Viral Gastroenteritis
1-14-13	Heartburn	Symptom Subsided by 10:30 pm After Administration of Mylanta
1-19-18	Syncope	Unwitnessed; Out of Bed to Urinate
1-20-19	Syncope	Untreated Orthostatic Hypotension
1-24-24	(a) Extra Insulin Dose (b) Gastroparesis	Extra Meal as a Result of Extra Insulin Dose
2-09-09	Increased Ascites	Existing Congestive Heart Failure
2-13-13	Urinary Tract Infection	Neurogenic Bladder
2-14-14	Elevated Glucose Levels in Blood & Urine	Diabetes Mellitus
3-02-02	Abdominal Discomfort	Concomitant Medication - Sinemet
4-01-01	Confusion	Possibly Related to Hospitalization
5-03-00	Supine Hypertension	Pre-existing Condition

MRO Comments:

This very specific study evaluated a highly selected group of patients proven or thought to have responded to midodrine. The patients were sought from 5 centers yet over half came from one center. The population represents many patients with primary autonomic dysfunction but also many with just diabetes or Parkinson's disease and even some with just mitral prolapse. Only a single dose level of midodrine was given--10 mg (tid) which is rather high considering that the starting dose recommended by the sponsor is 2.5 mg. The duration of action of this 10 mg dose in these selected responders using a single blind (!!) method appeared to best last for 3 hours and at a stretch may be 4-6 hours. Using only evaluable patients with full data sets in this selective protocol of a 10 mg tid dose level, there is an effect compared to placebo of midodrine to increase blood pressure and decrease the symptoms of dizziness but not clearly visual blurring for at least 3 hours and possibly 6 hours. The adverse profile of skin effects, increased blood pressure and ??syncope seen in 11+2 or 13/64 or about 20% in this 48 hour exposure period vs 0% on placebo over 24 hours is notable.

In conclusion, I believe this study documents that a 10 mg dose given tid of midodrine in selected known responders to the drug shows a pharmacological effect on blood pressure and some symptoms of orthostatic hypotension. **This dataset thus becomes supportive to the sponsor's claim of a safe and effective drug that hitherto was not considered yet proven.** Whether these data thus effect the overall decison of approvability for the NDA will require further review and a policy decision.

signed: _____
Joel Morganroth, MD

dated: 11/29/92

MEDICAL OFFICER'S REVIEW

TITLE: A DOUBLE-BLIND COMPARISON OF MIDODRINE AND PLACEBO IN PATIENTS WITH ORTHOSTATIC HYPOTENSION (study #20,762-11A)

NDA# 19-815

Date received at FDA: 11-29-90

Date received by medical review officer: 12-7-90

Date of this report: 12-12-90

Sponsor: Roberts Pharmaceutical Corporation

DETAILS OF PROTOCOL

OBJECTIVE:

To evaluate the efficacy and safety of midodrine versus placebo in patients with moderate to severe orthostatic hypotension.

STUDY DESIGN:

This was a multicenter out-patient placebo-controlled double-blind parallel group evaluation of midodrine at 2.5, 5.0, and 10.0mg. administered t.i.d. The goal was to have 80 patients enter the double-blind portion of the study with the hope of having 4 to 12 patients at each investigational site.

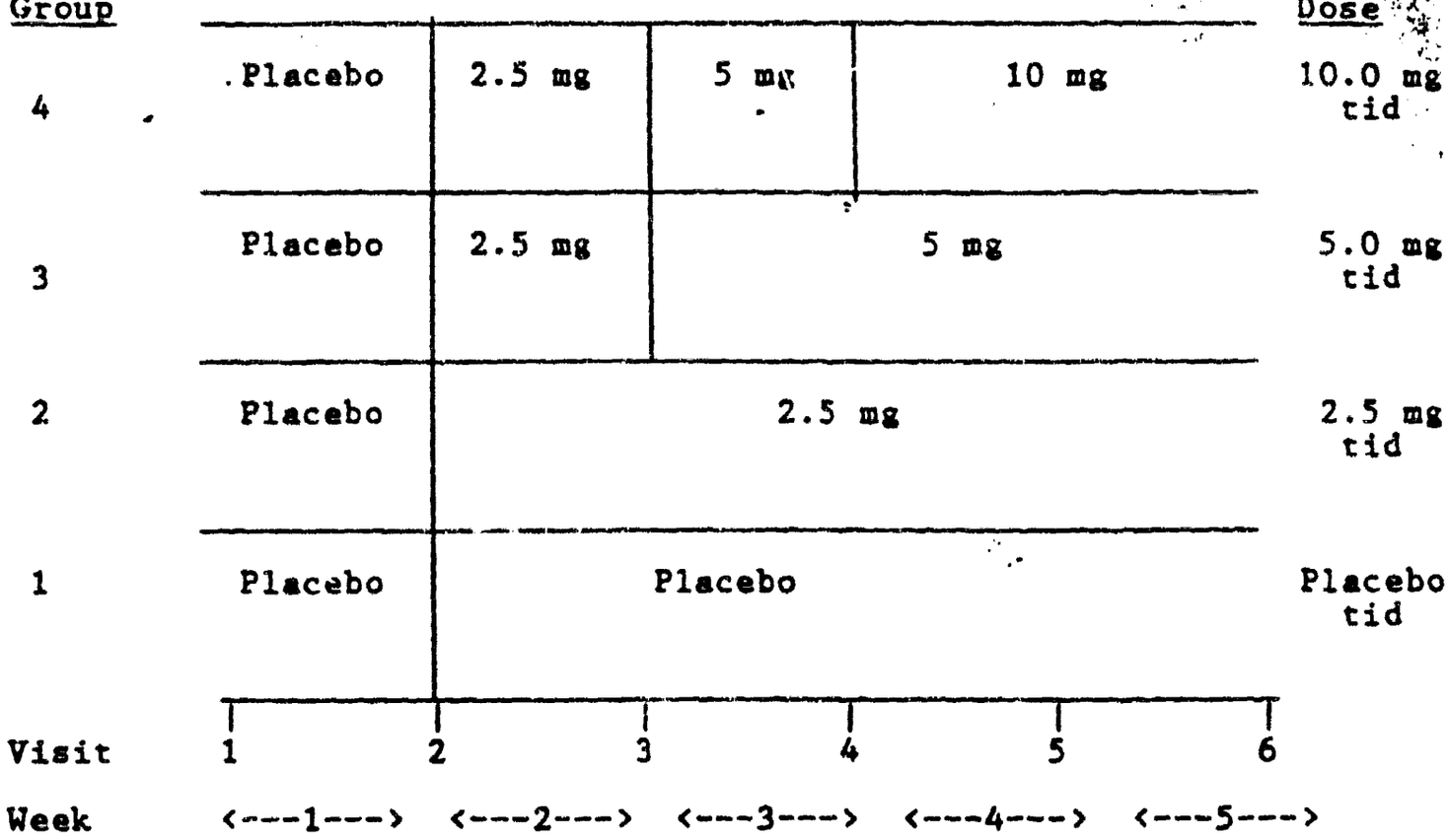
After enrollment patients were randomly assigned to: placebo t.i.d., midodrine 2.5mg. t.i.d., midodrine 5.0mg. t.i.d., midodrine 10.0mg. t.i.d.

Each group was to enter a one week, single-blind, placebo lead-in period with sympathomimetic medications being withdrawn at the initiation of lead-in. Patients were to remain on their fixed dose for a period of two to four weeks with clinic visits every week. The protocol flow sheet demonstrating dose escalation and procedures is attached from the sponsor's report. The protocol called for the omission of this at five based on the patient's response to the medication. At completion of the trial patients can be continued to an open-label compassion study under separate protocol.

The study population included those patients who are over the age of 18, who signed a consent form, and who had the diagnosis of moderate to severe orthostatic hypotension with progressive autonomic failure with or without peripheral or central nervous system involvement. Therefore patients with ideopathic orthostatic hypotension, Shy-Drager syndrome, diabetes mellitus, and Parkinsonism disease could be enrolled.

MIDODRINE

DOSE ESCALATION FLOWSHEET



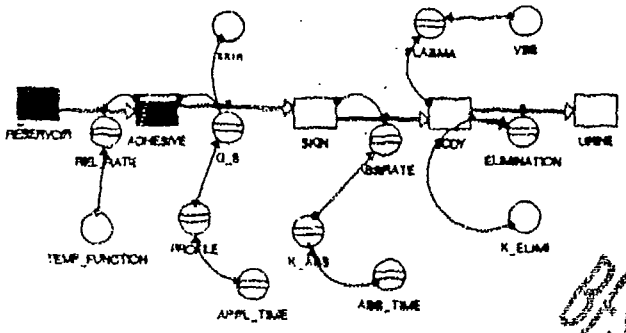
GROUP 1 - Placebo tid.

GROUP 2 - Midodrine 2.5 mg tid

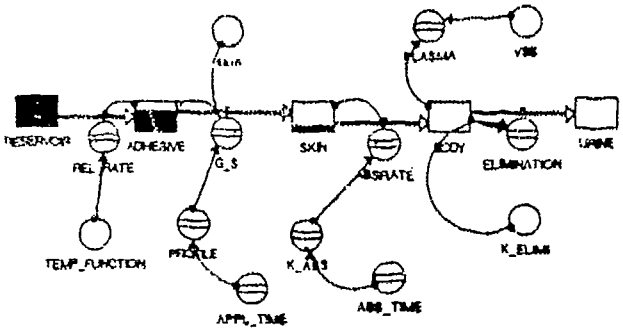
GROUP 3 - Midodrine 5.0 mg tid

GROUP 4 - Midodrine 10.0 mg tid

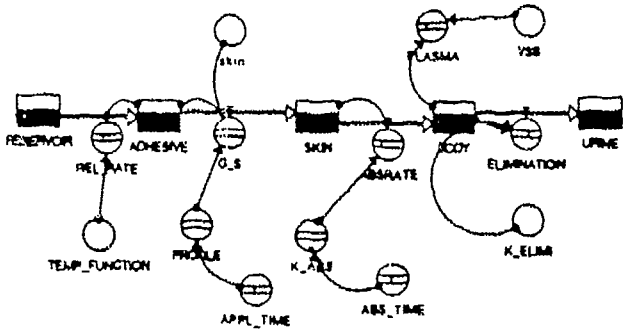
time= 0.1h



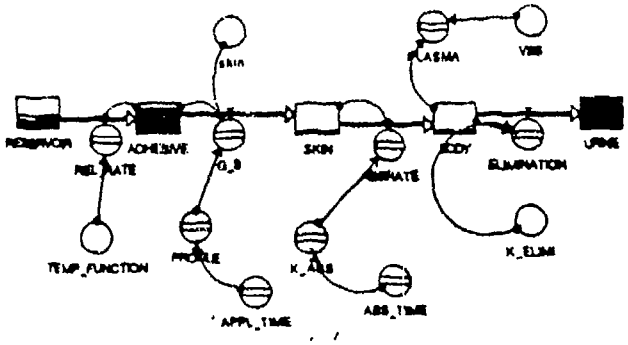
time= 6h

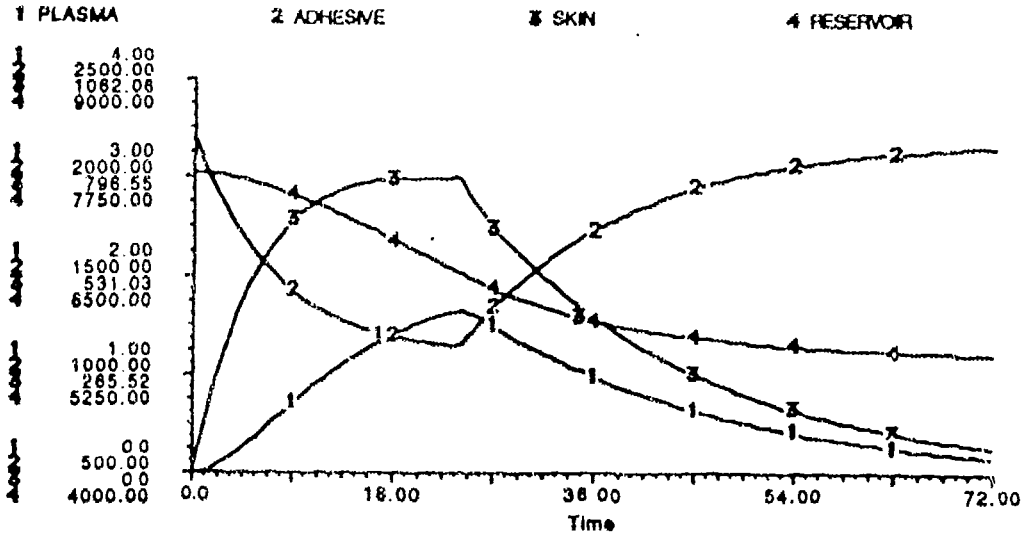


time= 24h



time= 72h





The sponsors did investigate the kinetics of fentanyl in a limited number of patients using a tri-exponential model of IV infusion with the following results:

Subject	Vc Liters	Vss Liters	Cl Liters/hr	MRT Hours
950	35.2	731	74.7	9.7
951	15.5	330	82.4	4.0
952	22.9	268	32.4	8.2
953	10.5	198	44.1	4.4
954	18.4	285	41.8	6.8
955	6.9	377	21.7	17.3
956	8.0	549	42.7	12.8
957	9.1	446	30.5	14.6
Mean	15.8	398	46.3	9.7
SD	10.2	185	22.8	5.1
CV	64%	46%	49%	52%

If this data is generalizable (N=8), and since the blood level at pseudo-steady state will be determined by the relationship between the flux into the body and the clearance of the drug, the observed 50% CV for the clearance of fentanyl suggests that the best that the system could achieve is a target blood level +/- 50%. This corresponds to the following distribution for 100 patients wearing the TTS 75 system.

MIDODRINE

STUDY PROCEDURES FLOWSHEET

	Placebo Lead-In Period	Double Blind Period				
Visit	1	2	3	4	5*	6
Medical History	X					
Physical Examination	X					X
Clinical Laboratory Tests	X					X
EKG	X					X
Body Weight Measurements	X	X	X	X	X	X
BP, Pulse Measurement	X	X	X	X	X	X
Target Symptom Checklist	X	X	X	X	X	X
Investigator's Global Assessment			X	X	X	X
Patient's global Impression of Therapeutic Response						X
Investigators global Impression						X

* Optional Visit

The patient also had to have symptoms of syncope or pre-syncope on assuming an upright position and also evidence of a change in systolic blood pressure of at least 15mm from supine standing with at least two symptoms of moderate severity. Patients were excluded who had incapacitating symptoms unable to meet the requirements of the protocol or a disease process advanced to the point that prolonged in-hospital dose titration was necessary. Also pre-existing supine hypertension defined as greater than 190/100, clinically significant renal or hepatic impairment, concomitant administration of sympathomemetic or alpha receptor agonists agents, other investigational agents, investigational drugs within one month, or any of the following diagnoses: pheochromocytoma, severe cardiac disease, acute nephritis, thyrotoxicosis, uncontrolled diabetes mellitus, history of cerebral vascular accident, angina pectoris, severe cardiac arrhythmias, coagulopathies, concomitant anticoagulation usage, complete urinary retention, seizure disorder, other neurologic disease impairing ability to stand or walk, pregnancy or child bearing potential.

DRUG DISPENSING:

Patients were given bottles A & B and were instructed to take 2 tablets three times daily, one from bottle A and one from bottle B.

RANDOMIZATION:

In order to qualify for enrollment in the double-blind portion of the study after the initial single-blind placebo week, the patient has to demonstrate a 15mm decrease in systolic blood pressure upon standing and two symptoms that were considered moderate to marked as defined on the target symptom check list. This check list is attached. Patients were given drug t.i.d. with at least three hours lapse between doses. The following medications were allowed to be used concomitantly and were to be kept stable: fludrocortisone, indomethacin, cardiac glycosides, Jobst support, stable dietary sodium intake, other medications for pre-existing diseases.

Therapeutic response planned was to identify three target symptoms that were considered to be the most severe which would be used as a symptom endpoint. Medication diaries were used as well as a seven-point global assessment impairing visits three through six with the visit two.

Blood pressure was obtained at each visit using the same arm with a standard sphygmomanometer. The blood pressure was to be obtained after the patient had been supine for at least three minutes and again after assuming a standing position for one minute. Sitting blood pressure was to be used if the patient could not stand.

PROTOCOL NO. 2 0 7 6 2 - 1 1 INVESTIGATOR

PATIENT INITIALS PATIENT NO. DATE

VISIT 4

TARGET SYMPTOM CHECKLIST

The following thirteen (13) symptoms have been reported by persons having a condition similar to yours. Please read the list carefully and circle one choice for each symptom which best describes how severe or frequent it was over the past week. Check the box next to the three (3) symptoms that were the most distressing to you. If you have symptoms not on this list, write them in items fourteen (14) and fifteen (15).

SYMPTOM	SEVERITY OR FREQUENCY OVER THE PAST WEEK			
☐ 1. Lightheadedness, dizziness	NONE	MILD	MODERATE	SEVERE
☐ 2. Feelings of weakness, fatigue, or tiredness	NONE	MILD	MODERATE	SEVERE
☐ 3. Pain in shoulder or neck muscles	NONE	MILD	MODERATE	SEVERE
☐ 4. Shortness of breath on exertion	NONE	MILD	MODERATE	SEVERE
☐ 5. Impotence	ABSENT	PRESENT	UNKNOWN	N/A
☐ 6. Loss of interest in my usual activities	NONE	SOME	MARKED	COMPLETE
☐ 7. Episodes of blurred vision or vision "white-out"	NONE	1-2 DAYS	3-5 DAYS	6-7 DAYS
☐ 8. Fainting or loss of consciousness	NONE	1-2 DAYS	3-5 DAYS	6-7 DAYS
☐ 9. Frequent urination (especially at night)	NONE	1-2 DAYS	3-5 DAYS	6-7 DAYS
☐ 10. Loss of control of urine (incontinence)	NONE	1-2 DAYS	3-5 DAYS	6-7 DAYS
☐ 11. Constipation	NONE	1-2 DAYS	3-5 DAYS	6-7 DAYS
☐ 12. Reduced ability to sweat	NONE	SOME	MARKED	COMPLETE
☐ 13. Dry mouth or reduced saliva	NONE	MILD	MODERATE	SEVERE
☐ 14.	NONE	MILD	MODERATE	SEVERE
☐ 15.	NONE	MILD	MODERATE	SEVERE

On the day of a scheduled visit, the medication was to be administered in the investigator's office but no specific time of taking blood pressure was noted in the protocol in reference to taking study medication. The complete study was defined after four weeks of treatment with double-blind medication and patients could be discontinued, of course, at their request or lack of cooperation or noncompliance or the occurrence of a significant intercurrent illness. In addition, supine hypertension of greater than 230/110 or at the investigator's discretion or an increase in diastolic pressure by 30mm above baseline or the development of symptomatic bradycardia or other intolerable side-effects.

STATISTICAL PROCEDURES:

The protocol called for an interim analysis after one-quarter of the patients were completed to determine the definitive sample size required.

The data was planned to be analyzed using a repeated measurement design evaluating in the analysis of variance between patients: investigator drug, drugs, drug X investigator interaction between patient error (a) and within patient: time, drug X time within patient error (b). The analysis will be intent to treat with all patients with at least one follow-up visit will be included in the analysis using the last assessment for the current dose.

Incidence of laboratory abnormality and adverse reaction was planned to be compared using the ordered contingency table mode to determine whether there is a dose response.

The protocol was amended on 6-12-89 and included the following changes: blood pressure readings were to be done in triplicate, revising of the symptom and rating scale for the symptomatology questionnaire and requiring that visit 5 be mandatory. In addition, the protocol further amended to allow patients to have either 15mm drop in blood pressure or two symptoms rather than both. It turns out that 92 of the 104 patients or 88% actually met the original protocol requirement of having both of these parameters. Of the 75 patients eligible for the last visit blood pressure analysis, 10 patients did not meet the original protocol requirement of having both blood pressure and symptoms at the same time. Thus, 65 of the 75 or 87% of the patients did, however, meet this criteria. In addition, the protocol was amended to allow for baseline blood pressures of 180/110 to be acceptable for entry rather than the original 190/100. In addition, patients with stable angina could be enrolled.

The original protocol was titled Study 11 and the amended protocol 11A. Total number of patients in Study 11 and Study 11A are shown in the accompanying two tables from the sponsor's report. It appears that approximately 24 patients of the 104 were in protocol 11 versus protocol 11A.

TIMING OF THE STUDY:

The first patient was enrolled on January 17, 1989 and the 104th patient on May 21, 1990.

The sponsor's study report notes in their introduction that patients other than the inclusion criteria in the protocol were allowed for various etiologies orthostatic hypertension and stated by the addition of "and other". In addition, the objective of the trial defined in their study report notes the fact that in Study 11A an additional change in the protocol had blood pressures now to be obtained in one hour post dosing the projected time of peak effect. This presumably was done in Study 11A but not in Study 11. Primary efficacy endpoints were not specifically defined in the protocol but in the study report were said to be: key syncopal symptoms which were defined as syncope and dizziness as well as the effect on blood pressure. The effect of midodrine on other symptoms was to be considered supportive.

It is important to note that the placebo and 2.5mg. subgroups were, of course, at constant doses throughout the double-blind phase but that the 5 and 10mg. group did not reach that dose of midodrine until visit 4 and therefore the visit 5 and 6 blood pressure and symptoms were assessed at that time.

The official endpoint for efficacy is defined by the sponsor in their study report included: 1)standing systolic blood pressure; 2) difference in the supine versus standing blood pressure and an aggregate of the two principal symptoms of syncope and dizziness. In addition, specific comparisons were employed: tests for linearity of the dose response 10mg. versus placebo; 5 and 10mg. doses together versus placebo and all midodrine doses together versus placebo.

In regards to symptoms, the frequency used in Study 11A included a zero measure for off and always a 1 for sometimes and 2 for never occurring. A 1 was added to each score to facilitate calculation of percentage change. The two key symptoms, syncope and dizziness, were evaluated separately and averaged together.

APPENDIX TABLE A1
IDENTIFICATION OF PATIENTS
IN
STUDY 11 AND 11A

DE#	STUDY	PTSS#	PT#	D4-6	IN#
1	21	068	777	777	01
2	21	066	777	777	01
3	11	001	301	2.5	15
4	11	002	302	10	15
5	11	003	303	0	15
6	11	004	304	5	15
7	11	006	305	5	15
8	11	005	306	0	15
9	11	007	307	2.5	15
10	11	008	308	10	15
11	11	011	309	5	08
12	21	777	310	2.5	08
13	11	012	312	0	08
14	11	016	313	10	01
15	11	017	314	5	01
16	11	018	315	0	01
17	11	019	316	2.5	01
18	11	009	321	2.5	15
19	21	010	322	5	15
20	21	031	325	0	26
21	11	036	329	2.5	14
22	11	037	330	0	14
23	11	051	341	2.5	14
24	11	039	343	10	14
25	21	020	333	0	01
26	21	067	334	5	01
27	21	070	336	2.5	01
28	21	091	373	10	38
29	21	092	374	5	38
30	21	096	377	2.5	01
31	21	013	311	10	08
32	11	021	317	10	19
33	11	041	333	0	22
34	21	057	345	5	44
35	21	053	337	2.5	14
36	11	038	331	5	14
37	21	056	777	777	44
38	21	058	346	10	44
39	11	040	332	10	14
40	21	054	344	0	14
41	21	069	355	10	01
42	21	093	375	2.5	38
43	21	094	376	0	38
44	21	061	349	5	02
45	21	131	410	0	02
46	21	062	350	10	02
47	21	133	409	10	02
48	21	063	351	2.5	02
49	21	064	352	0	02
50	21	071	359	5	14
51	21	076	362	10	40
52	21	027	324	10	15
53	21	032	326	2.5	26
54	21	046	337	10	13

TITLES: DE# (PATIENT DATA ENTRY #); PTSS # (PATIENT SINGLE BLIND #);
PT# (PATIENT DOUBLE BLIND #); D4-6 (DESIGNATED DOSE);
IN# (INVESTIGATOR #)

CODES: 11=STUDY 11; 21=STUDY 11A

N=104 (24 PATIENTS TREATED UNDER STUDY 11, 80 PATIENTS TREATED UNDER 11A)

APPENDIX TABLE A1

IDENTIFICATION OF PATIENTS IN STUDY 11 AND 11A

DE#	STUDY	PTSB#	PT#	D4-6	IN#
55	21	047	338	5	13
56	21	042	334	10	22
57	21	109	392	0	08
58	21	108	391	10	08
59	21	097	378	5	01
60	21	026	323	0	15
61	21	125	401	10	38
62	21	098	379	0	01
63	21	065	411	5	02
64	21	139	418	5	46
65	21	073	366	5	14
66	21	074	367	2.5	14
67	21	142	777	2.5	46
68	21	101	385	5	45
69	21	055	358	10	14
70	21	102	386	10	45
71	21	072	360	0	14
72	11	052	342	5	14
73	21	103	777	777	45
74	21	141	419	0	46
75	21	140	417	10	46
76	21	087	370	0	11
77	21	088	371	10	11
78	21	048	339	0	13
79	21	086	369	2.5	11
80	21	028	405	2.5	15
81	21	081	365	10.0	14
82	21	059	347	2.5	44
83	21	124	404	5	38
84	21	049	340	2.5	13
85	21	147	428	10	13
86	21	099	380	10.0	01
87	21	146	427	2.5	01
88	21	114	382	5.0	07
89	21	104	388	0	45
90	21	136	414	10.0	35
91	21	014	393	0	08
92	21	135	413	2.5	35
93	21	089	372	5	11
94	21	149	430	5	11
95	21	113	381	2.5	07
96	21	117	395	2.5	43
97	21	118	777	0	43
98	21	153	436	2.5	01
99	21	154	437	5	01
100	21	077	777	777	40
101	21	029	406	5	15
102	21	150	431	0	11
103	21	075	368	0	14
104	21	050	429	2.5	13

TITLES: DE# (PATIENT DATA ENTRY #); PTSB # (PATIENT SINGLE BLIND #),
PT# (PATIENT DOUBLE BLIND #); D4-6 (DESIGNATED DOSE);
IN# (INVESTIGATOR #)
CODES: 11=STUDY 11; 21=STUDY 11A
N=104 (24 PATIENTS TREATED UNDER STUDY 11, 80 PATIENTS TREATED UNDER 11A)

EXCLUSION OF PATIENTS:

Blood pressure data were not included in the analysis and no medication was taken at the study visit and all blood pressure measurements included were in a window of 35 minutes at 2.5 hours after dosing. Blood pressure readings taken in the sitting position were not used in the last visit analysis of standing blood pressures.

Patients evaluable for symptoms were those who complied with the medication dosing scheme during the preceeding week and had no concomitant events that could interfere with assessments. Tables C-2 and C-3 from the sponsor's report are now attached to detail the reasons the patients were excluded from the blood pressure and symptom analyses.

RESULTS:

The attached table which is from the sponsor's protocol lists with each of the 18 centers and the number of patients recruited at each of the centers. Note that 7 of the 18 centers did not meet protocol requirement of having at least 4 patients enrolled.

Attached is the sponsor's table 4 which details the demographic distribution specifically highlighting the diagnostic groups. Note that only 18% of the study population has the targeted indication plan by the sponsor for Shy-Drager syndrome.

TABLE 4
PATIENT DISTRIBUTION

	PBO RUN-IN	RANDOMIZED				TOTAL	
		0	2.5	5	10	N	(%)
TOTAL							
No. PTS	7	23	24	24	26	104	
No. MEN		12	13	13	15	53	(55%)
No. WOMEN		11	11	11	11	44	(45%)
MEAN AGE (YRS)		61	60	59	65	--	
DIAGNOSTIC GROUPS							
IOH		5	4	6	5	20	(21%)
Shy-Drager		3	6	1	7	17	(18%)
Parkinson's		5	6	6	5	22	(23%)
Diabetes		8	5	6	8	27	(28%)
Other		2	3	5	1	11	(11%)

PTS ENTERED DOUBLE BLIND = 97

APPENDIX TABLE C2

PATIENTS EXCLUDED FROM BLOOD PRESSURE EFFICACY ANALYSIS MIDODRINE STUDY 11 AND 11A

REASON	DE #
0 MG GROUP	
DROPOUT	25
CONCOMITANT EVENT	57
ADR	43
MISSED V5/ NONCOMPLIANCE (MEDS) V6	5
	91
2.5 MG GROUP	
DROPOUT	
ADR	90
	79 ***
	27
PROTOCOL VIOLATION	12 *
	95 **
V5 SITTING BP/ V6 NONCOMPLIANCE (MEDS	3
	53
5.0 MG GROUP	
DROPOUT	36
ADR	83
CONCOMITANT EVENT	
PROTOCOL VIOLATION	88 **
V5 OPTIONAL, V6 NON COMPLIANCE (MEDS)	7
FLORINEF DOSE CHANGE	63
10 MG GROUP	
DROPOUT	
ADR	31
CONCOMITANT EVENT	32
NON COMPLIANCE (MEDS)	58
	69
V5 FLORINEF DOSE CHANGE/ V6 ADR	70
TOTAL	22

N = 104 ENROLLED; 7 NOT RANDOMIZED; 22 UNEVALUABLE; 75 EVALUABLE PATIENTS

* DOSED DOUBLE BLIND MEDICATION DURING PLACEBO

** INCORRECT DOSING SEQUENCE

*** MEDICATION READJUSTED AND LATER RE-ENTERED

TITLES: DE# (PATIENT DATA ENTRY #)

APPENDIX TABLE C3

PATIENTS EXCLUDED FROM SYMPTOM ANALYSIS
MIDODRINE STUDY 11A

PLACEBO

REASON	DE#
VISIT 2	
MISSING 1 OR MORE QUESTIONS ONLY	
Q5.10	71
Q9	60,76
Q10	16
VISIT 3	
DROPOUT	25,57
MISSING 1 OR MORE QUESTIONS ONLY	
Q5.10	71
Q9,10	60
Q10	16
VISIT 4	
DROPOUT	25,57
CONCOMITANT EVENT	43
MISSING 1 OR MORE QUESTIONS ONLY	
Q5,9,10	71
Q9	76,78
Q10	16
VISIT 5	
DROPOUT	25,57
CONCOMITANT EVENT	43
MISSING 1 OR MORE QUESTIONS ONLY	
Q90	20,76
Q9,10	16,71
Q10	49
VISIT 6	
DROPOUT	25,57
CONCOMITANT EVENT	43
MISSING 1 OR MORE QUESTIONS ONLY	
Q9	20,45,60,74,76,78
Q10	16,71
VISIT 7	
DROPOUT	25,57
CONCOMITANT EVENT	43
MISSING 1 OR MORE QUESTIONS ONLY	
Q9	20,76
Q10	16,71

N=63 EVALUABLE PTS. ALSO EXCLUDED FROM ANALYSIS WERE 20 PTS. FROM STUDY 11, 7 PTS. NEVER RANDOMIZED, AND DE# 91, TREATED UNDER PROTOCOL 11A, ANSWERED SYMPTOMATOLOGY ON THE ORIGINAL FORM. 4 PTS. FROM STUDY 11 (DE# 14, 15, 16, 17) ANSWERED SYMPTOMATOLOGY ON THE REVISED FORM AND WERE INCLUDED IN THE SYMPTOM ANALYSIS.
TITLES: DE# (PATIENT DATA ENTRY #)
ABBREVIATIONS: ADR (ADVERSE DRUG REACTION); Q (QUESTION #)

APPENDIX TABLE C3

PATIENTS EXCLUDED FROM SYMPTOM ANALYSIS
MIDODRINE STUDY 11A

2.5 MG

REASON	DE#
VISIT 2	
PROTOCOL VIOLATION	12,95
MISSING 1 OR MORE QUESTIONS ONLY	
Q9,10	84
Q10	17
VISIT 3	
PROTOCOL VIOLATION	12,95
LOST TO FOLLOW-UP	27
DROP OUT - SUPINE HYPERTENSION	79
MISSING 1 OR MORE QUESTIONS ONLY	
Q9	17,84
Q10	98
VISIT 4	
PROTOCOL VIOLATION	12,95
LOST TO FOLLOW-UP	27
DROP OUT - SUPINE HYPERTENSION	79
DROP-OUT	96
MISSING 1 OR MORE QUESTIONS ONLY	
Q10	17,84
VISIT 5	
PROTOCOL VIOLATION	12,95
LOST TO FOLLOW-UP	27
DROP OUT - SUPINE HYPERTENSION	79
DROP OUT	96
MISSING 1 OR MORE QUESTIONS ONLY	
Q9	98
Q10	17,84
VISIT 6	
PROTOCOL VIOLATION	12,95
LOST TO FOLLOW-UP	27
DROP OUT - SUPINE HYPERTENSION	79
DROP OUT	96
20 LB. WT. LOSS	42
MISSING 1 OR MORE QUESTIONS ONLY	
Q9	98
Q10	17,35,84
VISIT 7	
PROTOCOL VIOLATION	12,95
LOST TO FOLLOW-UP	27
DROP OUT - SUPINE HYPERTENSION	79
DROP OUT	96
MISSING 1 OR MORE QUESTIONS ONLY	
Q9	98
Q10	17,84

N=63 EVALUABLE PTS. ALSO EXCLUDED FROM ANALYSIS WERE 20 PTS. FROM STUDY 11, 7 PTS. NEVER RANDOMIZED, AND DE# 91, TREATED UNDER PROTOCOL 11A, ANSWERED SYMPTOMATOLOGY ON THE ORIGINAL FORM. 4 PTS. FROM STUDY 11 (DE# 14, 15, 16, 17) ANSWERED SYMPTOMATOLOGY ON THE REVISED FORM AND WERE INCLUDED IN THE SYMPTOM ANALYSIS.
TITLES: DE# (PATIENT DATA ENTRY #)
ABBREVIATIONS: ADR (ADVERSE DRUG REACTION); Q (QUESTION #)

APPENDIX TABLE C3

PATIENTS EXCLUDED FROM SYMPTOM ANALYSIS
MIDODRINE STUDY 11A

5.0 MG

REASON	DE#
VISIT 2	
PROTOCOL VIOLATION	88
MISSING 1 OR MORE QUESTIONS ONLY	
Q5.9	93
Q7.10	65
Q9.10	19
Q10	15.44.63.68
VISIT 3	
PROTOCOL VIOLATION	88
MISSING 1 OR MORE QUESTIONS ONLY	
Q7.10	65
Q9	101
Q9.10	19
Q10	15.44.63.68
VISIT 4	
PROTOCOL VIOLATION	88
MISSING 1 OR MORE QUESTIONS ONLY	
Q7.10	65
Q9	83.93.101
Q9.10	19
Q10	15.44.63.68
VISIT 5	
PROTOCOL VIOLATION	88
FLORINEF DOSE CHANGE V4	63
MISSING 1 OR MORE QUESTIONS ONLY	
Q5	50
Q7.10	65
Q9	83.101
Q9.10	19
Q10	15.44.68
VISIT 6	
PROTOCOL VIOLATION	88
FLORINEF DOSE CHANGE VISIT 4	63
DROP OUT - SUPINE HYPERTENSION	83
MISSING 1 OR MORE QUESTIONS ONLY	
Q7.10	65
Q9	101
Q9.10	19
Q10	15.44.68
VISIT 7	
PROTOCOL VIOLATION	88
FLORINEF DOSE CHANGED VISIT 4	63
MISSING 1 OR MORE QUESTIONS ONLY	
Q7.10	65
Q9	101
Q9.10	19
Q10	15.44.68

N=63 EVALUABLE PTS. ALSO EXCLUDED FROM ANALYSIS WERE 20 PTS. FROM STUDY 11, 7 PTS. NEVER RANDOMIZED, AND DE# 91, TREATED UNDER PROTOCOL 11A, ANSWERED SYMPTOMATOLOGY ON THE ORIGINAL FORM. 4 PTS. FROM STUDY 11 (DE# 14, 15, 16, 17) ANSWERED SYMPTOMATOLOGY ON THE REVISED FORM AND WERE INCLUDED IN THE SYMPTOM ANALYSIS.
TITLES: DE# (PATIENT DATA ENTRY #)
ABBREVIATIONS: ADR (ADVERSE DRUG REACTION); Q (QUESTION #)

APPENDIX TABLE C3

PATIENTS EXCLUDED FROM SYMPTOM ANALYSIS
MIDODRINE STUDY 11A

10.0 MG

REASON	DE#
VISIT 2	
NON-COMPLAINT	69
MISSING 1 OR MORE QUESTIONS ONLY	
Q5	81
Q9	86
Q10	14,61,70
VISIT 3	
NON-COMPLAINT	69
MISSING 1 OR MORE QUESTIONS ONLY	
Q5	81
Q9	75,86
Q10	14,61,70
VISIT 4	
NON-COMPLAINT	69
DROP OUT - ADR	31
MISSING 1 OR MORE QUESTIONS ONLY	
Q9	77
Q10	14,61,70
VISIT 5	
NON-COMPLAINT	69
DROP OUT - ADR	31
DROPOUT	58
FLU	75
MISSING 1 OR MORE QUESTIONS ONLY	
Q8,10	61
Q9	77,86
Q10	14,70
VISIT 6	
NON-COMPLAINT	69
DROP OUT - ADR	31
DROPOUT	58,70
LOST TO FOLLOW-UP	14
FLORINEF DOSE CHANGE	52
MISSING 1 OR MORE QUESTIONS ONLY	
Q8,10	61
Q9	56,86
VISIT 7	
NON-COMPLAINT	69
DROP OUT - ADR	31
DROP OUT	58
MISSING 1 OR MORE QUESTIONS ONLY	
Q8,10	61
Q9	86
Q10	14,17

N=63 EVALUABLE PTS. ALSO EXCLUDED FROM ANALYSIS WERE 20 PTS. FROM STUDY 11, 7 PTS. NEVER RANDOMIZED, AND DE# 91, TREATED UNDER PROTOCOL 11A, ANSWERED SYMPTOMATOLOGY ON THE ORIGINAL FORM. 4 PTS. FROM STUDY 11 (DE# 14, 15, 16, 17) ANSWERED SYMPTOMATOLOGY ON THE REVISED FORM AND WERE INCLUDED IN THE SYMPTOM ANALYSIS.
TITLES: DE# (PATIENT DATA ENTRY #)
ABBREVIATIONS: ADR (ADVERSE DRUG REACTION); Q (QUESTION #)

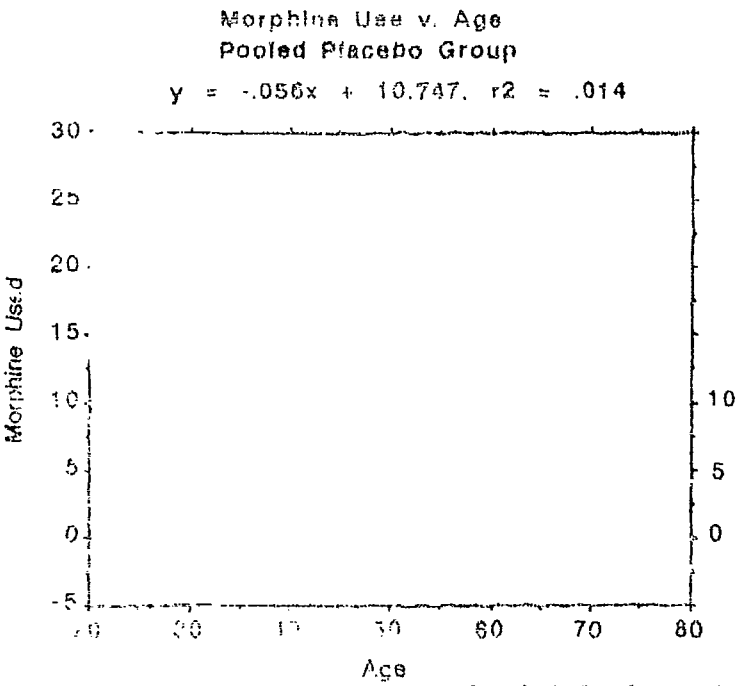
LIST OF INVESTIGATORS PARTICIPATING IN MIDODRINE STUDY 11 AND 11A

	INV#	NAME	INSTITUTION	#PTS
1.	01	JANKOVIC, J.	BAYLOR COLLEGE HOUSTON, TX	17
2.	02	KAUFMANN, H.	MT. SINAI MEDICAL CENTER NEW YORK, NY	7*
3.	07	STREETEN, D.	SUNY HEALTH SCIENCE CENTER SYRACUSE, NY	2
4.	08	BROWN, D.	ABBOTT NORTHWESTERN HOSPITAL MINNEAPOLIS, MN	7
5.	11	COGHLAN, C.H.	UNIV. OF ALABAMA AT BIRMINGHAM BIRMINGHAM, AL	6
6.	13	FOUAD-TARAZI, F.	THE CLEVELAND CLINIC FOUNDATION CLEVELAND, OH	6
7.	14	GILDEN, J.	THE CHICAGO MEDICAL SCHOOL VAMC NORTH CHICAGO CHICAGO, IL	16
8.	15	HINER, R.	MARSHFIELD CLINIC MARSHFIELD, WI	14
9.	19	PFIEFFER, M.	LEXINGTON VA MEDICAL CENTER LOUISVILLE, KY	1
10.	22	BRESLIN, D.	THE LAHEY CLINIC MEDICAL CENTER BURLINGTON, MA	2
11.	26	JONES, C.	UNIVERSITY OF UTAH MEDICAL CENTER SALT LAKE CITY, UT	2
12.	30	POSASH, L.	EAST ORANGE VA MEDICAL CENTER EAST ORANGE, NJ	2
13.	36	TIFFT, C.P.	BOSTON UNIV SCHOOL OF MEDICINE BOSTON, MA	2
14.	38	RUBIN, M.	N.Y. CORNELL MEDICAL CENTER NEW YORK, NY	6
15.	43	BERGENSTAL, R.	INTERNATIONAL DIABETES CENTER MINNEAPOLIS, MN	2
16.	44	CARROLL, J.R.	DOCTOR'S CLINIC RESEARCH CENTER VERO BEACH, FL	4
17.	45	GOETZ, C.	RUSH PRESBYTERIAN HOSPITAL CHICAGO, IL	4
18.	46	LEVY, R.	ST. THOMAS MEDICAL CENTER AKRON, OH	4
TOTAL				104

N = 104; (*) ONE PATIENT'S CASE REPORT FORM RECEIVED AFTER DATA BASE CLOSED AND ANALYSIS UNDERWAY

partial regression (as opposed to fitting all adjustments "en-bloc") going from the most independent variables (presumably least confounded) toward the more highly confounded ones was then selected.

Using this strategy the first adjustment was performed using the placebo group and regressing age against MS usage:



(* each patient has a value at 9,15 & 21 hours)

As may be seen, there is a small age effect in the trials, which accounts for less than 1-2% of the variance, and corresponds to a hypothetical 7.5 mg, q6hr morphine demand for a 20 year old declining to a 5 mg/q6hr morphine demand for an eighty year-old. This finding is consistent with altered pharmacodynamics for opioids with aging, the magnitude of the adjustment is small.

The values for morphine use for the entire data-set were thus adjusted to the grand-mean for age, subtracting 0.056 mg/q6hr for every year below the mean age of 46 and adding 0.056 mg/q6hr for every year above age 46 for every data-point. This adjustment was then rechecked against the original variable and the adjustment was found to have collapsed the age effect as intended.

Checking the effect of the adjustment on the data, the effects are barely perceptible.

The other reasons for orthostatic hypotension in 11 patients included amyloidosis, peripheral neuropathy, multiple sclerosis, and mitral valve prolapse.

There were 104 patients enrolled in this study (an additional 1 patient did not arrive in time and was excluded) and 97 patients were randomized to the double-blind phase of the study. Eighty-three completed the study. The attached table from the sponsor details the reasons for non-study completion by dose group.

EFFICACY:

Pre-study blood pressure profile (visit 1) for all patients eligible for the last visit analysis is presented in the accompanying table from the sponsor's report. Standing systolic blood pressure (pooled for all groups).

LAST VISIT ANALYSIS:

The accompanying table 6, details the effect of midodrine on standing systolic blood pressure in all patients by dosing group. Standing systolic blood pressure was elevated by 9, 4, 22mm Hg. for the 2.5, 5 and 10mg groups respectively. The only significant effect was at the 10mg. group versus placebo. When the 5 and 10 and the 2.5 5 and 10 groups were combined, statistical significance at the 05 level was reached compared to the 001 level for the 10mg. group itself. Table 7 details the linear dose response relationships at visits 4, 5, 6 and 7 for each of the groups. Blood pressure response showed a decrease over time (28mm Hg at visit 4 versus 22 at visit 5 or 6).

DIFFERENCES IN SUPINE TO STANDING BLOOD PRESSURE:

The fall in the blood pressure standing as compared to supine was 67 pre-dose and 58 post-dose in the 10mg. group at visit 7. This reduction, even at the 10mg. dose, orthostatic hypotension was not statistically significant. The sponsor argues that the level of standing systolic blood pressure which was higher for the 10mg. group may be sufficient to effect symptoms and may be a more meaningful parameter of efficacy than the actual change in the postural fall in systolic blood pressure itself. The actual data regarding these differences in supine and standing is shown in tables 8 and 9 which are attached and it is important to note that for 2.5 and 5mg. midodrine dosing groups there is no change at all. Standing and supine diastolic blood pressure at the last visit is shown in Figure 2 and demonstrates no significant effect. There was no important effect on pulse rate.

APPENDIX TABLE B7
STUDY COMPLETION SUMMARY
MIDODRINE STUDY 11 AND 11A

COMPLETION STATUS	PLACEBO n	PLACEBO %	0 mg n	0 mg %	2.5 mg n	2.5 mg %	5 mg n	5 mg %	10 mg n	10 mg %	TOTAL n	TOTAL %
(1) STUDY COMPLETED	6	6	20	80 ***	20	83	22	92	21	81	85	80
(2) INSUFFICIENT THERAPEUTIC RESPONSE	0	0	0	0	0	0	0	0	1	4 *	1	1
(3) ADR	2	29	1	4	3	13 **	1	4	2	7 ***	9	8
(4) PROTOCOL VIOLATION	1	14	0	0	1	4	0	0	1	4	3	3
(5) INTERCURRENT ILLNESS (NR)	1	14	1	4	0	0	0	0	1	4	3	3
(6) OTHER	3	43	1	4	0	0	1	4	0	0	5	5
TOTAL (N=106)	7	100	25	100	24	100	24	100	26	100	106	100

* 1 PATIENT 10 MG GROUP CLASSIFIED AS 2,3,4 GROUPED WITH 2

** 1 PATIENT 2.5 MG GROUP CLASSIFIED AS 3,4 GROUPED W/ 1 PATIENT PBO NON-NR CLASSIFIED AS 3,4 GROUPED WITH 3

*** DECIMAL ROUNDING TO SUM TO 100%

TABLE 1

PATIENT SYSTOLIC BLOOD PRESSURES (mm Hg) AT STUDY INITIATION VISIT 1

MIDODRINE STUDY 11 AND 11A

VARIABLE	N	MEAN	S.D.	MIN	MAX
PRE STANDING	86	97	24	40	156
POST STANDING	82	100	26	50	171
PRE SUPINE	87	141	24	90	191
POST SUPINE	83	143	25	92	191
CHANGE (STANDING)	82	4	17	-28	60
% CHANGE (STANDING)	82	6	23	-36	130
DELTA PRE	86	44	27	2	117
DELTA POST	82	43	27	-3	110
DELTA OF DELTAS	82	-2	16	-54	34

PRE (PRE PLACEBO), POST (1 HR POST PLACEBO)
CHANGE = POST MINUS PRE
% CHANGE = POST MINUS PRE/PRE
DELTA = SUPINE MINUS STANDING
DELTA OF DELTAS = DELTA POST MINUS DELTA PRE

TABLE 6

EFFECT OF MIDODRINE ON STANDING SYSTOLIC BLOOD PRESSURE (mm Hg) IN PATIENTS WITH ORTHOSTATIC HYPOTENSION

MIDODRINE STUDY 11 AND 11A

		PRE-DOSE		POST-DOSE		CHANGE (POST-PRE)		% CHANGE (POST-PRE/PRE)	
GROUP	N	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
0	18	105	5	108	5	3	4	4	4
2.5	17	106	8	114	6	9	3	14 (*)	6
5	19	100	7	104	8	4	3	5	4
10	21	94	7	116	7	22 ***	4	28 ***	6

LAST VISIT (VISIT 7) ANALYSIS; MEASUREMENT TAKEN 1 HR POST DOSE
P VALUES BASED ON ONE TAILED T-TEST OR F-TEST VS. PLACEBO;
(*) P < 0.1; *** P< 0.001

CHANGE AND % CHANGE:

LINEAR DOSE RESPONSE (p<0.001)
5 AND 10 MG (P<.05)
2.5, 5 AND 10 MG (P<.05)

TABLE 7

STANDING SYSTOLIC BLOOD PRESSURE (mm Hg) AT DESIGNATED DOSE

MIDODRINE STUDY 11 AND 11A

	PRE				POST				CHANGE				P VALUES						% CHANGE				P VALUES					
VISIT	0	2.5	5	10	0	2.5	5	10	0	2.5	5	10	LIN	5+10	ALL	2.5	5	10	0	2.5	5	10	LIN	5+10	ALL	2.5	5	10
VISIT 4																												
MEAN	97	101	97	104	102	120	103	132	5	19	6	28	0.003	0.031	0.019	0.046	0.463	0.004	6	29	8	35	0.028	0.076	0.041	0.064	0.406	0.005
SEM	5	8	5	6	5	7	5	6	3	7	4	6							4	13	4	5						
N	20	18	20	22	20	18	20	22	20	18	20	22							20	18	20	22						
VISIT 5																												
MEAN	102	106	91	108	107	112	99	132	5	6	8	24	0.001	0.020	0.010	0.307	0.251	0.007	5	12	9	26	0.006	0.040	0.056	0.192	0.314	0.005
SEM	5	9	6	7	6	6	7	8	4	3	3	6							4	6	3	7						
N	17	17	16	18	17	17	16	18	17	17	16	18							17	17	16	18						
VISIT 6																												
MEAN	104	104	103	98	103	114	107	115	-1	10	4	17	0.003	0.012	0.009	0.030	0.175	0.001	-0.3	12	5	19	0.004	0.015	0.012	0.035	0.205	0.001
SEM	6	8	8	8	6	7	9	9	4	3	4	4							4	4	4	5						
N	13	13	16	16	13	13	16	16	13	13	16	16							13	13	16	16						
VISIT 7 (LAST)																												
MEAN	105	106	100	94	108	114	104	116	3	9	4	22	0.0003	0.014	0.025	0.131	0.377	0.0003	4	14	5	28	0.001	0.020	0.025	0.081	0.371	0.001
SEM	5	8	7	7	5	6	8	7	4	3	3	4							4	6	4	6						
N	18	17	19	21	18	17	19	21	18	17	19	21							18	17	19	21						

TITLES: PRE (PRE DOSE); POST (1 HR POST DOSE); CHANGE (POST-PRE); % CHANGE (POST-PRE/PRE); P VALUES (BASED ON ONE TAILED T TEST OR F-TEST);
LIN (LINEAR DOSE RESPONSE); 5+10 (5 AND 10 MG DOSES TOGETHER VS. PLACEBO); ALL (2.5, 5 AND 10 MG DOSES TOGETHER VS. PLACEBO); 2.5, 5 AND 10 (EACH DOSE VS PLACEBO).

TABLE 8

EFFECT OF MIDODRINE ON THE SUPINE TO STANDING FALL IN BP (mm Hg) IN PATIENTS WITH ORTHOSTATIC HYPOTENSION

MIDODRINE STUDY 11 AND 11A

		PRE-DOSE DELTA		POST-DOSE DELTA		CHANGE DELTA OF DELTAS		% CHANGE DELTA OF DELTAS	
GROUP	N	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
0	18	33	8	28	7	-5	4	-3	20
2.5	17	37	9	36	8	-2	3	14	17
5	19	47	7	45	8	-2	3	3	14
10	21	67	8	58	8	-9	5	-20	10

LAST VISIT (VISIT 7) ANALYSIS; MEASUREMENT TAKEN 1 HR POST DOSE
DELTA (SUPINE MINUS STANDING SYSTOLIC BLOOD PRESSURE).

TABLE 9

SUPINE TO STANDING DROP IN BLOOD PRESSURES (mm Hg) AT DESIGNATED DOSE
"DELTA OF DELTAS"
MIDODRINE STUDY 11 AND 11A

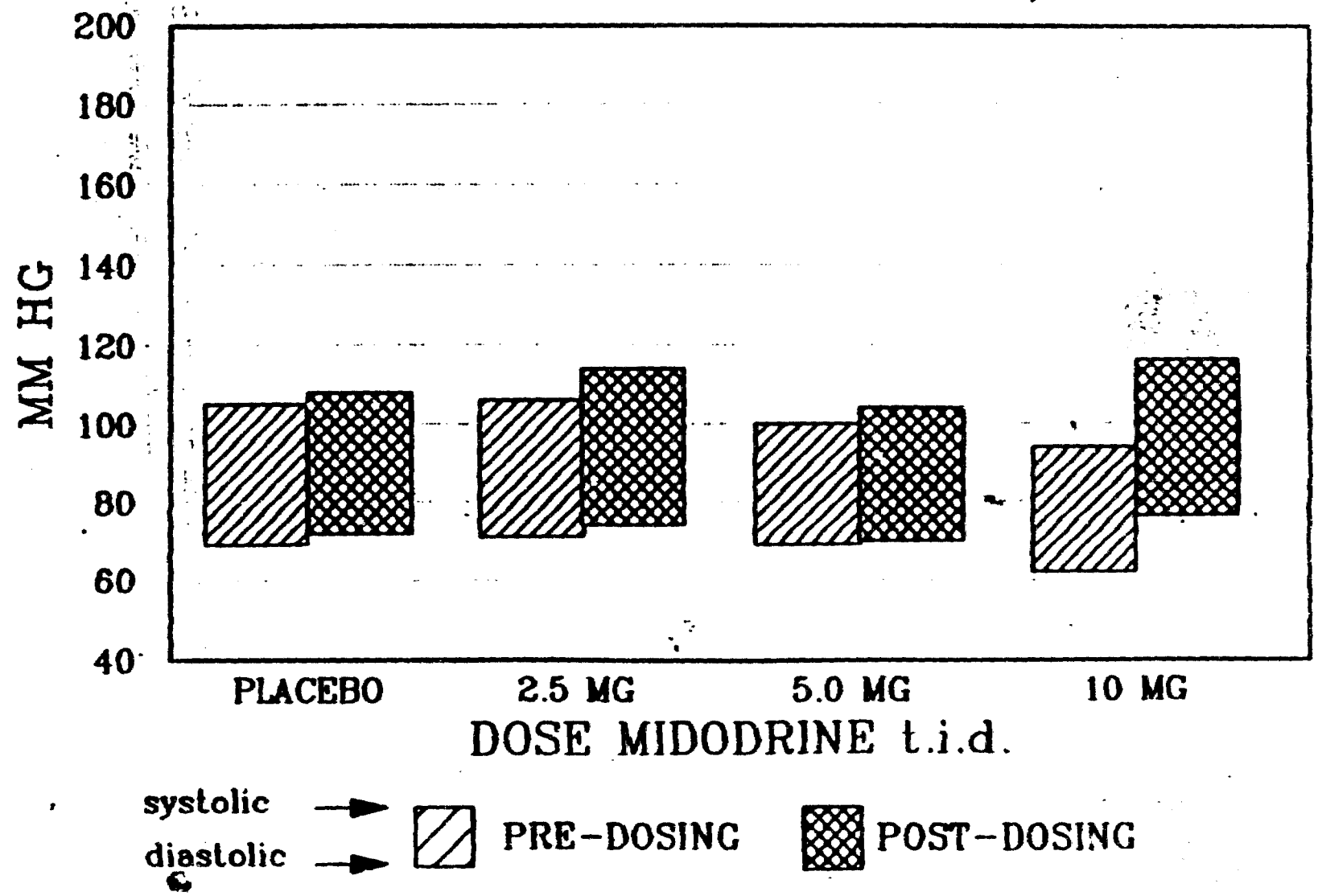
	PRE DELTAS				POST DELTA				CHANGE DELTA OF DELTAS				P VALUES CHANGE						% CHANGE DELTA OF DELTAS				P VALUES % CHANGE					
	0	2.5	5	10	0	2.5	5	10	0	2.5	5	10	LIN	5+10	ALL	2.5	5	10	0	2.5	5	10	LIN	5+10	ALL	2.5	5	10
VISIT 4																												
MEAN	38	39	43	52	30	28	41	37	-8	-11	-2	-15	0.136	0.440	0.386	0.308	0.159	0.099	-37	-25	-8	-29	0.356	0.170	0.188	0.300	0.102	0.354
SEM	8	7	6	7	8	8	6	6	4	5	3	4							19	23	11	9						
N	20	18	20	22	20	18	20	22	20	18	20	22							20	18	20	22						
VISIT 5																												
MEAN	34	38	45	51	31	34	41	47	-3	-3	-4	-4	0.451	0.443	0.460	0.499	0.408	0.468	50	15	-8	-13	0.076	0.057	0.073	0.275	0.153	0.138
SEM	8	9	7	6	8	8	8	10	3	3	3	8							54	19	6	16						
N	17	17	16	18	17	17	16	18	17	17	16	18							17	17	15	16						
VISIT 6																												
MEAN	32	34	44	64	29	32	44	58	-2	-3	-1	-6	0.296	0.428	0.429	0.463	0.425	0.292	10	-7	6	-18	0.161	0.231	0.217	0.292	0.428	0.132
SEM	9	8	8	10	8	8	9	11	5	5	4	5							27	30	17	13						
N	13	13	16	16	13	13	16	16	13	13	16	16							12	13	16	16						
VISIT 7																												
MEAN	33	37	47	67	28	36	45	58	-5	-2	-2	-9	0.186	0.495	0.483	0.271	0.258	0.246	-3	14	3	-20	0.135	0.385	0.456	0.223	0.399	0.218
SEM	8	9	7	8	7	8	8	8	4	3	3	5							20	17	14	10						
N	18	17	19	21	18	17	19	21	18	17	19	21							18	17	19	21						

TITLES: SYSTOLIC BLOOD PRESSURES PRE (PRE DOSE); POST (1HR POST DOSE); CHANGE (POST-PRE); % CHANGE ((POST-PRE)/PRE);
P VALUES BASED ON ONE TAILED T-TEST OR F-TEST.
LIN (LINEAR DOSE RESPONSE), 5+10 (5 AND 10 MG DOSES TOGETHER VS PLACEBO); ALL (2.5, 5 AND 10 MG DOSES TOGETHER VS PLACEBO); 2.5, 5 AND 10 (EACH DOSE VS PLACEBO)

FIGURE 2

EFFECT ON STANDING BP

MIDODRINE DOUBLE BLIND STUDY 11, 11A



98

CHANGES IN SYMPTOMATOLOGY:

The principal endpoint for symptoms were syncope and dizziness. Table 13 attached demonstrate that the only improvement in these symptoms (using the sponsor's definition and analysis techniques) was for the 10mg. midodrine dose when combining syncope and dizziness. However, table 14A demonstrates for syncope alone which is a much more important symptom in this reviewer's mind, there appears to be no statistically significant effect at any dose when using a change rather than a percent change. Table 14B adds additional symptoms. Note that in general all the other symptoms listed by the sponsor using even the percent change mode of analysis details no supportive information for the effectiveness of midodrine. The FDA biostatistics group must look at these statistical analyses carefully since this reviewer believes that they may be potentially misleading in light of the use of only a one tailed analysis and the nature of looking at change of changes.

GLOBAL EVALUATIONS:

The investigator obtained weekly global evaluations and the results are presented in table 16. There was no statistical significant improvement using the global evaluation for any of the midodrine groups. The lack of differentiation the sponsor argues that the investigators did not focus on the parameters which were of prime importance to the patients. When patient's global impression rather than investigator's global impression was used, statistical significance was demonstrated at the 2.5 and 10mg. groups.

SAFETY:

The overall adverse drug reaction rate is demonstrated in table 17 from the sponsor's report.

TABLE 17
OVERALL ADR REACTION RATE
DOUBLE BLIND PHASE

RANDOMIZED DOSE GROUP	NO. PTS WITH 1 OR > ADRS NO. TREATED (N/TOTAL N)	(%)
0	5/23	22%
2.5	9/24	38%
5	2/24	8%
10	9/26	35%
TOTAL(2.5-10)	20/74	27%

TABLE 13

EFFECT OF MIDODRINE ON THE "KEY SYNCOPAL SYMPTOMS" (SYNCOPE AND DIZZINESS/LIGHTHEADEDNESS) IN PATIENTS WITH ORTHOSTATIC HYPOTENSION

MIDODRINE STUDY 11A

		VISIT 1		VISIT 7		CHANGE VISIT(7-1)		% CHANGE VISIT(7-1)	
GROUP	N	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
0	14	2.2	0.1	2.6	0.2	0.36	0.11	17	5
2.5	14	1.9	0.1	2.4	0.2	0.46	0.16	30	12
5	17	1.8	0.1	2.3	0.2	0.56	0.16	38	14
10	18	1.6	0.1	2.3	0.1	0.67	0.13	53 *	13

LAST VISIT (VISIT 7) ANALYSIS; SYMPTOM RESPONSES WERE CODED AS:
SYNCOPE (0=SEVERAL TIMES WEEKLY; 1=< 1 TIME WEEKLY; 2=NEVER)
DIZZINESS (0=OFTEN; 1=SOMETIMES; 2=NEVER).
A ONE WAS ADDED TO EACH SCORE FOR PURPOSES OF ANALYSIS.
P VALUES BASED ON ONE TAILED T-TEST OR F-TEST VS. PLACEBO; * P<.05

% CHANGE: LINEAR DOSE RESPONSE (P<.05)
5 AND 10 MG (P<.05)
2.5, 5 AND 10 MG (P<.10)

TABLE 14a

SYMPTOMATOLOGY: LAST VISIT ANALYSIS
MIDODRINE STUDY 11A

SYMPTOM	VISIT 1				VISIT 7				CHANGE				P VALUES					
	PBO	2.5	5	10	PBO	2.5	5	10	PBO	2.5	5	10	LIN	5+10	ALL	2.5	5	10
KEY SYNC. SYM (4+1)	2.2	1.9	1.8	1.6	2.6	2.4	2.3	2.3	0.36	0.46	0.56	0.67	0.120	0.164	0.242	0.623	0.334	0.135
SEM	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.11	0.16	0.17	0.13						
N	14	14	17	18	14	14	17	18	14	14	17	18						
DIZZINESS (1)	1.9	1.6	1.3	1.2	2.3	2	2.1	1.9	0.43	0.36	0.77	0.67	0.109	0.110	0.228	0.399	0.104	0.366
SEM	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.20	0.20	0.20	0.14						
N	14	14	17	18	14	14	17	18	14	14	17	18						
WEAK/FATIGUE (2)	1.5	1.6	1.4	1.3	1.7	2	1.9	1.7	0.21	0.43	0.59	0.39	0.263	0.107	0.115	0.208	0.070	0.481
SEM	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1	0.16	0.17	0.21	0.14						
N	14	14	17	18	14	14	17	18	14	14	17	18						
BLURRED VISION (3)	2.3	2.1	1.7	1.9	2.4	2.6	2.1	2.4	0.07	0.5	0.41	0.56	0.080	0.057	0.048	0.084	0.125	0.100
SEM	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.17	0.2	0.23	0.2						
N	14	14	17	18	14	14	17	18	14	14	17	18						
FAINTING/FALLS (4)	2.6	2.2	2.2	1.9	2.9	2.8	2.6	2.6	0.29	0.57	0.35	0.67	0.108	0.163	0.133	0.147	0.398	0.140
SEM	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.13	0.2	0.19	0.18						
N	14	14	17	18	14	14	17	18	14	14	17	18						
ENERGY LEVEL (5)	1.7	1.4	1.4	1.3	2.1	2.4	2.2	2.4	0.39	0.93	0.76	1.17	0.013	0.019	0.018	0.050	0.114	0.007
SEM	0.2	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.21	.20	0.22	.22						
N	13	14	17	18	13	14	17	18	13	14	17	18						

SYMPTOM RESPONSES WERE CODED FROM 0=OFTEN TO 3=NEVER FROM THE CASE REPORT FORM. HIGHER SCORES INDICATE LESS FREQUENCY OF SYMPTOM.

A ONE WAS ADDED TO EACH SCORE FOR PURPOSES OF ANALYSIS.

P VALUES (BASED ON ONE TAILED T-TEST OR F-TEST); LIN (LINEAR DOSE RESPONSE); 5+10 (5 AND 10 MG DOSES TOGETHER);

ALL (2.5, 5 AND 10 MG DOSES TOGETHER); 2.5, 5 AND 10 (EACH DOSE GROUP VS PLACEBO).

TABLE 14a

SYMPTOMATOLOGY: LAST VISIT ANALYSIS
MIDODRINE STUDY 11A

	VISIT 1				VISIT 7				% CHANGE				P VALUES					
SYMPTOM	PBO	2.5	5	10	PBO	2.5	5	10	PBO	2.5	5	10	LIN	5+10	ALL	2.5	5	10
KEY SYNC. SYM (4+1)	2.2	1.9	1.8	1.6	2.6	2.4	2.3	2.3	17	30	38	53	0.016	0.031	0.053	0.225	0.113	0.018
SEM	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1	5	12	14	13						
N	14	14	17	18	14	14	17	18	14	14	17	18						
DIZZINESS (1)	1.9	1.6	1.3	1.2	2.3	2	2.1	1.9	29	32	74	67	0.031	0.028	0.082	0.444	0.035	0.059
SEM	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1	15	17	20	14						
N	14	14	17	18	14	14	17	18	14	14	17	18						
WEAK/FATIGUE (2)	1.5	1.6	1.4	1.3	1.7	2	1.9	1.7	18	32	59	39	0.167	0.069	0.102	0.230	0.050	0.129
SEM	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.1	11	15	21	14						
N	14	14	17	18	14	14	17	18	14	14	17	18						
BLURRED VISION (3)	2.3	2.1	1.7	1.9	2.4	2.6	2.1	2.4	8	43	41	47	0.095	0.059	0.054	0.103	0.104	0.066
SEM	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	10	20	20	18						
N	14	14	17	18	14	14	17	18	14	14	17	18						
FAINTING/FALLS (4)	2.6	2.2	2.2	1.9	2.9	2.8	2.6	2.6	14	37	24	51	0.046	0.090	0.083	0.134	0.317	0.030
SEM	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2	6	15	14	15						
N	14	14	17	18	14	14	17	18	14	14	17	18						
ENERGY LEVEL (5)	1.7	1.4	1.4	1.3	2.1	2.4	2.2	2.4	32	75	74	108	0.007	0.013	0.017	0.081	0.079	0.005
SEM	0.2	0.1	0.1	0.1	0.2	0.2	0.2	0.2	17	20	19	21						
N	13	14	17	18	13	14	17	18	13	14	17	18						

SYMPTOM RESPONSES WERE CODED FROM 0=OFTEN TO 3=NEVER FROM THE CASE REPORT FORM. HIGHER SCORES INDICATE LESS FREQUENCY OF SYMPTOM.

A ONE WAS ADDED TO EACH SCORE FOR PURPOSES OF ANALYSIS.

P VALUES (BASED ON ONE TAILED T-TEST OR F-TEST); LIN (LINEAR DOSE RESPONSE); 5+10 (5 AND 10 MG DOSES TOGETHER);

ALL (2.5, 5 AND 10 MG DOSES TOGETHER); 2.5, 5 AND 10 (EACH DOSE GROUP VS PLACEBO).

TABLE 14b

SYMPTOMATOLOGY: LAST VISIT ANALYSIS
MIDODRINE STUDY 11A

SYMPTOM	VISIT 1				VISIT 7				CHANGE				P VALUES					
	PBO	2.5	5	10	PBO	2.5	5	10	PBO	2.5	5	10	LIN	5+10	ALL	2.5	5	10
STANDING (6)	2.2	1.7	1.8	1.7	2.4	2.3	2.2	1.8	0.14	0.57	0.41	0.11	0.295	0.323	0.156	0.036	0.113	0.908
SEM	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.19	0.25						
N	14	14	17	18	14	14	17	18	14	14	17	18						
WALKING (7)	2.6	2.4	2.1	1.9	2.7	2.2	2.2	2	0.14	-0.1	0.06	0.11	0.399	0.393	0.251		0.306	0.911
SEM	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2	0.1	0.1	0.1	0.2						
N	14	14	16	18	14	14	16	18	13	14	16	18						
DEPRESSION (8)	2.4	2.4	2.1	2.2	2.4	2.5	2.3	2.6	0	0.14	0.18	0.35	0.026	0.048	0.070	0.163	0.176	0.017
SEM	0.2	0.1	0.1	0.1	0.2	0.1	0.2	0.1	0.10	0.10	0.15	0.12						
N	14	14	17	17	14	14	17	17	14	14	17	17						
WORST SYMPTOM TIME (9)	1.6	1.8	1.5	1.4	1.8	1.8	1.2	1.3	0.25	-.08	-.31	-.06						
SEM	0.3	0.3	0.2	0.2	0.3	0.3	0.2	0.2	0.32	0.34	0.17	0.18						
N	12	13	13	17	12	13	13	17	12	13	13	17						
ACTIVITY IMPROVEMENT (10)	1.9	1.8	1.9	1.9	2.3	2.5	2.5	2.5	0.42	0.67	0.58	0.6						
SEM	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.23	0.26	0.19	0.21						
N	12	12	12	15	12	12	12	15	12	12	12	15						

SYMPTOM RESPONSES WERE CODED FROM 0=OFTEN TO 3=NEVER FROM THE CASE REPORT FORM. HIGHER SCORES INDICATE LESS FREQUENCY OF SYMPTOM.

A ONE WAS ADDED TO EACH SCORE FOR PURPOSES OF ANALYSIS.

P VALUES (BASED ON ONE TAILED T-TEST OR F-TEST); LIN (LINEAR DOSE RESPONSE); 5+10 (5 AND 10 MG DOSES TOGETHER);

ALL (2.5, 5 AND 10 MG DOSES TOGETHER); 2.5, 5 and 10 (EACH DOSE GROUP VS PLACEBO).

TABLE 14b

SYMPTOMATOLOGY: LAST VISIT ANALYSIS
MIDODRINE STUDY 11A

	VISIT 1				VISIT 7				% CHANGE				P VALUES					
SYMPTOM	PBO	2.5	5	10	PBO	2.5	5	10	PBO	2.5	5	10	LIN	5+10	ALL	2.5	5	10
STANDING (6)	2.2	1.7	1.8	1.7	2.4	2.3	2.2	1.8	7	43	36	25	0.335	0.130	0.085	0.043	0.056	0.183
SEM	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	5	19	17	19						
N	14	14	17	18	14	14	17	18	14	14	17	18						
WALKING (7)	2.6	2.4	2.1	1.9	2.7	2.2	2.2	2	12	-5	3	26	0.107	0.428	0.391		0.181	0.246
SEM	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2	9	3	3	18						
N	14	14	16	18	14	14	16	18	14	14	16	18						
DEPRESSION (8)	2.4	2.4	2.1	2.2	2.4	2.5	2.3	2.6	1	7	13	21	0.023	0.041	0.074	0.187	0.126	0.018
SEM	0.2	0.1	0.1	0.1	0.2	0.1	0.2	0.1	4	5	9	7						
N	14	14	17	17	14	14	17	17	14	14	17	17						
WORST SYMPTOM TIME (9)	1.6	1.8	1.5	1.4	1.8	1.8	1.2	1.3	1	7	17	24						
SEM	0.3	0.3	0.2	0.2	0.3	0.3	0.2	0.2	5	5	11	8						
N	12	13	13	17	12	13	13	17	12	13	13	17						
ACTIVITY IMPROVEMENT (10)	1.9	1.8	1.9	1.9	2.3	2.5	2.5	2.5	29	46	38	40						
SEM	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	18	19	16	16						
N	12	12	12	15	12	12	12	15	12	12	12	15						

SYMPTOM RESPONSES WERE CODED FROM 0=OFTEN TO 3=NEVER FROM THE CASE REPORT FORM. HIGHER SCORES INDICATE LESS FREQUENCY OF SYMPTOM.
A ONE WAS ADDED TO EACH SCORE FOR PURPOSES OF ANALYSIS.

P VALUES (BASED ON ONE TAILED T-TEST OR F-TEST); LIN (LINEAR DOSE RESPONSE); 5+10 (5 AND 10 MG DOSES TOGETHER);
ALL (2.5, 5 AND 10 MG DOSES TOGETHER); 2.5, 5 AND 10 (EACH DOSE VS PLACEBO).

Using this data set, serum fentanyl level was then regressed against patient weight, lean body mass, ideal body mass, surface area, body mass index, and total body water. All regressions were significant, but no derived measure was sufficiently better than weight in kilos to warrent their increased complexity and weight was used in subsequent calculations. The sponsor did a similar regression using the data from the Stanski BA study in which fentanyl clearance was measured directly. The relationships they observed are:

Stanski BA study
IV Fentanyl
Clearance v. Demographic Variables

Variable	F Value	R-Square	p-Value
Weight	4.561	.0559	.0359
Height	5.025	.0491	.0279
Surface Area M sq.	5.666	.0685	.0198
Lean body Mass (Peck)	5.216	.0634	.0251
Age	0.000	0.000	.999
Body Mass Index	.922	.0118	.3398
Ideal Body Weight	5.171	.0629	.0258
Lean Body Mass (H20)	5.368	.0652	.0232

The scatterplots for each TTS size by body weight are as shown:

TABLE 16

INVESTIGATOR AND PATIENT GLOBAL ASSESSMENTS OF THERAPEUTIC RESPONSE
MIDODRINE STUDY 11A

	INVESTIGATOR WEEKLY GLOBAL ASSESSMENTS																		END ASSESSMENT					
	VISIT 2			VISIT 3			VISIT 4			VISIT 5			VISIT 6			VISIT 7			INVESTIGATOR			PATIENT		
DOSE	IMPROVED			IMPROVED			IMPROVED			IMPROVED			IMPROVED			IMPROVED			IMPROVED			BETTER		
GROUP	TOTAL	N	%	TOTAL	N	%	TOTAL	N	%	TOTAL	N	%	TOTAL	N	%	TOTAL	N	%	TOTAL	N	%	TOTAL	N	%
0	16	3	19	14	7	50	13	5	39	13	6	46	13	6	46	13	6	46	13	8	62	13	5	39
2.5	16	4	25	14	6	43	13	9	69	13	10	77	12	9	75	13	10	77	13	10	77	13	10	77*
5	17	3	18	17	5	29	17	7	41	15	4	27	15	7	47	16	7	44	16	9	56	16	8	50
10	19	4	21	19	12	63	17	11	65	16	9	56	15	10	67	17	10	59	17	11	65	17	12	71*

WEEKLY GLOBALS: INVESTIGATOR'S GLOBAL ASSESSMENT OF PATIENT'S SYMPTOMS IN COMPARISON TO V1: IMPROVED (YES/NO)

END PATIENT GLOBAL: PATIENT'S GLOBAL IMPRESSION OF THERAPEUTIC RESPONSE - I FEEL BETTER (YES/NO)

END INVESTIGATOR GLOBAL: INVESTIGATOR'S OVERALL IMPRESSION OF THERAPEUTIC RESPONSE - PATIENT'S CONDITION HAS IMPROVED (YES/NO)

END GLOBALS BASED ON EVALUABILITY CODE FOR VISIT 7 ANALYSIS

* P<0.05 (ONE-TAILED TEST VS. PLACEBO) BASED ON A STANDARD NORMAL TEST ON THE LOGISTIC REGRESSION MODEL PARAMETERS

The specific ADR's are detailed in table 18 as well as compared to placebo in table 19.

TABLE 18
TREATMENT RELATED SIDE EFFECTS

REACTION	INCIDENCE N (%) PBO (N=104)	MIDO (N=74)
PRURITUS (SCALP)	2 (2%)	7 (9%)
SUPINE HYPERTENSION	1 (1%)	6 (8%)
TINGLING (SCALP)	0 (0%)	3 (4%)
URIN URGE	0 (0%)	3 (4%)
HEADACHE	1 (1%)	2 (3%)
PRURITUS	1 (1%)	1 (1%)
TINGLING	0 (0%)	1 (1%)
URINARY FREQUENCY	0 (0%)	1 (1%)
GI DISTRESS	1 (1%)	1 (1%)
NAUSEA	1 (1%)	1 (1%)
BACKACHE	0 (0%)	1 (1%)
CANKER SORE	0 (0%)	1 (1%)
FLUSHING	0 (0%)	1 (1%)
HEAD, FULLNESS	0 (0%)	1 (1%)
ANXIETY	0 (0%)	1 (1%)
FATIGUE	2 (2%)	0 (0%)
SWEATING	1 (1%)	0 (0%)
ALTERED MENSTRUAL CYCLE	1 (1%)	0 (0%)
HOT LEFT FACE	1 (1%)	0 (0%)
FEELS WARMER	1 (1%)	0 (0%)
DIZZINESS/WEAKNESS/ MALAISE	1 (1%)	0 (0%)
COLD LEGS	1 (1%)	0 (0%)
ATRIAL FIB	1 (1%)	0 (0%)

Adverse effects likely due to midodrine include: pruritus, supine hypertension (8% vs. 1%), scalp tingling, urinary urgency and headache.

TABLE 19

ADVERSE DRUG REACTIONS (MIDODRINE AND PLACEBO)
FREQUENCY AND RATE
MIDODRINE STUDY 11 AND 11A

BODY SYSTEM	EVENT	PLACEBO TOTAL		MIDODRINE TOTAL	
		NR	R	NR	R
BODY	HEADACHE	1(1%)	1(1%)	0(0%)	2(3%)
CV	HYPERTENS SUPINE	0(0%)	1(1%)	0(0%)	6(8%)
	FIBRILLAT ATR	0(0%)	1(1%)	0(0%)	0(0%)
DIG	GI DIS	0(0%)	1(1%)	0(0%)	1(1%)
	NAUSEA	0(0%)	1(1%)	1(1%)	1(1%)
MISC	WEIGHT INC	1(1%)	0(0%)	0(0%)	0(0%)
	COLD LEGS	0(0%)	1(1%)	0(0%)	0(0%)
	DIZZINESS/WEAK/MALAISE	0(0%)	1(1%)	0(0%)	0(0%)
	FATIGUE	0(0%)	2(2%)	0(0%)	0(0%)
	FEELS WARMER	0(0%)	1(1%)	0(0%)	0(0%)
	HOT LEFT FACE	0(0%)	1(1%)	0(0%)	0(0%)
	BACKACHE	0(0%)	0(0%)	0(0%)	1(1%)
	BASAL SK CARC REMOVED	0(0%)	0(0%)	1(1%)	0(0%)
	CANKER SORE	0(0%)	0(0%)	0(0%)	1(1%)
	FLUSHING FACE	0(0%)	0(0%)	0(0%)	1(1%)
	HEAD, SENSE OF FULLNESS	0(0%)	0(0%)	0(0%)	1(1%)
NER	TREMOR INC	1(1%)	0(0%)	0(0%)	0(0%)
	ANXIETY INC	0(0%)	0(0%)	0(0%)	1(1%)
	TINGLING	0(0%)	0(0%)	0(0%)	1(1%)
	TINGLING (SCALP)	0(0%)	0(0%)	0(0%)	3(4%)
SKIN	PRURITUS	0(0%)	1(1%)	0(0%)	1(1%)
	PRURITUS (SCALP)	0(0%)	2(2%)	0(0%)	7(9%)
	SWEAT	1(1%)	1(1%)	0(0%)	0(0%)
GU	ALTERED MENSTRUAL CYCLE	0(0%)	1(1%)	0(0%)	0(0%)
	URIN FREQUENCY	0(0%)	0(0%)	0(0%)	1(1%)
	URIN URGENCY	0(0%)	0(0%)	0(0%)	3(4%)
SS	TINNITUS	1(1%)	0(0%)	0(0%)	0(0%)
RES	PNEUMONIA ASPIR	1(1%)	0(0%)	0(0%)	0(0%)

TITLES: NR(NOT RELATED); R(RELATED)
20 MIDO TREATED PTS HAD 1 OR MORE ADR; 35 REPORTS (2 PTS REPORTED SAME ADR 2X)
N=74 TREATED WITH MIDODRINE
14 PBO TRTD PTS HAD 1 OR > ADR; 22 REPTS; PTS PBO TREATED (RUN-IN; OR RANDOMIZED)
N=104 PTS TREATED WITH PLACEBO AT SOME TIME DURING STUDY
11 REPTS DURING STUDY, DOSE=0; 11 REPTS PBO RUN-IN

62

Tables 20 to 22 from the sponsor's report detail the adverse drug reactions by severity. Finally table 23 details the number of patients with supine systolic blood pressure reading greater than 180 and show a clear effect on this parameter.

TABLE 23
NO. OF PTS WITH A SUPINE SYSTOLIC BLOOD PRESSURE READING > 180 mm Hg

DOSE RECEIVED	TOTAL PT#	PRE DRUG N (%)	POST DOSE N (%)
0	97	6 (6)	10 (10)
2.5	74	3 (4)	11 (15)
5	50	6 (12)	9 (18)
10	26	7 (27)	14 (56)

DERIVED FROM APPENDIX TABLE D3

Clinical laboratory evaluations did not demonstrate any clear-cut treatment-related abnormalities. There were no clear-cut effects on the electrocardiogram.

OVERALL MEDICAL REVIEW OFFICER'S SUMMARY:

There are major problems with this study. Obviously many of the centers did not recruit the appropriate number of patients and the total sample size is relatively small in light of the many diagnostic groups. There is no argument provided as to why was idiopathic orthostatic hypotension evaluated in patients with mitral valve prolapse, diabetes, peripheral nauropathy, and amyloidosis, would respond similarly to patients whose orthostatic hypotension due to a central nervous system etiology such as most pertinently the target indication of Shy-Drager Syndrome. From an efficacy point of view, this reviewer believes that midodrine did not affect orthostatic hypotension which was to be a principal endpoint. While there is an apparent effect on systolic blood pressure for just the 10mg. dose, there is no dose response effect shown and no effect on the presumed principal mechanism of action of the drug that is on orthostatic hypotension. The fact that midodrine did not clearly effect symptoms of syncope and only when syncope and dizziness was combined was there some improvement at the 10mg. dose again suggests a heterogeneity of response that may well be nonspecific. In fact, a formal biostatistical analysis of this study is extremely important since all of the significance seen may be in large part due to the use of a one-tailed rather than a two-tailed test and truely intention to treat approach.

TABLE 20

ADVERSE REACTIONS (MIDODRINE TREATED)
NUMBER OBSERVED AND RATE
MIDODRINE STUDY 11 AND 11A

BODY SYSTEM	EVENT	MILD				MODERATE				SEVERE				TOTAL	
		NR	PO	PR	D	NR	PO	PR	D	NR	PO	PR	D	NR	R
BODY	HEADACHE						2(3%)							0(0%)	2(3%)
CV	HYPERTENS SUPINE				1(1%)		1(1%)	2(3%)	1(1%)			1(1%)		0(0%)	6(8%)
DIG	GI DIS						1(1%)							0(0%)	1(1%)
	NAUSEA	1(1%)	1(1%)											1(1%)	1(1%)
MISC	BACKACHE		1(1%)											0(0%)	1(1%)
	BASAL SK CARC REMOVED					1(1%)								1(1%)	0(0%)
	CANKER SORE						1(1%)							0(0%)	1(1%)
	FLUSHING FACE	1(1%)												0(0%)	1(1%)
	HEAD, SENSE OF FULLNESS						1(1%)							0(0%)	1(1%)
NER	ANXIETY INC									1(1%)				0(0%)	1(1%)
	TINGLING	1(1%)												0(0%)	1(1%)
	TINGLING (SCALP)			1(1%)	1(1%)		1(1%)							0(0%)	3(4%)
SKIN	PRURITUS	1(1%)												0(0%)	1(1%)
	PRURITUS (SCALP)	1(1%)	1(1%)				1(1%)	4(5%)						0(0%)	7(9%)
GU	URIN FREQUENCY	1(1%)												0(0%)	1(1%)
	URIN URGENCY		1(1%)*				2(3%)							0(0%)	3(4%)

TITLES: NR(NOT RELATED); PO(POSSIBLY); PR(PROBABLY); D(DEFINITELY)

20 MIDODRINE TREATED PTS REPORTED 1 OR MORE ADR'S; 35 REPORTS (*) TWO REPORTS SAME PT;

PT 38 REPORTED ADR 2X, DIFFERENT SEVERITY, COUNTED 1X; N=74 TREATED WITH MIDODRINE

TABLE 21

ADVERSE REACTIONS (PLACEBO TREATED)
NUMBER OBSERVED AND RATE
MIDODRINE STUDY 11 AND 11A

BODY SYSTE	EVENT	MILD				MODERATE				SEVERE				TOTAL	
		NR	PO	PR	D	NR	PO	PR	D	NR	PO	PR	D	NR	R
BODY	HEADACHE	1(1%)				1(1%)								1(1%)	1(1%)
CV	HYPERTENS SUPINE											1(1%)		0(0%)	1(1%)
	FIBRILLAT ATR		1(1%)											0(0%)	1(1%)
DIG	GI DIS					1(1%)								0(0%)	1(1%)
	NAUSEA		1(1%)											0(0%)	1(1%)
MISC	WEIGHT INC	1(1%)												1(1%)	0(0%)
	COLD LEGS		1(1%)											0(0%)	1(1%)
	DIZZINESS/WEAK/MALAISE												1(1%)	0(0%)	1(1%)
	FATIGUE		1(1%)				1(1%)							0(0%)	2(2%)
	FEELS WARMER		1(1%)											0(0%)	1(1%)
	HOT LEFT FACE		1(1%)											0(0%)	1(1%)
NER	TREMOR INC					1(1%)								1(1%)	0(0%)
SKIN	PRURITUS			1(1%)										0(0%)	1(1%)
	PRURITUS (SCALP)			1(1%)					1(1%)					0(0%)	2(2%)
	SWEAT					1(1%)	1(1%)							1(1%)	1(1%)
UG	ALTERED MENSTRUAL CYCLE		1(1%) *											0(0%)	1(1%)
SS	TINNITUS	1(1%) *												1(1%)	0(0%)
RES	PNEUMONIA ASPIR									1(1%)				1(1%)	0(0%)

TITLES: NR(NOT RELATED); PO(POSSIBLY); PR(PROBABLY); D(DEFINITELY)

14 PLACEBO TREATED PTS REPORTED 1 OR MORE ADR'S; 22 REPORTS; PTS TREATED WITH PBO DURING RUN-IN OR RANDOMIZED TO PBO IN DOUBLE BLIND

N=104 PTS TREATED WITH PLACEBO AT SOME TIME DURING STUDY

DE/93 - NAUSEA REPORTED AS REMOTE, CODED AS POSSIBLY

11 REPORTS DURING STUDY, DOSE=0; 11 REPORTS DURING PBO RUN-IN; (*) OBSERVED BEFORE START OF STUDY

TABLE 22

ADVERSE REACTIONS BY BODY SYSTEM
MIDODRINE STUDY 11 AND 11A

	DE #	DOSE GROUP (MG)	ADR DOSE (MG)	DUR (DAYS)	S	R
SKIN						
SWEAT	76	0	0	3	2	2
SWEAT	27	2.5	PBO	9	2	1
PRURITUS (SCALP)	20	0	0	>14	1	3
PRURITUS (SCALP)	104	2.5	2.5	C	2	3
PRURITUS (SCALP)	35	2.5	2.5	22	2	3
PRURITUS (SCALP)	84	2.5	2.5	16	1	3
PRURITUS (SCALP)	83	5	5	<29	2	3
PRURITUS (SCALP)	77	10	10	C	1	2
PRURITUS (SCALP)	54	10	PBO	33	2	4
PRURITUS (SCALP)	85	10	2.5	30	2	3
PRURITUS (SCALP)	38	10	2.5,5	3,12	1,2	2,2
PRURITUS	76	0	PBO	46	1	3
PRURITUS	85	10	5	23	1	2
CARDIOVASCULAR						
HYPERTENS SUPINE	89	0	0	1	3	3
HYPERTENS SUPINE	80	2.5	2.5	34	2	2
HYPERTENS SUPINE	79	2.5	2.5	8	2	3
HYPERTENS SUPINE	83	5	5	7	1	4
HYPERTENS SUPINE	77	10	10	C	2	3
HYPERTENS SUPINE	31	10	5	4	2	4
HYPERTENS SUPINE	70	10	10	15	3	3
FIBRILLATION ATRIAL	60	0	0	C	1	2
RESPIRATORY						
PNEUMONIA ASPIRATION	43	0	0	1	3	1
MISCELLANEOUS						
DIZZINESS/WEAK/MALAISE	67	777	PBO	1	3	4
COLD LEGS	37	777	PBO	9	1	2
HOT LEFT FACE	37	777	PBO	9	1	2
FATIGUE	76	0	0	9	2	2
FATIGUE	78	0	0	22	1	2
FEELS WARMER	78	0	0	C	1	2
CANKER SORE	82	2.5	2.5	C	2	2
BACKACHE	82	2.5	2.5	1	1	2
BASAL SK CARC REMOVED	82	2.5	2.5	1	2	1
HEAD, SENSE OF FULLNESS	96	2.5	2.5	6	2	2
FLUSHING FACE	85	10	5	12	1	2

N=104 PTS TREATED WITH PBO AT SOME TIME DURING THE STUDY: 74 WITH MIDODRINE

TITLES: DE#=PATIENT DATA ENTRY NUMBER; ADR DOSE OF OCCURRENCE
DUR (DURATION OF ADVERSE DRUG REACTION)
S=SEVERITY (1 MILD; 2 MODERATE; 3 SEVERE);
R=RELATIONSHIP (1 NOT RELATED; 2 POSSIBLY; 3 PROBABLY; 4 DEFINITELY)

CODES: PBO=ADR DURING PLACEBO RUN-IN WEEK; OBS=OBSERVED BEFORE STUDY START
C=CONTINUING; 777=NOT RANDOMIZED TO DOSE GROUP

DE #53 RELATIONSHIP REPORTED REMOTE, CODED POSSIBLY
777=NOT RANDOMIZED TO A DOSE GROUP

TABLE 22

ADVERSE REACTIONS BY BODY SYSTEM
MIDODRINE STUDY 11 AND 11A

	DE #	DOSE GROUP (MG)	ADR DOSE (MG)	DUR (DAYS)	S	R
GENITAL URINARY						
URIN FREQUENCY	39	10	5	15	1	2
URIN URGENCY	35	2.5	2.5	21	2	3
URIN URGENCY	12	2.5	2.5	2	2	3
URIN URGENCY	51	10	10	3.8	1.1	3.3
ALTERED MENSTRUAL CYCLE	76	0	OBS	50	1	2
BODY						
HEADACHE	78	0	0	C	1	1
HEADACHE	82	2.5	2.5	1	2	2
HEADACHE	28	10	PBO	30	2	2
HEADACHE	77	10	2.5	C	2	2
NERVOUS SYSTEM						
TREMOR INC	37	777	PBO	9	2	1
ANXIETY INC	11	5	5	1	3	2
TINGLING (SCALP)	62	2.5	2.5	C	1	3
TINGLING (SCALP)	69	10	2.5	32	2	2
TINGLING (SCALP)	90	10	2.5	28	1	4
TINGLING	11	5	2.5	1	1	2
DIGESTIVE						
NAUSEA	33	0	PBO	8	1	2
NAUSEA	56	10	10	2	1	1
NAUSEA	38	10	10	1	1	2
GI DISCOMFORT	82	2.5	PBO	31	2	2
GI DISCOMFORT	38	10	10	1	2	2
METABOLIC AND NUTRITIONAL						
WEIGHT INC	96	2.5	PBO	C	1	1
SOMATOSENSORY						
TINNITUS	78	0	OBS	C	1	1

N=104 PTS TREATED WITH PBO AT SOME TIME DURING THE STUDY; 74 WITH MIDODRINE

TITLES: DE#=PATIENT DATA ENTRY NUMBER; ADR DOSE OF OCCURRENCE

DUR (DURATION OF ADVERSE DRUG REACTION)

S=SEVERITY (1 MILD; 2 MODERATE; 3 SEVERE;

R=RELATIONSHIP (1 NOT RELATED; 2 POSSIBLY; 3 PROBABLY; 4 DEFINITELY)

CODES: PBO=ADR DURING PLACEBO RUN-IN WEEK; OBS=OBSERVED BEFORE STUDY START

C=CONTINUING; 777=NOT RANDOMIZED TO DOSE GROUP

DE #53 RELATIONSHIP REPORTED REMOTE, CODED POSSIBLY

777=NOT RANDOMIZED TO A DOSE GROUP

The lack of any supportive effect of midodrine on other symptoms or on global evaluation by the physician again supports the conclusion that this trial does not demonstrate clear-cut efficacy of midodrine. There were, however, no safety concerns identified in this trial that were not already addressed in the previous NDA evaluation.

FINAL MEDICAL REVIEW OFFICER'S RECOMMENDATION:

Continued disapproval of midodrine.

SIGNATURE: _____

JOEL MORGANROTH, M.D.

Buehler

OCT - 6 1988

MEDICAL OFFICER'S REVIEW
NDA 19-815
AMENDMENT - MIDODRINE (AMATINE) SAFETY UPDATE REPORT

DATE: SEPTEMBER 9, 1988

FROM: ROBERTS LABORATORIES, INC.
JOHN A. SOLEWSKI, ASSOCIATE DIRECTOR

MEDICAL REVIEW OFFICER: JOEL MORGANROTH, M.D.

DATE SENT TO FDA: SEPTEMBER 28, 1988

The previously reviewed NDA 19-815 on midodrine for idiopathic orthostatic hypotension was submitted to the Food and Drug Administration on April 26, 1988. This review represents the data submitted by Roberts Laboratories as a four month, post-NDA evaluation. This represents 19 patients who were treated with midodrine at the time of the NDA submission and on 4 additional patients who received midodrine after that time.

These patients were included in Protocols 20,762-05A which is an open, compassionate use study of oral midodrine in patients with severe orthostatic hypotension and also Protocol 20,762-10B which is a dose ranging efficacy study of oral midodrine and placebo in patients with severe orthostatic hypotension. At this time there are 18 patients who are receiving midodrine (date: August 25, 1988) which are derived from a total of 19 patients who were receiving treatment at the time of the data lock for the NDA, 4 patients who have subsequently entered these studies, 2 who have transferred from Study 10B to Study 5A and 7 who discontinued. The following table demonstrates this data.

PATIENT ENTRY STATUS
as of August 25, 1988

	Study 05A	Study 10B
Patients completed at data lock dates*	17	7
Patients discontinued prior to data lock dates	17	7
Patients in treatment at data lock dates	**17**	**2**
Patients entered after data lock dates	2	2
Patients transferred from Study 10B after data lock dates	2	
Patients discontinued from study since data lock dates	5	0
Total patients currently in treatment	16	2

* July 21, 1987 for Study 05A and

The attached Table 1 (from the sponsor) details the number of adverse reactions reported prior to the NDA, during the post-NDA period and an overall total.

Specific patients and adverse reactions identified since the NDA lock are shown in Table 2.

Four patients discontinued midodrine since July 31, 1987 which includes one patient, two of whom because of systemic hypertension in the supine position and two because the physician decided not to continue midodrine because of either fair response or that the regimen was too complex.

Patient #1203 had died since July 31, 1987 and that death was in a patient on 30 mg of midodrine per day who had supine hypertension for 2 years and had been on midodrine for 4 years. She had sudden cardiac death presumably due to ventricular fibrillation.

In reviewing Table 2, one notes that supine hypertension occurred in 8 patients in which 2 had their midodrine discontinued and the other 6 are continuing on that medication.

The other adverse effects had been noted in the previous safety evaluation and do not appear changed or altered in quality or quantity.

It should be noted of the 4 patients who had entered this NDA to be treated with midodrine, data are available on only 2. Patient #206 demonstrated little improvement with midodrine but nevertheless the patient was continued on the medication and no adverse effects have been noted to date. Patient #207 demonstrated minimal improvement on midodrine but continued long-term since some improvement was claimed. No adverse effects are noted.

MEDICAL REVIEW OFFICER'S EVALUATION OF THIS SAFETY UPDATE

No important qualitative or quantitative changes in the safety evaluation of midodrine are noted in this review of 19 patients. Only 18 patients are currently receiving the drug under this NDA. This report does not effect my previous review nor recommendations.

Signature:----------

Joel Morganroth, M.D.

TABLE 1

ADVERSE REACTIONS

NUMBER OF PATIENTS REPORTING ADVERSE EXPERIENCES WITHIN EACH SYSTEM-ORGAN CLASS (Protocol 20,762-05A)

SYSTEM-ORGAN CLASS	ADVERSE REACTIONS	NO. OF PATIENTS NDA TOTAL	POST-NDA TOTAL	UPDATED TOTAL
Cardiovascular	Chest Pain	2		2
	Flushing	1		1
	Palpitations	2		2
	Supine Hypertension	5	3	8
	Atrial Fibrillation	2		2
	Cardiac Failure	1		1
	Ventricular Arrhythmia	1	1	2
Central and Peripheral Nervous	Headache	1		1
	Cerebrovascular Disorder	2		2
	Hemiparesis	1		1
	Tremor	1		1
	Seizure		1	1
Gastrointestinal	Abdominal Discomfort	1		1
	Nausea	2		2
Integumentary	Pruritus (scalp)	5		5
	Piloerection	1		1
Musculoskeletal	Night Cramps	1		1
Respiratory	Respiratory Arrest	3		3
Urinary	Frequency	2	2	4
	Dysuria	1		1
	Incontinence	1		1
	Fullness of Bladder	1		1
Other	Chills	1		1
Total number of adverse reactions reported:		38*	7	45
Number (percent) of Patients reporting one or more ADR's:		18 (52.9)		23 (60.5)
Number of Patients reporting no ADR's:		16		15

*Multiple reports of the same ADR for a single patient are counted once.

TABLE 2

ADVERSE REACTIONS

IDENTIFICATION OF PATIENTS REPORTING ADVERSE REACTIONS WITHIN EACH SYSTEM-ORGAN CLASS (Protocol 20.762-05A)

SYSTEM-ORGAN CLASS	ADVERSE REACTION	PATIENT NO.
Cardiovascular	Chest Pain	0403, 0701
	Flushing	2102
	Palpitations	0403, 0701
	Supine Hypertension	0402, 1001, 1101, 1201, 1202, 1203, 1206, 2401
	Atrial Fibrillation	1201, 1206
	Cardiac Failure	1201
	Ventricular Arrhythmia	1202 (death) 1203 (death)
Central and Peripheral Nervous	Headache	0403
	Cerebrovascular Disorder	0501, 1201
	Hemiparesis	0501
	Tremor	1207
	Seizure	0401
Gastrointestinal	Abdominal Discomfort	0403
	Nausea	0501, 2102
Integumentary	Pruritus (scalp)	0401, 0403, 0601, 1203, 2102
	Piloerection	1403

TABLE 2 (continued)

SYSTEM-ORGAN CLASS	ADVERSE REACTION	PATIENT NO.
Musculoskeletal	Night Cramps	1204
Respiratory	Respiratory Arrest	0102 (death) 0301 (death) 1102 (death)
Urinary	Frequency	0401, 0402, 0403, 0404
	Dysuria	1801
	Incontinence	0401
	Fullness of Bladder	2102
Other	Chills	0403

FIGURE 5

Effect of TTS (fentanyl) Dose on Fentanyl AUC (72 hour Application)

[C-89-006-00 UK Study, Kenny,(N=13) & C-88-032-00, Portenoy ,(N=5)]

ALZA CORPORATION, PALO ALTO, CA 94303-0802

THE GRADUATE HOSPITAL
One Graduate Plaza, Philadelphia, Pa. 19146 • (215) 893-2000

July 27, 1988

Raymond J. Lipicky, M.D.
Director, Division of CardioRenal
Drug Products
Food and Drug Administration
Room 16-B-45
5600 Fishers Lane
Rockville, Maryland 20857

Dear Ray:

Enclosed please find my initial review of NDA 19-815 on midodrine by Roberts Laboratories. This review covers the clinical materials sent to me at the end of May 1988 but should not be considered final until the audit currently underway by Doralia Segal of the Scientific Investigation Branch has been completed.

After you have reviewed this material please let me know if I can provide you any clarifications or if any changes are required.

Thank you again for allowing me to provide you with my comments. Best personal regards.

Sincerely yours,

Joel Morganroth, M.D.
Director of Cardiac Research & Development

Professor of Medicine and Pharmacology
Hahnemann University

JM:jk

Enclosure

NDA: #19-815

SPONSOR: ROBERTS LABORATORIES

AGENT: MIDODRINE (AMATINE)

USE: ORAL THERAPY FOR ORTHOSTATIC HYPOTENSION

DATE RECEIVED BY CENTER FOR DRUG EVALUATION & RESEARCH: 4/28/88

DATE SENT TO MEDICAL REVIEW OFFICER: 5/30/88

DATE SENT TO FDA: 7/27/88

MEDICAL REVIEW OFFICER: JOEL MORGANROTH, M.D.

STATUS OF THIS REVIEW: COMPLETED WITH REGARD TO CLINICAL DATA BUT REQUIRES CORRELATION WITH PARALLEL SCIENTIFIC INVESTIGATION CURRENTLY UNDER PROGRESS

OVERALL MEDICAL REVIEW OFFICER'S SUMMARY OF THE NEW DRUG APPLICATION 19-815 (MIDODRINE)

On April 28, 1988 the Center for Drug Evaluation and Research received from Roberts Laboratories, Incorporated NDA 19-815 involving the orphan drug, midodrine, in which oral tablet therapy for the treatment of idiopathic orthostatic hypotension is requested for an approved claim.

The drug substance is manufactured by

This reviewer has not evaluated any of the data (if available) regarding this drug's manufacturing, packaging, or preclinical toxicology. The condition known as orthostatic hypotension is established by defining a decline in standing blood pressure which is of clinical importance best defined in patients who complain of cerebral hypoxic symptoms from such hypotension. These would be symptoms such as dizziness or frank syncope.

Idiopathic or primary orthostatic hypotension may be associated with somatic neurological abnormalities or not or may be secondary to other medical conditions that effect the autonomic system such as diabetes, Parkisonism, amyloidosis, etc. There is no uniformly effective excellent therapy though several available agents are currently used including Florinef, and several sympathomimetic agents.

In the 1960's a series of substituted phenylethanolamides were tested and a derivative known as midodrine was felt to be a pressor agent that poorly diffused across the blood vein barrier. This agent, midodrine, exerts its alpha sympathetic receptor agonism principally through its primary metabolite, des-gly-midodrine. Arterial and venous blood pressure tone increases and it was therefore felt that midodrine may be effective in patients with orthostatic hypotension. The drug has been widely used in Europe and elsewhere and is available in the following countries:

SEE ACCOMPANYING TABLE

The drug is marketed under the trade names Gutron or Hipertan and the trade name in the United States would be Amatine.

The chemical name for this agent is dl-alpha-(2,5-dimethoxyphenyl)-beta-glycinamido-ethanol hydrochloride and it is a white, microcrystaline powder which is soluble in water with stability for 3-5 years when protected from light. The tablet contains, in addition to midodrine, cellulose, cornstarch, talc and magnesium. It is available in both intravenous and oral formulations.

[illegible]

[illegible] 9.5 mg

[illegible]	[illegible]	[illegible]
[illegible]	15.[illegible]	2/27/74
[illegible]	[illegible]	7/15/77
Mexico	[illegible] S.S.A.	8/23/76
[illegible]	[illegible]	1979
[illegible]		1976
[illegible]	[illegible]	6/[illegible]/78
[illegible]	[illegible]	9/14/79
[illegible]	81/190/74-C	12/8/78
Switzerland	4846	
[illegible]	24519	12/7/81
[illegible]	501/80/07/01-09	7/28/80
[illegible]	07377	1980
[illegible]	69A/4169/11132	1981
[illegible]	M-13659	12/18/81
[illegible]	15994	1/15/82
Saudi Arabia	17/80/82 a 20	8/1/82
	18/80/81 a 50	8/1/82
[illegible]	25640	3/15/82
Portugal		
Italy		6/23/86
Dubai (U.A.E.)	R/228/6034	

[illegible] 5.0 mg

COUNTRY	REGISTRATION #	REGISTRATION DATE
[illegible]a	15.434	2/6/74
Mexico	99/09 S.S.A.	8/23/76
[illegible]key	23702	10/25/76
Venezuela	E.F. 19.216	9/8/76
Czechoslovakia	84/190/74-C	12/8/78
Argentina*	35.349	6/19/78

*In Argentina midodrine is marketed under the trade name HIPERTAN.

[illegible]

[illegible]	[illegible] #	[illegible] DATE
[illegible]	15.[illegible]	[illegible]/74
[illegible]	[illegible]	7/15/77
[illegible]	[illegible] S.S.A.	9/[illegible]/76
[illegible]		1976
[illegible]	[illegible]	6/19/78
[illegible]	[illegible]	12/8/76
[illegible]	[illegible]	
[illegible]	[illegible]	12/7/81
[illegible]	[illegible]	7/28/80
[illegible]	[illegible]	1981
Taiwan	[illegible]	1980
Saudi Arabia	[illegible]	8/1/82
[illegible]		
[illegible]		
[illegible] (U.A.E.)	[illegible]/6035	

[illegible] 1%

[illegible]	[illegible] #	REGISTRATION DATE
[illegible]	15.446	2/29/74
[illegible]	[illegible]	7/15/77
[illegible]	[illegible]871 S.S.A.	9/23/76
[illegible]		1975
[illegible]	33713	10/25/76
Afghanistan		1976
[illegible]	13720	1980
[illegible]	E.F. 19.682	2/[illegible]/78
[illegible]	34/108/74-C	12/8/76
[illegible]	[illegible]647	
[illegible]	HK-09139	9/14/79
[illegible]	14519 0.25%	12/7/81
[illegible]	501/08/07/0411	7/28/80
[illegible]**	35.349	6/19/78
[illegible]	[illegible]A/4169/11[illegible]32	1981
[illegible]	[illegible]33658	12/18/81
[illegible]		
Dubai (U.A.E.)	R/228/6037	

*Marketed in Egypt under trade name Midodrine
**Marketed in Argentine Hipertan

Preclinical pharmacological studies demonstrate that this agent stimulates the alpha adrenergic receptors comparable to norepinephrine. The activity resides in the l-isomer and, as stated above, is due to the hydrolysis of the parent compound to its primary metabolite. The alpha-agonist activity of midodrine is direct rather than the enhancement of intrinsic amines or due to elevation of receptor sensitivity. Little activity is observed when given by intramuscular or subcutaneous routes. Despinalization was used to demonstrate the pure peripheral site of action effect of this agent. Depletion of catecholamine stores did not effect its action providing further evidence for its direct effect on sympathetic receptors. Phentolamine significantly reduces its action whereas propranolol enhances its effect. MAO inhibition or COMT inhibition did not effect the pressor change therefore suggesting that these enzymes are not prominent in the degradation of midodrine. Treatment reduces acute injection and therefore tachyphylaxis is of some concern.

Direct mechanism of action studies were conducted in both dogs and cats. There was no evidence that midodrine effects beta receptors using isoproterenol studies.

While most of the activity of midodrine is due to its metabolite, it is possible that the identified metabolite is only an intermediate and that other metabolites may be effective.

In isolated rat right ventricle midodrine was a negative inotrope when used in high concentrations. This was also shown in other species. There was some increase in coronary flow. Midodrine effected the electrocardiogram by increasing both the QT and PR intervals. Midodrine increases pulmonary artery pressure which is equilibrated by reflex. There were no significant effects on the GI, GU or liver in preclinical studies but there was some questionable analgesic effect on the central nervous system and a decrease in the aqueous humour in the eye leading to pupillary dilitation. Inhibition of uterine contractions, a decrease in minute volume on the lungs and a decrease in the inflammatory process was noted as well as a tendency towards hyperglycemia. A half-life of the metabolite was 1.75 hours and the parent agent 1 hour. Over 95% is excreted in the kidney.

Clinical pharmacological data suggests that midodrine and its metabolite, desglymidodrine, has the major route of excretion through the kidney with a high proportion of conjugates. It is almost completely absorbed from the GI tract with a bioavailability of 93%. The half-life of desglymidodrine appears to be longer than midodrine.

Please see the review of the human pharmacology for further details.

The sponsor has provided clinical data to attempt to establish midodrine's safety and efficacy.

EFFICACY

The sponsor has provided two studies which it calls key in its attempt to provide efficacy data. These studies are 20,762-1 which is midodrine versus ephedrine and placebo in 8 patients and 20,7862-2A which is midodrine plus fludrocortisone versus fludrocortisone alone in 7 patients. These protocols drew patients from a variety of sources with both primary and secondary orthostatic hypotension and used single investigations. Additional protocols are reviewed which have been conducted in the United States involving midodrine compared to dihydroergotamine, placebo, an open label compassionate use and a Mayo Clinic experience.

PROTOCOL 20,762-1

This was a report as a single center study conducted by Dr. Tarazi at the Cleveland Clinic in which after a baseline 2 day in-hospital period, patients were randomized in a double blind fashion to either midodrine or ephedrine. An initial titration phase was concluded by a short maintenance phase and an interim placebo prior to crossover to the other active agent. This study was conducted on the background of fludrocortisone and Jobst garments. Eight patients were enrolled in this center and all completed both phases of the protocol except for 1 patient who did not enter ephedrine maintenance. Six patients had idiopathic orthostatic hypotension and 1 each, diabetes and Parkisonism. This reviewer found that 3 patients should have been excluded because of the presence of several readings of severe supine systolic hypertension with readings >180 mmHg at baseline and 3 additional patients who had infrequent blood pressures <80 mmHg with standing and therefore did not meet criteria for severe orthostatic hypotension. The data demonstrated by the sponsor suggests that midodrine and ephedrine produced statistically significant increases in supine blood pressure not different from each other and that standing blood pressure was better with midodrine compared to placebo than ephedrine's effect. More patients were able to stand on midodrine than on placebo.

It appears that this study was part of a multicenter double blind study that was called Protocol #20,762-1 in which a separate report for the other six centers was made in which 22 patients were entered but because so many patients did not meet study criteria, only 8 patients from 4 centers were evaluated. In these patients there was no demonstration of any efficacy on midodrine and in fact the data suggested that ephedrine was superior. I suspect that this extremely weak study (Protocol #20,762-1A) when combined with the relatively unimpressive in Protocol #20,762-1 (the Tarazi study) would not provide that this protocol, #20,762-1, demonstrates that midodrine is effective. In addition, the data from these studies suggests that the majority of patients enrolled did not meet the study criteria and the conduct of the study was questionable in that many of the blood pressures were not recorded as they were supposed to be per protocol. In addition, the sponsor shows not to compare the

effects of ephedrine and midodrine against the placebo baseline and used a least significant difference approach. The comments from the biostatistical group at the FDA need to be integrated with this report to determine whether the sponsor's statistical approach is valid.

PROTOCOL #20,762-2A

This is the second pivotal trial that the sponsor offers in support of this claim which was conducted at Mt. Sinai Hospital by Dr. Yahr which evaluated midodrine compared to fludrocortisone. It should be noted the protocol provided by the sponsor did not match the actual study reported and was presumably a logistic error. After a baseline period, patients underwent a 10-21 day midodrine titration and then maintenance and then a double blind crossover study. Midodrine plus fludrocortisone or placebo plus fludrocortisone was used for the first 5-8 days with a 2 day washout period in which placebo from midodrine and fludrocortisone were used followed by a crossover to the other regimen. **The sponsor in this trial chose to take the double blind blood pressure measurements and to combine them with the open label single blind midodrine phase arguing that the blood pressures were objectively taken by an automatic means. This medical reviewer objects to this practice.** The study population included 7 patients in which 6 were female, 4 having Parkisonism and the other 3 idiopathic orthostatic hypotension. A similar statistical analysis was performed as in the Tarazi study - #20,762-1. All 7 patients were not analyzed since 1 patient was excluded because 11% of that patient's baseline supine blood pressure readings were over 180 mmHg though another patient met this criteria 5.4% of the time but that patient was not excluded. It could also be argued that patient numbers 5306 and 5307 could also have been excluded by these mechanisms but were not by the sponsor. The patient that had an actual worse response on midodrine during the blood pressure measurements was patient 5302, excluded by the sponsor. This reviewer evaluated in individual patients mean standing systolic blood pressure during the double blind phase only comparing midodrine versus placebo and found that only 2 of the patients had a 10 mm change in midodrine whereas the other 5 patients did not. Only 1 patient (5305) demonstrated a marked clinical change in blood pressure on midodrine compared to placebo in supine systolic blood pressure.

Thus, this second pivotal trial offered by the sponsor recruited few patients despite the fact that the majority had Parkisonism which would have seemed to be a common enough condition that more patients with orthostatic hypotension due to this disease could have been enrolled. The only well controlled portion of this trial was the double blind phase and it is clear that the effectiveness of midodrine during this study was marginal at best.

Another double blind Phase III placebo controlled crossover comparison of midodrine with dihydroergotamine was performed by the sponsor but was not considered to be a pivotal trial. This was Protocol #20,762-3 conducted by Dr. Vinik at the University of Michigan.

A double blind trial design was used similar to the Tarazi study, #20,762-1 (midodrine versus ephedrine). According to the protocol, the medication was to be given open label though the medical study report suggests it was done double blind. Nine patients were analyzed in this trial in which 7 had orthostatic hypotension due to diabetes mellitus and only 2 had idiopathic orthostatic hypotension. No patient in this trial demonstrated efficacy from midodrine except for a tendency in 1 patient (5110) according to this medical reviewer, however, there is marked variability in the blood pressures between baseline placebo and interim placebo phases. The sponsor concluded the data demonstrated that placebo improved the patients 40% of the time compared to 40-60% on dihydroergotamine versus 60% on midodrine. The sponsor suggests that perhaps a carryover effect accounts for these results and of course if this is the case then the study is invalid as would be the previous studies discussed.

The sponsor also conducted a dose ranging study (Protocol #20,762-10) comparing midodrine to placebo. This protocol was begun in November of 1987. After an initial washout period of 2-5 days amended to 1-2 days, patients underwent a single blind dose ranging of midodrine from 2.5 mg to 12.5 mg though the 12.5 mg dose was deleted by an amendment. Thereafter, the patients underwent a Phase III single blind washout with placebo and then were randomized in a double blind fashion to either placebo or the dose that was found to be effective during the titration period. Dr. Polintsky, from the NIH, recruited 3 patients and 4 patients were enrolled by Dr. Freeman from New York Deaconess Hospital. Patients in this trial suffered from idiopathic orthostatic hypotension, the principal population sought for the claim for midodrine's use. This study demonstrated, to date, no evidence of midodrine efficacy and even more disturbingly no evidence of any dose blood pressure response to this agent. In this short term study Holter monitoring data was obtained in the first 6 patients and in at least 1 of these patients a serious atrial and ventricular arrhythmia developed on midodrine compared to placebo. More details about safety of the drug but little controlled information regarding efficacy could be provided by the compassionate use of oral midodrine conducted in Protocol #20,762 and by the Mayo Clinic experience in 176 patients reported by Dr. Alexander Schriger, et al. In the open and compassionate use study, 20,762-5 initiated in August 1983, 34 patients received midodrine many of whom were in previous protocols and as of 2/29/88 seventeen patients were continuing on the drug. No specific data regarding efficacy can be concluded.

Midodrine was also reported in 176 patients studied at the Mayo Clinic between 1976 and February 1988. These patients had a variety of primary and secondary causes for orthostatic hypotension and the entire study was conducted in an open label fashion over the course of many years. No controlled data regarding midodrine's efficacy could be demonstrated but there is no question that some of the patients in this series apparently had a marked effect from midodrine though variability of blood pressure response could not be evaluated.

Finally, the sponsor provides data regarding the clinical literature of midodrine which reports the use of this agent in close to 4000 patients with a variety of primary and secondary hypotensive disorders including urinary and ejaculatory disorders. Forty percent of the patients received only 1 dose per day with the majority of patients only being treated for 3-6 weeks. Thus, the majority of the clinical experience outside the United States appears to be the occasional single use or short term use of midodrine for subjective symptoms due to autonomic dysfunction from a variety of causes. The benefit versus risk ratio for this use has not been studied in the United States nor been provided as part of the domestic experience with this agent.

SAFETY

The safety data from the trials, literature, and from individuals with their own IND generally view midodrine over a short period in the controlled trials and in a variety of heterogenous patients over a few years.

The most frequent clinical adverse experiences include; pruritis of the scalp (9.2%), supine hypotension (3.4%), nausea and vomiting (3.4%), and chest pain, flushing, and urinary frequency - each with an incidence of 2.3%.

The following table details other adverse reactions on midodrine compared to other agents in controlled trials and points out the potential for syncope and cardiac symptoms as well as for supine hypertension.

In the Mayo Clinic experience, in 146 patients, the following table provides their adverse effects.

Additionally, 1 patient had angiitis and several patients have died from myocardial infarction, stroke, congestive heart failure, and arrhythmia all of which might have been potentially related to midodrine's effect on systemic blood pressure.

Laboratory data did not demonstrate many major safety concerns though some patients did have an increase in glucose which might have been predicted from the preclinical data.

	5	(3)
	5	(3)
	5	(3)
	4	(3)
	4	(3)
	3	(2)
Exacerbation of Prostatism	2	(1)
Arthritis	1	(1)
Other	7	(5)

Supine hypertension, which is an expected effect of this agent, is of principal concern and in patients on long term therapy 15% had blood pressures over 180 mmHg (supine systolic pressure) about 20% of time.

A most disturbing feature of this agent is its lack of any dose response relationship which perhaps is an important clue that supports the analysis of the trials which overall demonstrate weak to unconvincing evidence of efficacy of this agent.

Because of the major risks of midodrine which include systemic supine hypertension, the concerning negative interaction with midodrine and digitalis-like agents effecting AV conduction, the potential for significant cardiac arrhythmias, and the other pharmacological effects including urinary retention, etc. and the unimpressive benefit as demonstrated in controlled trials, this reviewer would conclude that the benefit to risk ratio is extremely poor. The sponsor's choice of splitting the ephedrine comparative pivotal trial into the Tarazi study and the others demonstrates their attempt to identify the occasional patient who may suggest an effect from this agent. It is clear however that an occasional patient appears to benefit from this drug on subjective terms, especially in the Mayo Clinic experience but because of the risks and because of the large potential for misuse of this agent by general physicians who may apply it to the patient with occasional dizziness, etc. I believe this drug does not warrant general approval. Since it is an orphan drug and since an occasional drug might benefit, a policy decision should be considered regarding its availability on a compassionate use individual case basis by the sponsor. Safeguards against general abuse must be considered.

Signature: _____

Joel Morganroth, M.D.

CLINICAL PHARMACOLOGY

NDA19-815

ROBERTS LABORATORIES (MIDODRINE)

Midodrine (AMATINE, Gutron, ST-1085) is metabolized to a major active metabolite, desglymidodrine (St-1059). This active metabolite is an alpha receptor sympathomimetic agonist with an elimination phase of approximately 5-6 hours whereas the parent compound has a relatively short half-life. The major route of excretion is urinary with a high proportion of conjugates.

Midodrine has a bioavailability of 93% and the hemodynamic study showed that midodrine produces vasoconstriction similar to norepinephrine but with less diminution in plasma volume. Thus midodrine increases venous tone prior to affecting systemic blood pressure.

The sponsor has conducted the following trials which include 6 human pharmacokinetics and bioavailability studies as detailed in Tables 1A and 1B.

In addition, the sponsor has conducted 7 pharmacodynamic studies as demonstrated in Table 11.

SINGLE ORAL DOSE URINARY EXCRETION STUDY TO EVALUATE MIDODRINE METABOLITES (STUDY 058-37)

This study investigated 6 healthy male volunteers who received one 5 mg midodrine tablet orally with urinary collections over 12 hours. Urinary concentration of the metabolite using a fluormetric assay demonstrated that an average of 30% of the administered midodrine doses are excreted in urine as the metabolite over the 8 hour period. None was found thereafter. Thus, midodrine is readily absorbed and rapidly metabolized and the appearance of the metabolite correlated with the subjective effect of chills in these normal volunteers. The data are demonstrated in Table 2.

TABLE 1A

MIDODRINE HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES

Report Number	Date of Report	Nature of Study	Number of Subjects	Age (yr)	Weight (kg)	Height (cm)	Dose (mg)	Investigator
058-37	2/74	Single-dose Urinary excretion Normal volunteers	6M	27-59	68-90	N. S.	5 mg tablet p.o.	F. Takacs Chemie Linz, A.G.
058-38	3/74	Multiple-dose Urinary excretion Normal volunteers	"	"	"	"	5 mg tablet x 3 p.o. q4 hr	F. Takacs Chemie Linz, A.G.
058-39	7/78	Single-dose 3H-labeled drug Metabolic study Normal volunteer	1M	43	85	186	5.11 mg i.v. (764.6 μCi)	F. Takacs Chemie Linz, A.G.
058-40	4/81	Single-dose 3H-labeled drug Pharmacokinetic study Randomized 2-way crossover Normal volunteers	3F,3M	20-27	N. S.	N. S.	5 mg i.v. (268.1 μCi) 5.3 mg p.o.* (282.6 μCi)	W.R. Kukovetz Graz University
058-40a	10/81	Single-dose 3H-labeled drug Further pharmacokinetic study of plasma and urine samples from 058-040 (4/81)	"	"	"	"	"	"
058-133a	12/87	Single-dose Bioavailability study Randomized 3-way crossover	12M	21-36	63-88	175-190	2.5 mg i.v. 2.5 mg solution p.o. 2.5 mg tablet p.o.	H. Grobecker et al Regensburg University

All midodrine was used as the hydrochloride salt.

N. S. - not stated.

* Solution in gelatin capsule

Based on the probable widespread use of this convenient dosage form the following phase IV studies should be considered:

1. Either find in the literature or perform an experimental study of the volume of distribution and clearance of fentanyl in patients with hepatic disorders resulting in impaired drug metabolism.

2. Performing an experimental study of the pharmacodynamic effects of TTS or IV fentanyl on oxygen saturation, respiratory rate, paCO2 (or end expiratory CO2), and CO2 sensitivity in normal volunteers in the presence and absence of a typical postoperative CNS sedative and/or alcohol. It would be prudent to include some measure of the magnitude of time course (hysteresis effects) in such a study.

3. Performing an experimental study of the pharmacodynamic effects of TTS or IV fentanyl on oxygen saturation, respiratory rate, pCO2, and CO2 sensitivity in patients with compensated COPD such as might receive the patch for same day surgery.

4. Perform abuse liability testing in experienced drug users if any schedule other than CII is desired (CIII may be possible).

Safety Conclusions

Postoperative use

The TTS fentanyl system had been shown to have typical opioid safety characteristics in clinical trials in postoperative pain. The most significant side effect observed in the trials was the capacity of the system to produce hypoventilation, hypercarbia, and hypoxia at times when the patient was asleep. This effect was clearly related to blood fentanyl level and did not occur at blood levels below approximately 2.0 ng/ml. In consequence, the 50 µg/h dose produced no such episodes, the 75 µg/h resulted in 6 episodes in 177 applications (**3%**), and the 100 caused 7 in 105 applications (**6%**). Respiratory depression was more common in patients who had had **pulmonary surgery**, received full doses of **concurrent CNS medication**, had received large amounts of **rescue analgesic**, who were **under 63 kilos in weight**, and who were **ASA Class III & higher**. It may reasonably be expected that the frequency of this adverse effect will increase should TTS use spread into more debilitated populations on the medical services and into less well supervised postoperative settings.

Until more is known about the pharmacodynamics of respiratory depression caused by low dose fentanyl it would be prudent to allow the 50 µg/h dose into general use, restrict the 75µg/h dose to clinical settings which would allow immediate recognition of hypoventilation, and restrict the postoperative use of the 100 µg/h dose to patients in closely monitored settings who have known opioid tolerance, high estimated clearance, or procedures known to cause several days of intense pain.

Unanswered is the question as to how clinicians should modify the doses of other concurrent analgesic or CNS active medication in patients

TABLE 1b

MIDODRINE HUMAN PHARMACOKINETICS
AND BIOAVAILABILITY STUDIES

Report Number	Study Conclusion
058-37	30% of administered midodrine is excreted in urine as active metabolite (desglymidodrine) in 8 hours after a single oral dose.
058-38	44.9% of administered Midodrine is excreted in urine as active metabolite (desglymidodrine) within 24 hours following multiple oral doses.
058-39	Midodrine shows a rapid elimination from plasma, in contrast to the prolonged levels of active major metabolite (desglymidodrine). 50% of the total radioactivity injected was excreted into urine over 4 hours and 93% was excreted over 7 days. The largest single component of urinary radioactivity is due to active metabolite.
058-40	76% and 82% of the total midodrine dose administered was excreted in urine after oral and i.v. doses, respectively, over 3 days. A comparison of i.v. and p.o. data indicates complete oral absorption.
058-40a	There is a rapid disappearance of midodrine from plasma, a rapid appearance of desglymidodrine in plasma and a majority of the urinary activity (51-66%) is due to desglymidodrine, which indicates it is the major metabolite of midodrine.
058-133b	The bioavailability of a 2.5 mg midodrine tablet is considered equivalent to 2.5 mg midodrine given i.v. and to 2.5 mg given p.o. as a solution. The absolute bioavailability of the tablet is 93% (95% confidence limits: 84-108%). Excellent bioavailability is demonstrated.

TABLE II

MIDODRINE CLINICAL PHARMACOLOGY STUDIES - SUMMARY TABLE FOR PHARMACODYNAMICS

Report Number	Date of Report	Nature of Study	Number of Subjects	Age (yr)	Weight (kg)	Daily[a,b] Dose	Investigating Group
058-41	5/81	Double blind crossover, Midodrine vs placebo	6F, 6M	23-50	49-92	1 x 2.5 mg p.o.	Chemie Linz, AG
058-42	1/79	Double blind crossover, Midodrine vs ST-1059 vs placebo	2F, 5M	29-43	58-82	M: 1 x 5 mg p.o. ST: 1 x 4 mg p.o.	Chemie Linz, AG
058-43	76	Tolerance: respiratory, cardiovascular, renal, urinary, intestinal and hematologic effects	74	N. S.	N. S.	1 x 0.15 mg/kg i.v. urinary study: 3-4 x 5 mg p.o. (1-8 wks) other studies	Chemie Linz, AG
058-44	73	Open parallel, hemodynamic effects of midodrine (M) vs norepinephrine (NE), M effects in patients with cardiac catheter	6 6 3	25-64 24-65 N. S.	N. S. N. S. N. S.	M: 1 x 0.5 mg/kg i.v. NE: 1 x 1-8 µg/min i.v. M: 1 x 0.3 mg/kg i.v.	Chemie Linz, AG
058-45	4/71	Single blind parallel, hemodynamic effects of midodrine vs placebo	10 placebo 11 midodrine	21-43	N. S.	1 x 5 mg i.v.	First Medical Clinic, Vienna University
058-46	5/67	Open, rheography in head, finger and arm after midodrine.	17F, 5M	38-72	N. S.	1 x 5 mg. p.o.	Chemie Linz, AG
		Chronic treatment of headache with midodrine	10	N. S.	N. S.	3 x 2.5 mg p.o. (4-6 wks)	Chemie Linz, AG
058-47	77	Open, carbohydrate & fat metabolism in normal (N) and diabetic (D) subjects after midodrine.	N: 2F, 3M D: 4F, 2M	42±13 36±17	120±21[a] 125±33[a]	1 x 5 mg i.v.	Chemie Linz, AG
			D: 2F, 3M (a) D: 3F, 2M (b) D: 3F, 2M (c)	46±16 68± 9 68±10	113±33[a] 104±11[a] 107±26[a]	3 x 5 mg p.o. (5 days)	

a All midodrine was used as the hydrochloride salt and was administered for 1 day only, unless noted otherwise.
b % weight, Broca = 100%
N. S. - not stated.

(a) Diabetes controlled by diet only.
(b) Diabetes controlled by oral drugs.
(c) Diabetes controlled by insulin.

TABLE 2

URINARY ELIMINATION OF DESGLYMIDODRINE AFTER ORAL ADMINISTRATION OF MIDODRINE

Study Report Number	Nature of Study	Mean Urinary Elimination of Desglymidodrine (µg) In Time Periods (hr)					Total Recovery (% dose)	n
		0-2	2-4	4-8	8-12	12-24		
058-37	Single dose 5 mg	526	320	179	0	N.D.	30.0	6
058-38	Multiple doses 3 X 5 mg 4 hr	-	960*	1476	1445	685	44.9	6

* Represents 0-4 hr fraction

MULTIPLE ORAL DOSE URINARY EXCRETION STUDY TO EVALUATE MIDODRINE METABOLITES (REPORT 058-38)

Another group of 6 normal healthy male volunteers received three doses of 5 mg of midodrine on a 4 hourly basis. Urine was collected over 24 hours and demonstrated a total elimination of desglymidodrine of 44.9% of the administered dose. The amount of metabolite excreted was similar for the intervals of 0-4, 4-8, and 8-12 hours and therefore the sponsor argued that there is no evidence of accumulation of metabolite.

This reviewer believes that a more prolonged, multiple day, multiple dose study would provide higher confirmation to these results.

SINGLE IV DOSE TO EVALUATE MIDODRINE METABOLITES (REPORT 058-39)

Tritiated midodrine was given to only 1 subject who received 5.11 mg of midodrine by intravenous injection and thin layer chromatography was used to separate midodrine from its metabolites. The initial distributive phase was of 30 minutes and elimination phase with a half-life of 5-6 hours. After 48 hours a very slow secondary clearance phase was evident with a half-life in excess of 160 hours. By 30 minutes, most of the radioactivity was in metabolites and by 60 minutes desglymidodrine was the major compound identified. (See Table 3 for separation of plasma radioactivity).

Total urinary excretion accounted for 93% of the administered dose over 168 hours. Thus, desglymidodrine has a longer plasma half-life and the sponsor believes that this metabolite is responsible for the pharmacological properties of midodrine.

MIDODRINE SINGLE DOSE IV PO STUDY TWO-WAY CROSSOVER - METABOLIC STUDY (REPORT 058-40)

An extensive metabolic study in 6 subjects (3 females) received a tritiated 5 mg intravenous dose of midodrine and an oral dose of 5.3 mg of midodrine was studied in a 2-way crossover design. Thin layer radiochromatography was used with recovery of 56 ±8% of applied radioactivity for plasma and 61±1% for urine. Blood radioactivity was evenly distributed between plasma and formed elements.

Pharmacokinetic parameters are detailed in Table 6. The major clearance half-life for oral and intravenous administration was similar at approximately 3.6-3.9 hours. Bioavailability was close to 109% for oral midodrine essentially identifying complete absorption. Tmax was 0.66 hours. Midodrine disappeared rapidly from plasma being undetectable after 60 minutes and the major metabolite, desglymidodrine, was significant at 1 hour after oral and 2 hours after intravenous dosing. Pharmacokinetic analysis of desglymidodrine clearance could not be performed due to insufficient data. Fecal elimination is minor (2% of dose).

TABLE 6

MAJOR PHARMACOKINETIC PARAMETERS FOR MIDODRINE CALCULATED FROM RADIOACTIVITY DATA OF TABLE 5

	$t_{\frac{1}{2}\alpha}$ (hr)	$t_{\frac{1}{2}\beta}$ (hr)	AUC 0-∞ $\left(\frac{ng \times hr}{ml}\right)$	$V_{d\ area}$ (ml)	C_{max}** (ng/ml)	t_{max} (hr)	Cl_{tot} (ml/min)
Intravenous Administration*							
Mean	0.06	3.87	268.67	106.21	214.30	--	319.60
S.E.+	0.01	0.12	19.37	7.11	28.18	--	26.45
Oral Administration*							
Mean	--	3.58	307.93	100.11	53.91	0.66	--
S.E.	--	0.19	25.93	12.59	4.00	0.12	--

* Parameters were calculated on the basis of one- (oral) or two-compartment (intravenous) models. The doses were: Oral, 5.3 mg; Intravenous, 5.0 mg.

** In the case of intravenous administration, this value represents the extrapolation of the curve to time 0. In the case of oral administration, the corresponding extrapolated value was 64.24 ng/ml.

\+ Standard error of the mean.

Bioavailability of the oral drug was 93.3% based on urinary excretion. Unchanged midodrine appeared in the 0-2 hour urinary sample to exceed 10% and declined very rapidly thereafter.

SINGLE DOSE MIDODRINE BIOAVAILABILITY STUDY (REPORT 058-133)

This study investigated 12 healthy normal male volunteers who received 2.5 mg of midodrine intravenously, orally, and as a solution in a randomized 3-way crossover design. The 3 treatments were considered bioequivalent. These data are presented in Table 10A.

Finally, a comparison of the pharmacokinetic parameters of midodrine and its active metabolite, desglymidodrine, following oral by tablet was demonstrated in this study in Table 10B.

Seven studies were conducted to evaluate human pharmacodynamics of which 4 were exclusively single dose and 3 involved single and multiple dose phases.

SINGLE DOSE TOLERANCE (STUDY 058-41)

In this study, 12 normal volunteers received one 2.5 mg tablet of midodrine in the evening. Twelve hours later blood pressure and heart rate were measured supine and after standing for 1-3 minutes. Subjects recorded their state of vigilance on a scale of 0 meaning very alert to 100 meaning asleep.

There was no difference between the circulatory changes after single doses of midodrine and placebo for the group as a whole, but 5 subjects who the sponsor claims had orthostatic circulatory dysregulation showed improvement on midodrine but not placebo. Eleven of the 12 subjects reported sleeping well but 3 subjects reported pilomotor reactions.

A second single dose study compared midodrine with desglymidodrine (Report 058-42). This study involved 7 subjects who received 5 mg of midodrine and 4 mg of desglymidodrine in a 3-way, randomized study with placebo including a 3-5 day washout period. Sitting and standing blood pressure and heart rate were measured at 1,2,4 and 5 minutes before and 2 hours after each treatment. Hemodynamic parameters were not significantly affected except for a small drop in pulse rate after midodrine or its metabolite. Pilomotor reactions were more pronounced after desglymidodrine than midodrine. These reactions persisted for approximately 2-3 hours after desglymidodrine and 30-240 minutes after midodrine.

TABLE 10A

BIOAVAILABILITY OF 2.5 MG MIDODRINE GIVEN I.V., P.O. AS A SOLUTION AND P.O. OR A 2.5 MG TABLET (10 SUBJECTS) (REPORT 058-133a)

Parameter	Mean	95% Confidence Limits
Absolute Bioavailability of Solution, p.o.	90%	78-102%
Absolute Bioavailability of Tablet, p.o.	93%	84-108%
Relative Bioavailability of Tablet/Solution, p.o.	109%	90-122%

TABLE 10B

COMPARATIVE PHARMACOKINETIC PARAMETERS OF MIDODRINE AND THE ACTIVE METABOLITE, DESGLYMIDODRINE FOLLOWING ORAL DOSING BY TABLET (REPORT 058-133a)

Parameter	Midodrine	Desgly-midodrine
t_{max}	27 ± 12 min	1.1 ± 0.5 hr
C_{max} (ng/ml)	11.2 ± 3.9	5.0 ± 1.6
$t_{1/2}$ (hr)	0.49 ± 0.12	3.0 ± 0.5
AUC (ng x hr x ml^{-1})	9.46 ± 2.09	25.6 ± 6.2
Cl (ml/min)	--	1378 ± 319
V (l)	--	353 ± 80
U_{0-} hr (% of dose)	2.2 ± 0.6	34.4 ± 4.5

MULTIPLE DOSE TOLERANCE (STUDY 058-43)

This was a multi-institutional study detailing the effects of 15 or 20 mg of midodrine given in divided doses over 1-8 weeks in 74 male or female patients. Table 13 summarizes the tolerance study and the effects of midodrine on several systems. Midodrine caused a decrease in the diffusion capacity of the lung in 8 of 10 patients with a reduction of approximately 20%. This was probably due to a reduction in pulmonary perfusion and the sponsor claims that this effect was no longer seen after 22 days of therapy. Seventeen subjects had a reduction in mean heart rate from 78-69 beats per minute but this effect did not intensify with continued therapy. In 3 patients who had been digitalized, more marked effects were seen with the heart rate decreasing to 40 and 50 beats per minute and in a third subject to as low as 25 beats per minute with first degree AV block and a rise in the blood pressure to 230/80. Five days after discontinuing midodrine the heart rate in this third subject returned to 60-70 beats per minute. Without the digitalis this patient was rechallenged after 2 weeks and the heart rate decreased to no lower than 60 beats per minute.

Thus, potentiation of the negative chronotropic effect of digitalis by midodrine is demonstrated in this patient and cautions a serious warning for the combination of midodrine and digitalis.

Renal function demonstrated no significant effect on clearance but 10 patients with prostatic hypertrophy had an increase in residual urine volume and 20 subjects without prostatic disease experienced dysuria. There was an increase in internal sphincter tone and a delayed response to filling state of the bladder. Colonic tone was not effected. There were no abnormalities in the chemistry or blood parameters. There is evidence that midodrine can cause marked pruritis and generalized urticaria which may be due to an effect on histamine release. No effect on coagulation was noted.

Hemodynamic effects were evaluated in 3 studies, the first of which was Report 058-44 in which in one part 6 normal subjects from 25-64 years of age received an intravenous infusion of midodrine of 10 ug/kg/minute. These were compared to 6 other healthy volunteers from 26-65 years of age who received norepinephrine at 1 ug/minute and up to 8 ug/minute to achieve an increase of 40 mmHg in systolic pressure. In the second part, 3 patients undergoing cardiac catheterization had central pressures recorded after an infusion of 10 ug/kg/minute for 30 minutes of midodrine. Table 14 presents the data obtained in this study. Both midodrine and norepinephrine increased blood pressure but midodrine lowered pulse pressure markedly compared to norepinephrine 21 versus 6 beats/minute. Midodrine caused a lower reduction in plasma and blood volume. Midodrine caused an increase in both systemic and pulmonary blood pressures and stroke volume and pulse rate were decreased. Cardiac output failed while peripheral and pulmonary vascular resistances rose.

TABLE 13

MIOCORINE MULTI-DOSE TOLERANCE STUDY - SUMMARY TABLE (REPORT 05[illegible]-43)

Parameter	Investigator	Number of Subjects	Results
Pulmonary function	F. Witek (Wilhelminenspital, Vienna)	10 (with ED)*	Reduction in diffusion capacity and specific diffusion (8/10). Ventilation unchanged.
Cardiac function	E. Kiesewetter (Wilhelminenspital, Vienna)	17	Reduction in heart rate (17/17); negative T3 (1/17); potentiation of digitalis action (3/17).
Renal function	A. Hostbeck (Wilhelminenspital, Vienna)	7	No effect on renal function after 6 weeks.
Bladder dynamic function	R. Marson (Krankenhaus-Rudolfsstiftung, Vienna)	10 (with PH)	Increased residual urine volume (6/10) and total urine retention (4/10) after single i.v. dose (0.15 mg/kg).
		20 controls	Controls dysuric 10-15 min after single i.v. dose (0.15 mg/kg).
		10 (with PH)	No effect on micturition after 15 mg/day for 2 weeks.
Colonic tone	E. Deimer (Roentgenological Diagnostic Institute, Vienna University)	7 (with HVD)	No significant change in colon tone after 8 weeks at 15 mg/day.
Hematology and blood chemistry	E. Kiesewetter (Wilhelminenspital, Vienna)	17	No significant changes after 6 weeks.
Bone marrow status	P. Hocker (Hanusch-Krankenhaus, Vienna)	10	One female experienced allergic pruritis on second day; no bone marrow changes after 6 weeks.
Blood coagulation and fibrinolysis	M. Fischer (Municipal Hospital Lainz, Vienna)	10	No changes after 3 weeks.

Except where indicated under "Results," all doses were 20 mg/day p.o., and the drug was administered as the hydrochloride salt.

* ED = extrapulmonary disease, PH = prostatic hypertrophy, HVD = hypotensive vascular disorders.

TABLE 14

EFFECT OF MIDODRINE (10 µG/KG/MIN INFUSION: 50 MIN IN GROUP 1: 30 MIN IN GROUP 2) AND OF NOREPINEPHRINE (1-8 UG/MIN) ON CIRCULATORY PARAMETERS. (REPORT 058-44)

GROUP 1

	Blood Pressure (mm Hg)		Heart Rate	Hematocrit	Plasma Volume	Blood Volume
	Systolic	Diastolic	(beats/min)	(%)	(ml)	(ml)
Midodrine	+45**	+21*	-20.6	+0.66*	-210**	-301**
	(±17.5)	(±18.4)	(±13.06)	(±0.41)	(±120.7)	(±163.8)
Norepinephrine	+36**	+15.6	-5.6	+0.37 ns	-584**	-966
	(±14.8)	(±13.57)	(±2.61)	(±0.47)	(±251.2)	(±496.6)

GROUP 2

	Pressure (Aorta) (mm Hg)		Pressure Pulmonary artery (mm Hg)		Heart Rate	Minute Output	Stroke Volume	Peripheral Resistance	Pulmonary Circulation Resistance
	Systol.	Diastol.	Systol.	Diastol.	(beats/min)	(ml)	(ml)	(dn-S-dyn-sec)	(dn-S-dyn-sec)
Midodrine	+48*	+25 ns	+6.66 ns	+3.66 ns	-18.66 ns	-970*	+6.33 ns	+753.33**	+96.66*
	(±14.9)	(±19.0)	(±5.51)	(±3.01)	(±20.59)	(±329)	(±17.15)	(±177.85)	(±43.14)

* p < 0,05, ** p < 0,01, ns not significant

All subjects experienced piloerection and coldness and 1 patient had a desire to urinate without being able to empty the bladder. This condition was eliminated by phentolamine.

Report 058-45 was undertaken in 10 patients who had no signs of cardiovascular disease. Venous occlusion plethysmography was studied after midodrine was administered at a dose of 5 mg intravenously. Table 15 details these results and shows a small decrease in venous capacity with an effect on venous tone becoming noticible before a change in blood pressure. Reduction in heart rate that was statistically significant was also noted.

The final hemodynamic study was 058-46 which used a rheographic technique to measure electrical conductivity to assess tone. Measurements were made before and 30 minutes after an oral dose of 5 mg of midodrine. Eleven rheumatic patients and another 11 with vascular spondylogenous headaches were studied. There was a variable response in terms of index finger arterial pressure changes as well as a change in vertebral artery tone. Overall, an increase in tone was demonstrated in 15 cases, little change in 5 and constriction in 2 cases.

Report 058-47 evaluated normal and diabetic subjects who received intravenous midodrine at 5 mg. No significant effects on glucose tolerance, serum free fatty acids or lipids were noted.

CONCLUSIONS

The sponsor concluded that the pharmacological effects of midodrine are due principally to the active metabolite, desglymidodrine, and that midodrine qualitatively resembles norepinephrine in its vascular constrictor effects but has a less effect on diminishing plasma and blood volume. There is evidence that midodrine increases venous tone which may occur before systemic hypertension. This may decrease venous pooling in orthostatic hypotensive patients. Midodrine stimulates alpha receptors of the urinary bladder and can cause urinary retention but has no detrimental effect on renal, colonic or blood parameters. There is a decrease in pulmonary diffusion capacity.

It should be noted that all of these studies were performed outside of the United States and only minimal summaries were provided.

TABLE 15

THE EFFECT OF INTRAVENOUS INFUSIONS OF MIDODRINE (5.0 MG DOSE: 5 MIN INFUSION) ON CIRCULATORY PARAMETERS OF LOWER LEG AND FOOT (MEANS ± STANDARD DEVIATION) (REPORT 050-45)

Group	N	Baseline Value	Infusion Value	After 1 min	After 15 min	After 30 min
			Circulation (ml/100 ml tissue/min) change in comparision to baseline			
			Lower Leg			
Control+	10	2.70 ± 0.42	+0.07 ± 0.39	+0.17 ± 0.44	-0.21 ± 0.31	-0.09 ± 0.45
Midodrine	11	2.70 ± 0.91	-0.11 ± 0.17	+0.02 ± 0.19	-0.10 ± 0.21	-0.25 ± 0.32
			Foot			
Control	10	2.09 ± 1.92	-0.02 ± 0.65	-0.10 ± 0.81	-0.25 ± 0.85	-0.22 ± 0.66
Midodrine	11	1.87 ± 1.30	+0.04 ± 0.24	+0.16 ± 0.31	+0.20 ± 0.53	+0.21 ± 0.96
			Venous Capacity (ml/100 ml tissue) change in comparison to baseline			
Control	10	4.09 ± 0.91	+0.25 ± 0.52		+0.13 ± 0.24	+0.25 ± 0.32
Midodrine	10	4.04 ± 1.09	-0.11 ± 0.13**		-0.04 ± 0.17	+0.02 ± 0.27
p*			< 0.05		< 0.05	> 0.05
			Blood Pressure (mm Hg) change in comparison to baseline			
			Systolic pressure			
Control	10	102.8 ± 14.2	0.0 ± 3.8	+0.1 ± 2.3	-3.4 ± 6.7	-2.9 ± 6.3
Midodrine	11	113.1 ± 22.1	-1.0 ± 3.7	-2.0 ± 4.2	-1.5 ± 4.2	+3.5 ± 8.0
			Diastolic pressure			
Control	10	54.3 ± 6.5	+0.7 ± 2.0	+0.8 ± 1.8	-1.6 ± 3.9	-1.6 ± 4.7
Midodrine	11	61.5 ± 12.3	+1.0 ± 3.6	+0.2 ± 3.7	+1.5 ± 3.7	+0.8 ± 6.8
			Pulse Rate/min change in comparison to baseline			
Control	10	65.5 ± 11.1	+0.2 ± 1.0	+0.6 ± 2.0	+0.2 ± 2.4	+0.2 ± 2.5
Midodrine	11	65.0 ± 10.8	-1.4 ± 1.6	-2.7 ± 2.5	-6.5 ± 4.9	+4.9 ± 5.1
p*			< 0.05	< 0.01	< 0.01	< 0.01

* X-test according to van der Waerden
** Wilcoxon paired test (with preliminary value): p < 0.05
\+ Normal saline solution

NDA #19-815

ROBERTS LABORATORIES (MIDODRINE)

A DOUBLE BLIND PHASE III CROSSOVER COMPARISON OF THE SAFETY AND EFFICACY OF MIDODRINE AND EPHEDRINE IN PATIENTS WITH SEVERE IDIOPATHIC ORTHOSTATIC HYPOTENSION (PLACEBO WASHOUT)
PROTOCOL #20,762-1

INVESTIGATORS:

This is a single center study conducted at the Cleveland Clinic Foundation in Cleveland, Ohio by Drs. Robert Tarazi, F. Fouad and E. Bravo. The project was initiated in August of 1983 and completed in May of 1984.

PROTOCOL:

Figure 1 details the design of this study which included a single blind baseline period in which patients were hospitalized for 2 days and received an oral matching placebo on a tid basis. All previous pressor agents were withheld from the patients during this baseline period, however concomitant continued use of fludrocortisone (0.1-0.2 mg bid) and the continued wearing of a Jobst garment were permitted. The protocol called for this to be a multicenter trial in which each center was to enroll at least 10 to 20 patients. Patients were to have idiopathic orthostatic hypotension which was not specifically defined in the protocol under patient description nor inclusion criteria. These patients could have orthostatic hypotension due either on a primary basis (e.g. Shy-Drager) or secondary to conditions such as diabetes mellitus or Parkinsonism.

Exclusion criteria included the history of persistent supine hypertension >180/100 or severe symptomatic coronary artery disease, renal disease, thyrotoxicosis, or significant liver dysfunction. The presence of a pheochromocytoma, dementia, or concomitant use of MAO inhibitors were additional exclusion criteria.

The protocol suggested that several confirmatory diagnostic tests were to be included which included thermoregulatory sweat test, serum protein electrophoresis, cortisol, thyroxine, electrolytes, catecholamines, and a rectal biopsy for amyloid.

After the single blind placebo 2 day period, patients would enter a titration period for 3 to 5 days in which they were randomized in a 1:1 basis to initially receive midodrine or ephedrine. They were to be titrated to optimal blood pressure control which was defined as a supine systolic pressure of 140 to 180 with a diastolic blood pressure not greater than 100 with concomitant standing systolic pressure of >80 mmHg or/and improvement in subjective clinical condition. Medication was administered tid at least 30 minutes before meals and for

General Comments Regarding the Abuse Liability of TTS Fentanyl

The submission by this sponsor of an NDA for a new dosage form for fentanyl posed a new regulatory problem. It was the first of many "non-injection" parenteral delivery systems for older drugs, where modification of the pharmacokinetics of the delivery of an agent reveals a new dimension of the pharmacodynamic spectrum of the drug. Recent experience with the enhancement of the addictive potential of intranasal cocaine by its conversion to smoked cocaine or "crack", stands as a warning of the possibility of significantly altering the abuse pattern of a known drug of abuse by a change in the dosage form. As our ability to predict the abuse liability of drugs improves the relationship of the pharmacokinetics of the delivery system to the pharmacodynamics of abuse has become an important dimension in the evaluation of both licit and illicit narcotic drugs.

Fentanyl is not currently a drug of abuse for the general population, although the persistence of clandestine synthesis and illicit distribution shows that it is a desirable drug of abuse. The current low prevalence of abuse is probably due to the relative scarcity of access to the drug. Among health care providers with high access to the drug (anesthesiologists, operating room personnel, intensive care unit staff) it remains a significant drug of abuse and is second only to meperidine in total number of addicted health care professionals.

The TTS fentanyl system will be available from pharmacies, clinics, and patient's homes as well as the relatively controlled operating and recovery room environment. In order to evaluate the abuse liability of this new dosage form it will be necessary to answer the following questions:

1. What is the abuse and dependence potential of the TTS system to the intended users when used as directed?

2. What is the risk of abuse and dependence of the TTS system to health care providers handling the system?

3. What is the abuse and diversion potential of the intact TTS system?

4. What is the magnitude of the risk posed by the fentanyl in used or removed patches and what measures should be taken to control such risks?

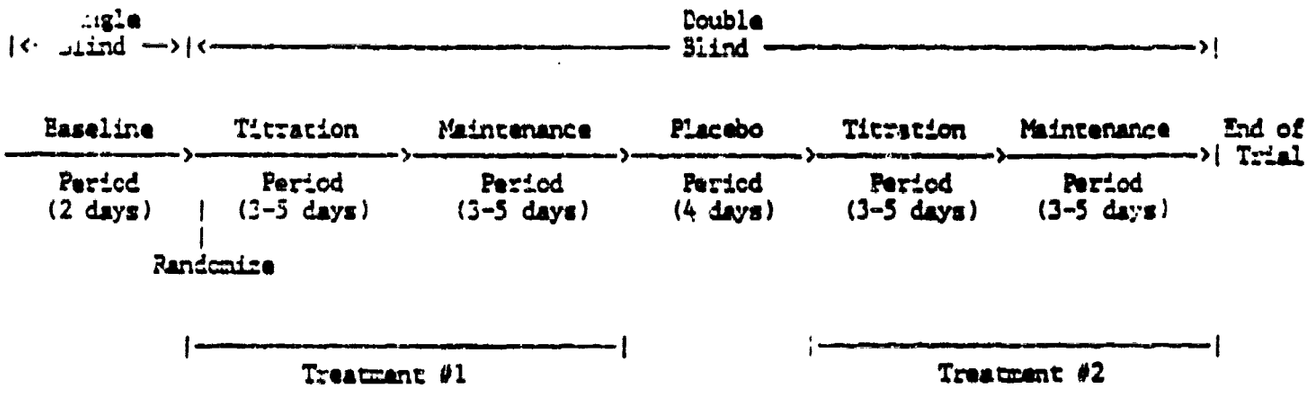
In an attempt to answer these questions a meeting was held on the 21st of February 1990 between representatives of the sponsor, FDA, NIDA, and DEA. The following is a review of that meeting and material provided by DEA, NIDA, and the sponsor addressing these questions.

Risk of abuse of TTS When Used as Directed

There was universal agreement among the parties to the meeting that the TTS system had pharmacokinetic properties which gave it less abuse potential than IV or IM fentanyl when used as directed. The TTS system

FIGURE 1

MIDODRINE STUDY DESIGN
(20,762-1)



administered tid at least 30 minutes before meals and for midodrine dose level was 2.5 mg tid titrating up to 5, then 7.5, then 10 mg tid. For ephedrine it was 6 mg tid to 12 to 18 to 24 mg tid.

Once a maximal accepted dose level was attained, that level was given for 3 to 5 days in a "maintenance period". This was followed by a 2 day placebo washout period. Patients were then crossed over to the other medication for a repeat of the titration and maintenance periods.

Blinding was achieved by placing 2.5 mg midodrine and 6 mg ephedrine tablets in opaque white gelatin capsules which were identical to placebo capules.

During the last day of the placebo run in period, baseline blood pressure determinations were conducted using an automated noninvasive blood pressure monitor from 8 A.M. to 4 P.M. These measurements were made after a 3 minute supine rest after a 3 minute sitting rest and after 1 minute of quiet standing. Radial pulse was measured at each interval. Signs or symptoms of hypotension were also recorded. During titration only 2 doses of medication were given on the first and if additional medication was required, a third single dose was permitted on Day 2. During the maintenance period the dosing was at 7:30 A.M., 12:30 P.M. and 5:30 P.M.

Adverse effects of pressor therapy could be treated if the supine blood pressure was >180/100 by using 5 mg intravenously of phentolamine and a reduction in the pressor drug dosage. Severe symptomatic bradycardia with a heart rate <40 beats per minute was to be treated with 0.5 to 1.0 intravenous atropine. Blood tests were obtained at baseline and after the first and second legs of the crossover study. Patients achieving a satisfactory clinical response were permitted to continue the drug as outpatients under a compassionate study.

The protocol defined patient failure as that which the patient had a blood pressure >180/100, bradycardia with symptoms requiring atropine therapy, persistent nausea, vomiting, piloerection, headaches or tingling, or failure to get a standing blood pressure >80 mmHg. If there was no control of symptomatic or systolic hypotension or change in the quality of life, this was also considered a treatment failure. It is in this phase of the protocol that there is a suggestion of a definition of orthostatic hypotension, of a drop in standing blood pressure by 30 mmHg systolic and 15 mmHg diastolic.

Efficacy in the protocol is defined as a decrease in the symptoms due to postural hypotension or a less decrease in standing blood pressure on drug if there was no hypertension defined as ≥180/100 supine blood pressure 1 hour after the morning dose. Efficacy would also be defined if this effect lasts for at least 3 hours and an absence of significant side effects.

Of the 9 patients entered into this study, 1 patient (4709) ›ed a cardiac arrhythmia during the initial placebo run in ır. . and therefore was dropped from the study and was not ıalyzed.

:ATISTICAL PLAN

Since effectiveness claims for midodrine are to be made ›mpared to ephedrine during maintenance therapy, the data ›tained during titration was not analyzed and statistical ›mparisons were made only during the maintenance phase. There ıs a great deal of variability in the number of blood pressures ıasured during each phase of the experiment and therefore data ıre presented using both mean and median descriptors. The ıvestigators did not employ a uniform procedure for making ıtries in the case report form when the patients were unable to :and and the statistical report points out that the blood :essures were not taken as per protocol often and therefore all lood pressure measurements before 6 A.M. and any blood pressure ıading <40 were deleted from the analyses. The sponsor ıerefore analysed unable to stand as either that that entry was resent in the case eport form or if no entry was in the case sport form but there was an entry for supine or sitting blood ressure but not for standing, it was assumed the patient met ıat criteria. A block design of analysis was used so that each ıtient could serve as his own control and a pooled error term rom the block design was used to make pair-wise comparisons via ıl ': test.

It should be noted that patient 4705 did not achieve aintenance well on ephedrine and this was treated as missing ata so that the block design had 1 empty cell. The sponsor used MDP program for statistical analysis.

ATIENTS ENTERED

All 8 patients underwent all phases of the protocol except or Patient 4705 which did not enter the ephedrine maintenance ince he did not have a clinical response that was satisfactory uring ephedrine titration. Patient randomization to study edication is demonstrated in Table 1 and demographics in Table .

The population comprised 4 men and 4 women with an average ge of 60 years with an average duration of orthostatic ypotension of 5 years. All 8 patients had severe symptoms from rthostatic hypotension and 1 patient each had diabetes and arkinsonism. One patient (4701) had a pacemaker which will omplicate the results of analysis. Table 3 details the baseline ardiovascular parameters and demonstrates an approximately 50 mm rop in systolic blood pressure accompanied by an increase of bout 6 beats per minute in heart rate. Standing systolic blood r-sure >80 occurred only 65% of the time in these patients. percent of the time, patients were unable to stand due to x. sive weakness, dizziness or syncope. It is important to

TABLE 1

PATIENT RANDOMIZATION TO
STUDY MEDICATION
(20,762-1)

PATIENT NO.	TREATMENT 1	TREATMENT 2
4701	midodrine	ephedrine
4702	ephedrine	midodrine
4703	ephedrine	midodrine
4704	ephedrine	midodrine
4705	midodrine	ephedrine*
4706	ephedrine	midodrine
4707	midodrine	ephedrine
4708	ephedrine	midodrine
4709**	none	none

* Patient 4705 did not complete the maintenance phase of ephedrine treatment (treatment #2).

** Patient 4709 was entered into the study and completed the initial placebo period. but never received active treatment.

TABLE 2

PATIENT ROSTER
(20.762-1)

PATIENT NUMBER	INITIALS	AGE	SEX	DIAG-NOSIS	YEAR Dx	START DATE	END DATE	COMMENTS
4701	.	78	M	IOH	1973	8/16/83	9/5/83	S/P Pacemaker (1973) Incontinence
4702	.	80	M	IOH	1969	9/12/83		—
4703	.	43	M	IOH	1980	10/10/83		Incontinence
4704	.	52	F	IOH	1982	11/8/83		Incontinence
4705	.	48	F	IOH	1982	1/9/84		—
4706	.	55	M	IOH	1980	2/13/84		—
4707	.	65	F	IOH	1980	7/9/84		—
4708	.	62	F	IOH	1984	9/21/84		Mild Diabetes (diet controlled)
4709	.	51	M	IOH	1982	4/30/84	5/10/84	Parkinsons Dis. COPD

TABLE 3

MEAN BASELINE CARDIOVASCULAR PARAMETERS,
SYMPTOM INCIDENCE AND DEMOGRAPHY IN STUDY PATIENTS
(20,762-1)

VARIABLE	VALUE
Number of Patients	8
Age	60.4 years
Duration of Disease	4.9 years
% Males	50
% Females	50
Supine Blood Pressure	147.0/85.7
Standing Blood Pressure	89.2/63.5
Supine Pulse Rate	74.6
Standing Pulse Rate	80.6
% Incidence Unable to Stand	10.7
% Incidence Standing Systolic BP > 80 mm Hg	65.0
% Incidence Systolic BP > 180 mm Hg:	
Supine	8.0
Sitting	0
Standing	0
% Incidence Systolic BP > 200 mm Hg:	
Supine	2.9
Sitting	0
Standing	0

note that patients 4701, 4702 and 4707 had supine systolic hypertension with several readings >180 mmHg during the baseline period. These patients technically should have been excluded according to the protocol. In addition, Patients 4703, 4704 and 4708 had infrequent blood pressures <80 mmHg with standing and therefore would not have met the criteria of severe orthostatic hypotension.

Table 4 details the supine and standing blood pressure results over the entire group throughout each phase of the study. Both midodrine and ephedrine produced statistically significant increases in both supine systolic and diastolic blood pressures compared to placebo but were not different between each other. Standing blood pressure with midodrine was statistically significantly greater than that produced by placebo, but ephedrine was not statistically different than placebo. P values for these comparisons are found in Table 5.

Table 6 details the mean change in blood pressure from the baseline which confirms this data.

Pulse rates increased for ephedrine but decreased for midodrine. The higher standing heart rate on ephedrine may be explained by a reflex component as well as partial beta agonism.

Tables 7 and 8 detail mean and mean change data.

The percentage of patients who were unable to stand at baseline was 10.7% and during the placebo washout, 14.2%. On midodrine this was 5.3% compared to 10% on ephedrine. The success rate attributable to midodrine was significantly greater than both placebo and ephedrine when there was an arc sine transformation waited by the reciprocal of the variances. The percentage of patients with standing systolic blood pressure ≥80 mmHg is demonstrated in Table 10 and again demonstrates a higher prevalence during midodrine than ephedrine compared to placebo. The smaller standard deviations during the midodrine maintenance period suggests greater consistency in response.

Table 11 details the doses used for midodrine and ephedrine during the maintenance period for each of the 8 patients.

SAFETY ANALYSIS

During this study patients received midodrine from 6 to 9 days with an average of 7.4 days and ephedrine for 7 to 10 days with an average of 7.8 days. Table 12 details the adverse reactions but the severity of these reactions were not reported by the investigator but no patient required discontinuation of medication. No deaths occurred in this study.

The percentage of patients with supine systolic blood pressure is >180 mmHg as shown in Table 13 and 200 mmHg in Table 14. Note that the incidence of severe hypertension >200 mmHg occurred in 12% of the patients during midodrine versus 7% on

TABLE 4

MEAN SUPINE AND STANDING
BLOOD PRESSURE (mm Hg) IN PATIENTS WITH SEVERE
IDIOPATHIC ORTHOSTATIC HYPOTENSION TREATED WITH
ORAL PLACEBO, MIDODRINE AND EPHEDRINE
(20,762-1)

	MEAN BLOOD PRESSURE (mm Hg) ± SD			
	SUPINE		STANDING	
TREATMENT	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
Baseline	147.0 ± 19.2	85.7 ± 7.5	89.2 ± 8.2	63.5 ± 7.1
Midodrine - Titration	164.0 ± 24.0	89.5 ± 10.0	97.8 ± 14.2	65.0 ± 7.0
Midodrine - Maintenance	165.8 ± 23.9	91.5 ± 8.8	105.6 ± 10.6	68.5 ± 9.4
Ephedrine - Titration	156.5 ± 21.9	88.0 ± 7.2	91.2 ± 15.0	61.7 ± 8.6
Ephedrine - Maintenance	161.6 ± 19.6	90.9 ± 7.8	90.4 ± 12.5	63.1 ± 9.0
Placebo	150.0 ± 19.2	85.2 ± 8.1	87.2 ± 13.4	60.6 ± 8.9

TABLE 5

PROBABILITY VALUES ASSIGNED TO COMPARISONS OF
MAINTENANCE THERAPY OF EACH ACTIVE TREATMENT VS. PLACEBO
(CARDIOVASCULAR PARAMETERS DURING THE STUDY)
(20.762-1)

PARAMETER MEASURED	PAIRED TREATMENT COMPARISONS		
	Mido.v.Pbo.	Eph.v.Pbo.	Mido.v.Eph.
Supine Systolic	< .001	< .01	N.S.
Supine Diastolic	< .01	< .01	N.S.
Sitting Systolic	< .001	N.S.	< .0001
Sitting Diastolic	< .002	N.S.	< .10
Standing Systolic	< .0001	N.S.	< .001
Standing Diastolic	< .001	N.S.	< .05
Supine Pulse	< .05	< .001	< .00001
Sitting Pulse	< .01	< .0001	< .0001
Standing Pulse	< .01	< .02	< .0001

TABLE 6

MEAN CHANGE FROM BASELINE IN SUPINE AND STANDING BLOOD PRESSURE (mm Hg) IN PATIENTS WITH SEVERE IDIOPATHIC ORTHOSTATIC HYPOTENSION AFTER ORAL PLACEBO, MIDODRINE AND EPHEDRINE
(20,762-1)

	MEAN CHANGE IN BLOOD PRESSURE (mm Hg)			
	SUPINE		STANDING	
TREATMENT	SYS.	DIA.	SYS.	DIA.
Placebo	3.0	-0.5	-2.0	-2.9
Midodrine - Titration	17.0	3.8	8.6	1.5
Midodrine - Maintenance	18.8	5.8	16.4	5.0
Ephedrine - Titration	9.5	2.3	2.0	-1.8
Ephedrine - Maintenance	14.6	5.2	1.2	-0.4

TABLE 7

MEAN SUPINE AND STANDING
PULSE RATES (bpm) IN PATIENTS WITH SEVERE
IDIOPATHIC ORTHOSTATIC HYPOTENSION TREATED WITH
ORAL PLACEBO, MIDODRINE AND EPHEDRINE
(20.762-1)

TREATMENT	MEAN PULSE RATE ±SD	
	SUPINE	STANDING
Baseline	74.6 ± 9.0	80.6 ± 10.7
Midodrine - Titration	76.8 ± 7.3	80.4 ± 11.9
Midodrine - Maintenance	73.8 ± 8.6	76.5 ± 8.0
Ephedrine - Titration	82.2 ± 6.1	88.3 ± 8.2
Ephedrine - Maintenance	84.2 ± 8.0	88.6 ± 8.1
Placebo	77.3 ± 6.8	83.0 ± 12.1

TABLE 8

MEAN CHANGE FROM BASELINE IN SUPINE AND STANDING PULSE RATES (bpm) IN PATIENTS WITH SEVERE IDIOPATHIC ORTHOSTATIC HYPOTENSION TREATED WITH ORAL PLACEBO, MIDODRINE AND EPHEDRINE
(20,762-1)

	MEAN CHANGE IN PULSE RATE (bpm)	
TREATMENT	SUPINE	STANDING
Placebo	2.7	2.4
Midodrine - Titration	2.2	-0.2
Midodrine - Maintenance	-0.8	-4.1
Ephedrine - Titration	7.6	7.7
Ephedrine - Maintenance	9.6	8.0

TABLE 10

PERCENTAGE OF STANDING SYSTOLIC BLOOD PRESSURE READINGS GREATER THAN 80 mm Hg
(20.762-1)

TREATMENT	MEAN % INSTANCES ±SD
Baseline	65.0 ± 18.3
Midodrine - Titration	74.[illegible] ± 21.1
Midodrine - Maintenance	81.8 ± 8.8
Ephedrine - Titration	63.3 ± 22.9
Ephedrine - Maintenance	59.1 ± 16.4
Placebo	54.8 ± 19.8

TABLE 11

INDIVIDUAL MAINTENANCE PERIOD DOSE LEVELS
OF MIDODRINE AND EPHEDRINE
ACHIEVED DURING THE STUDY
(20.762-1)

PATIENT NUMBER	MIDODRINE (mg TID)	EPHEDRINE (mg TID)
4701	7.5	18.0
4702	7.5	18.0
4703	10.0	24.0
4704	10.0	24.0
4705	10.0	N.D.*
4706	10.0	24.0
4707	7.5	24.0
4708	5.0	24.0
AVERAGE	8.4	22.3

* N.D.. not possible to determine as no maintenance dose could be established.

MEETING MINUTES
NDA 19-813

MAR 7 1989

DRUG: Transderamal Therapeutic System (Fentanyl)
SPONSOR: Alza Corporation
DATE: February 2, 1989
LOCATION: Conference Room 10B-45

ATTENDEES: P. Leber, M.D.
F. Vocci, Ph.D.
E. Nevius, Ph.D. (HFD-713)
P. Kelley, Ph.D. (HFD-713)
R. Temple (HFD-100)
P. Botstein (HFD-100)
C. Kovacs, CSO

SUBJECT: Working Meeting

Background:

The firm's application was transferred to this division in May, 1988. On June 17, 1988, the firm was informed by a teleconference that their proposed labeling claim was not supported by the type of preclinical and clinical data submitted. Instead of withdrawing the NDA and re-submitting a new package to support a revised claim, the firm amended their application with a revised indication: "...for the control of moderate to severe pain in patients requiring opioid analgesia following surgery or for palliative therapy in patients with cancer."

Dr. Leber stated that the purpose of this meeting was to discuss the difficulties in reviewing this application. The following was discussed:

1. Dr. Vocci made a presentation of the clinical studies performed by the firm in support of their post-op claim, their reported findings, and ADR's.

   There were 6 controlled studies performed in the perioperative/post-operative setting utilizing the fentanyl patch versus a placebo patch and evaluating the need for supplemental morphine and changes in pain intensity. Dr. Vocci pointed out the following:
   (1). Data from 5 of the studies demonstrates that the patch reduces but does not eliminate the need for supplemental morphine.
   (2). This reduction in need for supplemental morphine occurs over the 12-24 hour post-op period. During the first 0-12 hours post-op, the patch has sub-therapeutic effects.
   (3). Respiratory depression and nausea/vomiting increased in the fentanyl patch groups.
   (4). Instructions for the patch recommend a bolus of 100-300 micrograms of fentanyl intraoperatively.

   Dr. Kelley stated that in the Caplan study, the p value is slightly in favor of the fentanyl treatment.

   Dr. Leber agreed that over the time interval selected, the firm does demonstrate effectiveness of their product as an analgesic. However, questions and concerns regarding safety in the perioperative environment should not be made by this division. Dr. Leber recommended that a

TABLE 12

ADVERSE REACTIONS TO STUDY MEDICATIONS
(20,762-1)

TREATMENT GROUP	PATIENT NUMBER	ADVERSE REACTION REPORTED	
		EVENT	PRE-EXISTING CONDITION
Placebo	4701	Hypokalemia	No
Midodrine	4701	Dizziness	Yes
	4701	Lightheadedness	Yes
	4707	Hypokalemia	Yes
	4707	Scalp Pruritis	No
	4707	Scalp Tingling	No
Ephedrine	4701	Dizziness	No
	4701	Lightheadedness	No
	4705	"Cardiac Awareness"	No
	4705	Photosensitivity	No
	4705	"Pounding in Ears"	Yes
	4708	Dysequilibrium	Unknown

TABLE 13

MEAN PERCENT INSTANCES OF SYSTOLIC BLOOD PRESSURE (SBP) READINGS GREATER THAN 180 mm Hg IN PATIENTS WITH SEVERE IDIOPATHIC ORTHOSTATIC HYPOTENSION AFTER ORAL PLACEBO, MIDODRINE AND EPHEDRINE (20,762-1)

	% SBP > 180 mm Hg		
TREATMENT	Supine	Sitting	Standing
Baseline	8.0	0	0
Midodrine - Titration	26.4	4.8	0.3
Midodrine - Maintenance	25.2	3.5	0.4
Ephedrine - Titration	14.5	2.2	0
Ephedrine - Maintenance	24.8	0	0
Placebo	13.9	0.9	0

TABLE 14

MEAN PERCENT INSTANCES OF SYSTOLIC BLOOD PRESSURE (SBP) READINGS GREATER THAN 200 mm Hg IN PATIENTS WITH SEVERE IDIOPATHIC ORTHOSTATIC HYPOTENSION AFTER ORAL PLACEBO, MIDODRINE AND EPHEDRINE
(20,762-1)

	% SBP > 200 mm Hg		
TREATMENT	Supine	Sitting	Standing
Baseline	2.9	0	0
Midodrine - Titration	8.6	0.9	0.3
Midodrine - Maintenance	11.7	1.6	0.4
Ephedrine - Titration	6.5	0.6	0
Ephedrine - Maintenance	6.8	0	0
Placebo	3.4	0.3	0.3

ephedrine.

There is no dicernable trend or clear abnormalities in any of the chemistry or blood hematology values during this study.

MEDICAL REVIEW OFFICER'S COMMENTS ON THIS STUDY

It is clear that the sponsor offers this protocol as one of the two well controlled trials required for the establishment for the safety and efficacy of midodrine in idiopathic orthostatic hypotension. Unfortunately, this study fell down in quality in many aspects. From a protocol technical point of view, this study enrolled only 8 patients rather than a minimal of 10 patients required for each center. Only 1 center actually enrolled patients. The nature of the patients is not well defined and unfortunately 2 of them represent conditions substantially different from idiopathic orthostatic hypotension of the Shy-Drager or Bradbury-Eggleston variety. If one excludes these 2 patients since they did not have idiopathic orthostatic hypotension and also excludes those patients who were technically protocol violators since they had severe supine hypertension, then there are so few patients left that this protocol's data would be insufficient to analyze. The lack of the investigator following the protocol in obtaining blood pressure measurements when required as well as providing medication when required, presumably is the explanation for why the sponsor does not provide data regarding the duration of action, dose-effect data, etc. The statistical approach of omitting readings because of the investigator errors and omitting other data also weakens the analysis. The protocol stated that when a patient's blood pressure reached 180/100 they were to receive intravenous phentolamine. This appears not to have been done despite the fact that many such readings were recorded during the course of the trial.

It is unfortunate that patients with idiopathic orthostatic hypotension are so uncommon and that carefully controlled trials can not be performed in large numbers of patients in many centers. It is even more unfortunate that when such patients are found that the protocol was not followed meticulously to obtain the important data required to properly analyze midodrine's effectiveness. The confounding influence of the background of Florinef and Jobst garment are additional problems as well as the lack of data providing diagnostic confirmation as the protocol requested. The quality control of the automated blood pressure device used in this trial is not stated. From a statistical point of view, the placebo baseline was not used for comparison of the effects of ephedrine and midodrine with the argument that there were different periods of time during each of these phases in the protocol. The statistical approach was therefore a least significant difference. Another very weak factor is demonstrated in that the investigator did not record in the case report form that the patient could not stand (in several cases) which obviously was a key endpoint for analyses. The sponsor therefore concluded that if no entry was made but if there was a sitting or

supine blood pressure but not a standing blood pressure recorded that one could assume the patient did not stand. This obviously is hazardous and again points out the lack of careful conduct in this protocol.

From a safety point of view, this reviewer is concerned about the increased frequency of very severe hypertension in patients on midodrine compared to ephedrine. Twelve percent of patients on midodrine maintenance had a systolic blood pressure >200 compared to 7% on ephredrine. The fact that approximately 3% of patients had such blood pressures at baseline again underlines the lack of careful adherence to the protocol since this was an exclusion criteria. Since this study reports only short term experience averaging about 1 week on therapy, the long term effect of stroke, heart failure and other major complications from midodrine therapy could not be analyzed. In addition, the previously reported effects of marked bradycardia, though not seen in this study, apparently, might be due to the short duration of treatment.

Overall, the data do demonstrate that midodrine has a positive pressor effect as one would expect from the pharmacology of the drug but the proof of efficacy in patients with idiopathic orthostatic hypotension is not well demonstrated in this trial due to all the methodologic problems noted. A concern for safety has also been highlighted.

A CONTROLLED PHASE III STUDY OF THE EFFICACY AND SAFETY OF MIDODRINE ALONE, MIDODRINE PLUS FLUDROCORTISONE AND FLUDROCORTISONE ALONE IN PATIENTS WITH ORTHOSTATIC HYPOTENSION AND AUTONOMIC FAILURE

Protocol #20,762-2A

Investigator: Melvin D. Yahr, M.D. and co-workers at Mt. Sinai Hospital in New York.

Date Initiated: April, 1983

Date Completed: December, 1984

This is the second pivotal trial that the sponsor offers which is supposed to be well controlled to define the efficacy and safety of midodrine.

PROTOCOL

The protocol provided in Volume 13 of 37 does not match the actual study reported under the description in the title. The protocol details a design similar to the Tarazi study, 20,762-1, in which only 1 leg of the crossover was conducted. Therefore, all comments on this report will be as defined in the clinical report and statistical report as part of Volume 13.

Patients were hospitalized for periods from 4 1/2 to 7 weeks and all had a 4 to 8 day baseline period without any therapy for their idiopathic orthostatic hypotension. During that period of time, baseline laboratory and exclusion characteristics were to be defined. They were allowed to continue the Jobst garment and a weight maintaining diet containing 160 mEq of sodium per day. Beds were kept in the 30 degree tilt upright position and patients were not allowed to be recumbent during the 8 AM to 8 PM period except to obtain supine blood pressure measurements. Supine standing measurements were obtained after 10 minutes of quiet recumbency and 2 minutes after standing and an automated blood pressure recorder was used for all measurements. Symptoms of hypotension in the upright position were to be recorded.

Patients during baselines were to be excluded if they had a supine hypertension >180/100 or severe coronary artery disease, renal or liver dysfunction, thyrotoxicosis, pheochromocytoma, dementia, the use of MAO inhibitors or pre-menopausal women. After baseline, the patients all underwent a midodrine treatment starting at 2.5 mg one to three times daily and increased depending on the patient response until an optimal blood pressure control was achieved. The total daily dose was from 15 to 45 mg per day. Optimal response was to obtain a supine systolic pressure between 140 and 180 and supine diastolic >100 concomitantly with a standing systolic pressure of 80 mmHg or higher. One or two weeks were allowed during this titration

phase. Thereafter, patients underwent a midodrine maintenance for about one week which served as the reference measure for the doses chosen in the double blind phase.

The patients then underwent a crossover study in which each leg lasted approximately one week. Figure 1 details the design which demonstrates that the crossover legs were separated by 2 days of placebo plus fludrocortisone 0.1 mg plus matching placebo to midodrine which was single blind in nature. Patients received either fludrocortisone 0.1 mg plus midodrine on a tid to qid basis or fludrocortisone plus a placebo for midodrine. Blood pressure and pulse were to be recorded 1/2 to 1 hour after each medication dose and then at 2 hourly intervals throughout the day. **The sponsor and the investigator believe that since the blood pressure measurements were taken automatically that they could combine the data during the double blind with the data during the single blind phase. This medical reviewer strongly objects to this conclusion.**

STUDY POPULATION

The study population as shown in Table 1 consisted f 1 male and 6 females in which 4 had symptoms of Parkinson's disease, 1 had Shy-Drager syndrome, and the remaining 2 had orthostatic hypotension without neurologic manifestations, the so-called Bradbury-Eggleston syndrome. The average age of these 7 patients was 60 years with an average duration of orthostatic hypotension of 4 years. Table 2 details the ramdomization that was used for these 7 patients during the double blind period.

During the midodrine titration which lasted an average of 10 days (range 6-16 days) the dosage ranged from 2.5 to 7.5 mg whereas during the maintenance period lasting 4 to 6 days (mean 4.4 days) the daily total dosage ranged from 15 to 45 mg with an average of 25 mg prescribed in tid or qid dosing. The use of fludrocortisone was a 0.1 mg dose per day. The midodrine titration and maintenance as well as the baseline were all conducted under open label conditions. The crossover study, however, was double blind but the fludrocortisone was not blinded.

The effectiveness of midodrine was determined during the titration and maintenance open phases by 6 to 8 blood pressures taken between 8 AM and 8 PM.

In addition to patients wearing Jobst garments, fludrocortisone was discontinued in 4 patients (5302, 5304, 5306 and 5307) and 6 of the patients continued with concomitant medications, most of which were used for Parkinsonism though 3 patients were on sodium chloride and others as listed in the chart taken from the sponsor.

FIGURE 1

A CONTROLLED PHASE III STUDY OF THE EFFICACY AND SAFETY OF MIDRODRINE ALONE, MIDODRINE PLUS FLUDROCORTISONE AND FLUDROCORTISONE ALONE IN PATIENTS WITH ORTHOSTATIC HYPOTENSION AND AUTONOMIC FAILURE

(20,762-2A)

S T U D Y D E S I G N

Washout	Midodrine		Crossover Period		
Baseline Period	Midodrine Titration	Midodrine Maintenance	Midodrine + Fludrocortisone or Placebo + Fludrocortisone	Placebo + Fludro.	Placebo + Fludrocortisone or Midodrine + Fludrocortisone
4-8 days	10-21 days		5-8 days	2 days	6-12 days

TABLE 1

PATIENT ROSTER
(20,762-2A)

PATIENT NUMBER	INIT.	AGE	SEX	DIAGNOSIS	DURATION OF ILLNESS (YRS)	START DATE	END DATE
5301		63	F	PD, SDS	1	4/01/83	5/06/83
5302		69	F	PD, SDS	1	4/26/83	5/31/83
5303		57	M	PD, SDS.	3	5/11/83	6/13/83
5304		60	F	SDS	4	10/14/83	11/22/83
5305		49	F	IOH	15	1/10/84	2/10/84
5306		56	F	PD, SDS	1	4/10/84	5/15/84
5307		67	F	IOH	3	11/12/84	12/13/84

DIAGNOSIS

PD - Parkinson's disease
SDS - Shy-Drager Syndrome
IOH - Idiopathic orthostatic hypotension

TABLE 2

PATIENT RANDOMIZATION TO
STUDY MEDICATION
(20,762-2A)

PATIENT NO.	TREATMENT 1	TREATMENT 2
5301	Midodrine + fludrocortisone	Placebo + fludrocortisone
5302	Placebo + fludrocortisone	Midodrine + fludrocortison
5303	Midodrine + fludrocortisone	Placebo + fludrocortisone
5304	Placebo + fludrocortisone	Midodrine + fludrocortison
5305	Placebo + fludrocortisone	Midodrine + fludrocortison
5306	Midodrine + fludrocortisone	Placebo + fludrocortisone
5307	Midodrine + fludrocortisone	Placebo + fludrocortisone

The following medication was continued:

[illegible]	[illegible]	[illegible]
[illegible]	[illegible] (1)	25/100 x 7
	[illegible] (2)	2 mg x 4
	[illegible] (3)	5 mg x 6
	[illegible]	50/200 x 3
	[illegible] chloride	2 G daily
[illegible]	[illegible]	25/250 x 4
	[illegible] (4)	100 mg x 2
	Tofranil (5)	10 mg x 3
5304	Artane	2 mg x 3
	Sodium chloride	8 G daily
5306	Sinemet	25/100 x 4
	Sodium chloride	4 G daily
	Urecholine (6)	100 mg daily
5307	L-Tyrosine	500 mg daily
	Synthroid (7)	0.1 mg daily

1. Sinemet - carbidopa + levodopa
2. Artane - trihexyphenidyl
3. [illegible] - bromocriptine
4. [illegible] - amantadine
5. Tofranil- imipramine
6. Urecholine-bethanechol
7. Synthroid-levothyroxine

13

STATISTICAL PLAN

A block design was utilized similar to that performed in the Tarazi study, #20,762-1. All 7 patients completed the full course of the study ranging from 32 to 50 days.

All 7 patients are not analyzed since patient 5302 was excluded because 11% of that patient's baseline supine blood pressure readings were >180/100 mmHg. It is of interest to note that patient 5306 met this criteria 5.4% of the time but was not considered sufficient to exclude that patient. In fact, as shown in Table 3 patient 5304 also met the maximum criteria of 180 mmHg but was not excluded. In addition, standing systolic blood pressure >120 mmHg (Table 4) occurred in 1/3 of the readings in Patient 5302 which was also used as a justification for discontinuing this patient, however this criteria was also met in 16.7% of the readings for 5307 and 6.1% of the readings in Patient 5306 yet these 2 patients were not excluded. The nature of the patients are described in the following manner:

Table 5 details the individual patient changes in standing systolic blood pressure by treatment group together with the physician's global evaluation. This table details that 4 of the patients were considered to have an excellent global response whereas 1 was considered to be worse. The patient that was considered to have a worse effect was Patient 5302 that the sponsor excluded for reasons mentioned above. If one compares the change in mean standing systolic blood pressure in the double blind crossover phase between midodrine versus placebo, one can see that Patient 5301 and 5304 had a 10 mmHg change on midodrine compared to placebo where the other 5 patients did not demonstrate a 10 mmHg increase on midodrine compared to the effect of placebo.

Mean changes in supine systolic blood pressure are demonstrated in Table 7 in which only 1 patient (5305) demonstrated a marked clinical change in blood pressure on midodrine compared to the placebo in the double blind phase.

Mean values for blood pressures in the various phases are demonstrated in Table 9 with significant labels demonstrated in Table 10. The data suggests that midodrine caused a significant increase in systolic blood pressure compared to placebo.

In regard to pulse rates, midodrine caused a reduction from baseline and supine pulse rates of 4 to 5 beats per minute which was statistically significant. The standing pulse rates were unaffected in all treatment groups.

TABLE 3

BASELINE SUPINE SYSTOLIC BLOOD PRESSURES (mmHg)
(20,762-2A)

PATIENT NUMBER	MEAN ± S.D.	MAX	MIN	RANGE	Q3 (mmHg)	PERCENT >180mmHg
5301	123 ± 17	160	92		138	0
5302	142 ± 5	200	80		160	11.5
5303	140 ± 2	170	120		148	0
5304	142 ± 3	180	100		152	0
5305	105 ± 3	135	74		120	0
5306	136 ± 4	183	102		153	5.4
5307	144 ± 3	165	101		152	0

Q3 - 25% of blood pressure readings were greater than this number

TABLE 4

BASELINE STANDING SYSTOLIC BLOOD PRESSURES (mmHg)
(20,762-2A)

PATIENT NUMBER	MEAN ±	S.D.	MAX	MIN	RANGE	Q3 (mmHg)	PERCENT >120mmHg
5301	92 ±	10	120	70		96	1.8
5302	114 ±	7	196	68		130	33.3
5303	97 ±	2	120	78		102	0
5304	66 ±	3	110	42		80	0
5305	66 ±	2	87	50		70	0
5306	95 ±	3	152	53		104	6.1
5307	99 ±	4	131	71		117	16.7

Q3 - 25% of blood pressure readings were greater than this number

Cardiovascular Effects

Gardocki and Yelnosky gave dogs 2 doses of fentanyl (0.0025 and 0.005 mg/kg, i.v., 15 min apart). Blood pressure creased 20%, heart rate remained unchanged in 2 dogs and decreased (140-100 bpm) in 1 dog. ECG was unaffected. In another dog study, 0.010-0.040 mg/kg, i.v. caused immediately decreased blood pressure (maximum effect in 10 min) which lasted 30 min and bradycardia within 2 min. ECG showed ventricular premature contractions at 0.010 mg/kg, i.v. and prolongation of the P-R interval (1 animal at 0.010 mg/kg and all dogs at 0.040 mg/kg). pharmacologist review, 8-7-75) reported slight hypotension and intense bradycardia in nonanesthetized dogs receiving 0.05 mg/kg, i.v. fentanyl. Atropinization predisposes the dog to a pressor response to fentanyl.

Emesis

Gardocki and Yelnosky reported no emetic activity in dogs in doses up to 10 mg/kg, i.m.

Hypotension

Gardocki and Yelnosky reported that dogs given 4 doses of fetanyl (0.01-0.04 mg/kg, i.v.) at 30 min. intervals showed that the animals rapidly develop tolerance to the hypotensive effect of the drug.

Withdrawal

reported that fentanyl suppressed the withdrawal symptoms of morphine-addicted monkeys at 1/75 the morphine dose. When Innovar was given to monkeys for 2 weeks (b.i.d., s.c.) at the highest tolerated dose and abruptly withdrawn, signs of abstinence were very mild.

Neuromuscular Transmission

Gardocki and Yelnosky reported that fentanyl (up to 0.16 mg/kg, i.v.) did not affect neuromuscular transmission in anesthetized cats.

Femoral Blood Flow

Gardocki and Yelnosky reported that intra-arterial injections of 0.050 fentanyl did not affect femoral blood flow.

Hemolysis

reported that when heparinzed dog blood (1 ml) was added to either 0.05, 0.1, 0.25, 0.5, 0.75 or 1 ml of 0.01% fentanyl solution at the highest dilution there was 7% hemolysis.

[illegible] female)

[illegible] history of Parkinsonism; difficulty [illegible] failure. Multiple system atrophy with progressive autonomic failure. Orthostatic hypotension, urinary incontinence, [illegible].

[illegible] female)

[illegible] history of Parkinsonism; difficulty walking, [illegible] neurogenic bladder [illegible].

[illegible] (57 [illegible] female)

[illegible] history of Parkinsonism; [illegible] rigidity and [illegible]. Multiple system atrophy with [illegible] failure. Orthostatic hypotension, [illegible], neurogenic bladder, [illegible] at 3 years.

Patient 5304 (60 year old female)

Multiple system atrophy with progressive autonomic failure over previous 4 years. Cerebellar signs. Neurogenic bladder. Progressive deterioration with orthostatic hypotension, episodes of syncope, extrapyramidal signs, weakness and [illegible].

Patient 5305 (49 year old female)

15 year history of dysautonomia and progressive autonomic failure (POTS), severe orthostatic hypotension, dizziness, syncope, diminished sweating, tears, and saliva.

Patient 5306 (56 year old female)

14 year history of Parkinsonism. Multiple system atrophy with progressive autonomic failure. Bradykinesia., rigidity. neurogenic bladder,.orthostatic hypotension (1 year).

Patient 5307 (67 year old female)

3 year history of dizziness and blurred vision on standing. Over past year, almost daily episodes of syncope. Orthostatic hypotension unrelieved by fludrocortisone, and Jobst stockings. Urinary incontinence, constipation. Diagnosis of progressive autonomic failure without neurological manifestations (POM).

TABLE 5

INDIVIDUAL PATIENT MEAN CHANGES FROM BASELINE (mmHg)
IN STANDING SYSTOLIC BLOOD PRESSURE
BY TREATMENT PERIOD
(20,762-2A)

Patient Number	Global Response	Dose[1]	Baseline Mean	Midodrine Titration	Midodrine Maint.	Midodrine + Fludro.	Placebo + Fludro.
5301	Excellent	20.0	92.2	14.7	19.3	21.2	9.4
5302	Worse	22.5	114.4	-9.4	-12.1	-25.2	-26.5
5303	Fair	45.0	97.1	-8.1	-16.4	- 7.9	-1[illegible].3
5304	Excellent	25.0	66.3	1.7	- 0.8	10.7	1.1
5305	Excellent	30.0	66.5	4.0	- 1.6	4.8	0.5
5306	Poor	20.0	95.4	-7.9	- 4.7	- 4.3	2.4
5307	Excellent	15.0	98.7	24.7	19.1	42.8	32.0

Note: Positive numbers indicate an increase in systolic pressure over baseline; negative numbers indicate a decrease

1. Daily dose of midodrine (mg) during midodrine maintenance and cross-over phases.

TABLE 7

INDIVIDUAL PATIENT MEAN CHANGES FROM BASELINE (mmHg)
IN SUPINE SYSTOLIC BLOOD PRESSURE
BY TREATMENT PERIOD
(20,762-2A)

Patient Number	Global Response	Baseline Mean	Midodrine Titration	Midodrine Maint.	Midodrine + Fludro.	Placebo + Fludro.
5301	Excellent	123.5	6.7	11.9	10.3	5.3
5302	Worse	142.5	12.6	19.9	14.0	12.1
5303	Fair	139.9	-9.7	1.7	12.3	- 6.3
5304	Excellent	141.8	-1.4	7.0	5.5	- 6.6
5305	Excellent	105.4	22.3	25.0	30.1	7.7
5306	Poor	135.9	7.1	10.7	3.5	-1.1
5307	Excellent	143.7	13.0	11.5	15.1	8.0

Note: Positive numbers indicate an increase in systolic pressure over baseline; negative numbers indicate a decrease.

TABLE 9

MEAN SUPINE AND STANDING
BLOOD PRESSURE (mmHg)
BY TREATMENT GROUP
(20,762-2A)

	MEAN BLOOD PRESSURE ± S.D. (N=6)			
	SUPINE		STANDING	
TREATMENT	SYSTOLIC	DIASTOLIC	SYSTOLIC	DIASTOLIC
Baseline	132 ± 15	76 ± 9	86 ± 15	59 ± 8
Midodrine Titration	138 ± 11	77 ± 4	91 ± 21	61 ± 8
Midodrine Maintenance	143 ± 9	78 ± 6	80 ± 23	61 ± 6
Midodrine + Fludrocortisone	144 ± 10	78 ± 7	97 ± 26	61 ± 10
Placebo + Fludrocortisone	133 ± 12	76 ± 7	90 ± 25	59 ± 8

TABLE 10

MEAN CHANGES IN SUPINE AND STANDING BLOOD PRESSURES (mmHg)
AND SIGNIFICANCE LEVELS
BETWEEN TREATMENT GROUPS (N=6)
(20,762-2A)

	SUPINE								STANDING							
COMPARISON WITH:	SYSTOLIC				DIASTOLIC				SYSTOLIC				DIASTOLIC			
	M/T	M/M	M + F	PL + F	M/T	M/M	M + F	Pl + F	M/T	M/M	M + F	Pl + F	M/T	M/M	M + F	Pl + F
Baseline	6.35	11.3	12.8	1.1	0.77	1.7	2.0	-0.1	4.6	2.5	11.4	4.6	2.1	2.0	2.0	0.1
	.1	.01	.001	NS	NS	NS	NS	NS	NS	NS	.05	NS	NS	NS	NS	NS
Midodrine Maintenance			1.5	-10.2			0.34	-1.8			8.9	1.9			0.0	-2.6
			NS	.01			NS	NS			.1	NS			NS	NS
Midodrine + Fludrocortisone				-11.7				-2.1				-7.0				-2.6
				0.01				NS				NS				NS

TREATMENT GROUPS:

Baseline	(Baseline)
Midodrine titration	(M/T)
Midodrine maintenance	(M/M)
Midodrine + fludrocortisone	(M + F)
Placebo + fludrocortisone	(Pl + F)

CLINICAL RESPONSE TO STUDY MEDICATION

Of the 4 patients with an excellent response as detailed above, 5301 continued until her death 14 months later, 5304 maintained her improvement for 10 months at which time midodrine was discontinued because of noncompliance, 5307 continued on the agent for 3 years to the end of the study, and 5305 discontinued midodrine and refused further treatment after 2 months. Individual patient doses during maintenance and crossover were demonstrated in Column 3 on Table 5.

SAFETY

The total duration of midodrine treatment averaged 21.9 days with a range of 17 to 33 days in this study. Six patients continued to take midodrine as noted above after exit from this protocol as part of a compassionate use program.

Patient 5302 developed a worsening of her baseline supine hypertension while on treatment with midodrine and Patients 5304 and 5307 developed transient scalp itching due to the drug. No patients died. No other adverse effects occurred during the short term phase of the study.

In the compassionate use program, Patient 5305 developed urinary retention in part related to midodrine. No clinical laboratory abnormalities were seen.

MEDICAL REVIEW OFFICER'S EVALUATION OF THIS PROTOCOL

Once again it is clear that the study site recruited very few patients, the majority of which were complicated because of the underlying condition of Parkinson's disease and the multiple medications those patients were on. The double blind portion of this protocol is the only well controlled portion and the individual data provides the hardest evaluation of efficacy rather than mean data for reasons mentioned above. It is clear that the sponsor chose to exclude 1 patient because of baseline protocol violation but did not exclude other patients meeting this criteria. The patient excluded had a clear worsened response on midodrine. Only 2 patients (5301 and 5304) had what this reviewer would regard as a change in systolic standing blood pressure that would have been clinically significant but unfortunately their supine systolic blood pressure measurements were less impressive in regards to an increase. Large variability obviously exists. Therefore, larger numbers of patients with homogenous diagnoses would be necessary to clearly define the dose, dose effect, duration of effect, and expected response to midodrine. Nevertheless, it is apparent that midodrine can be effective in an occasional patient. The sponsor does not detail secondary diagnostic tests as recommended in the protocol nor any data regarding duration of action or dose effect. The use of the automated blood pressure without demonstrating quality control is again a major weakness in this trial.

A DOUBLE BLIND PHASE III PLACEBO CONTROLLED CROSSOVER COMPARISON OF THE SAFETY AND EFFICACY OF MIDODRINE AND DIHYDROERGOTAMINE IN PATIENTS WITH SEVERE ORTHOSTATIC HYPOTENSION

PROTOCOL #20,762-3

Investigator: Aaron Vinik, M.D.
Stefan Fajans
University of Michigan

Date Initiated: May 6, 1983

Date Completed: October 23, 1984

The purpose of this study was to evaluate midodrine as compared to dihydroergotamine in severe orthostatic hypotension utilizing a double blind randomized protocol in hospitalized patients. The protocol design is demonstrated in Figure 1.

A 2 day single blind placebo baseline was used during which oral placebo was administered on a background of concomitant fludrocortisone (0.1-0.2 mg bid) and Jobst garments. The protocol called for 12 insulin dependent diabetics between the ages of 20 and 45 with autonomic neuropathy with a fallen systolic blood pressure at least 30 mmHg or to 80 mmHg or lower on standing. Patients with supine hypertension of 200/100 or greater as well as those with nephritis, renal failure, thyrotoxicosis, significant liver disease, pheochromocytoma, or dementia were excluded. Informed consent was obtained.

If the baseline characteristics were met, the patients entered a 3-5 day titration period during which they received up to 4 doses of midodrine from 2.5 to 5.0 to 7.5 to 10 mg tid or dihydroergotamine from 5 to 10 to 15 to 20 mg tid. Successful control was defined as attaining a supine systolic blood pressure between 140 and 180 and a supine diastolic blood pressure no greater than 100 mmHg concomitant with a standing systolic blood pressure >80 mmHg. Medication was administered 30 minutes before meals. Medication was given open label treatment according to the protocol though the medical study report suggests this was done double blind.

Thereafter, patients underwent a 2 day placebo period to washout medication just received and thereafter were crossed over to receive a titration and maintenance period similar to the ones just described using the other agent.

Eleven patients were entered into this trial and their detailed demographics are demonstrated in Table 1.

FIGURE 1

MIDODRINE STUDY DESIGN
(20,762-3)

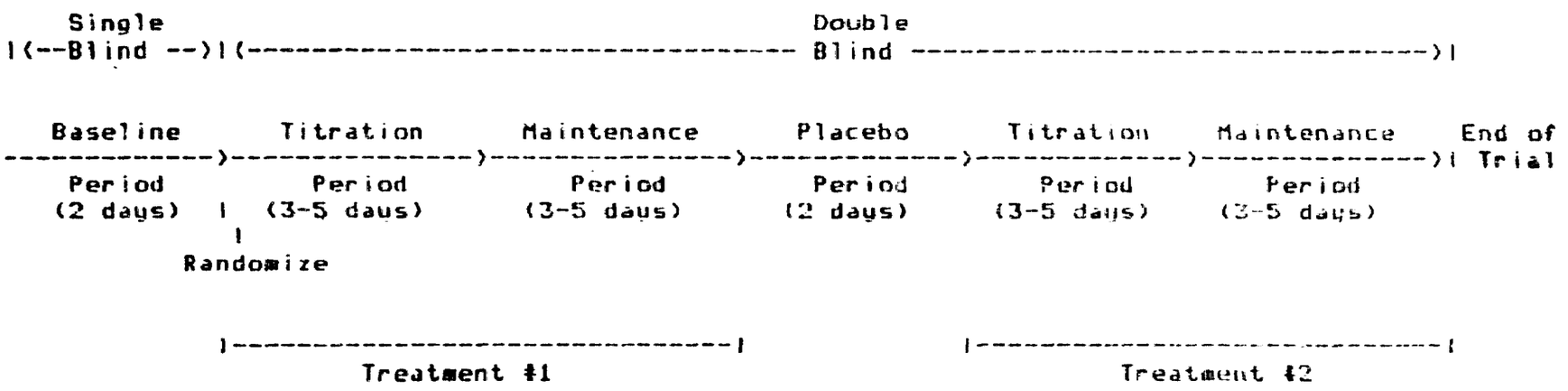


TABLE 1

PATIENT ROSTER
(20,762-3)

PATIENT NUMBER	AGE	SEX	DIAG-NOSIS	YEAR Dx	START DATE	END DATE	COMMENTS
5101	35	M	OH-Da	1961	5/6/83	5/24/83	Insulin dependent
5102	36	M	OH-D	1970	6/21/83	7/12/83	Insulin dependent
5103	47	F	OH-D	1961	5/6/83	5/24/83	Insulin dependent
5104	28	M	OH-D	1972	12/1/83	12/24/83	Insulin dependent
5105	72	F	IOH	1983	9/20/83	10/18/83	-
5106	38	F	OH-D	1964	12/6/83	1/8/84	Insulin dependent
5107	37	M	OH-D	1972	2/10/84	2/28/84	Insulin dependent
5108b	26	M	OH-D	1969	8/9/83	8/11/83	Insulin dependent
5109c	-	M	OH-D	1969	3/22/84	3/23/84	Insulin dependent
5110	41	M	OH-D	1968	8/23/84	9/12/84	Insulin dependent
5111	57	F	IOH	1984	10/4/84	10/23/84	-

a. Orthostatic hypotension concomitant with diabetes.

b. Study drop-out, during Day 3 pre-active drug period. Refused to stop smoking.

c. Study drop-out, during Day 2 pre-active drug period. Refused to stop smoking.

Table 2 details the randomization of drug use and the medical writeup suggests that these were done in a double blinded fashion using opaque gelatin capsules which has been stuffed with the appropriate active medication. It should be noted that patients 5108 and 5109 did not receive any treatment because they dropped out having refused to stop smoking.

During this protocol hourly blood pressures were obtained between 8 A.M. and 4 P.M., 3 minutes during supine rest and then in duplicate after intervals of 1 and 3 minutes of quiet standing. If standing was not possible, sitting blood pressures were used. The pulse rates were also recorded. Blood pressures were to be measured prior to and 1/2 hour after drug administration and hourly until 4 PM. Medication was to be given at 7:30 AM, 12:30 PM and 5:30 PM. Laboratory tests were obtained at baseline and following the first and second legs of the crossover. Readings after 4 PM of blood pressure were to be taken by family members. All blood pressure readings between midnight and 6 AM were excluded from analysis since there were few readings between these time periods. Statistical analysis was by block design and during the crossover periods, analyses were limited to the maintenance rather than titration periods.

RESULTS

Nine patients were analyzed and Table 3 details the mean demographic data of these 9 patients in which 2 had idiopathic orthostatic hypotension and 7 orthostatic hypotension due to diabetes mellitus.

Table 4 details the doses that were used of each of the agents during the crossover period. These doses range from the lowest to the highest allowable.

INABILITY TO STAND

Table 5 details the number of times a patient could stand as compared to the number of times a patient was asked to stand during each of the periods of the protocol. This data, which is extremely important, demonstrates no patient receiving efficacy from midodrine except for a tendency in Patient 5110, but obvious variability between baseline placebo and the interim placebo phases need to be noted. The sponsor has interpreted this data in Table 6 to suggest that the percent of patients showing some placebo improvement occurred in 40% compared to 40-60% of patients on dihydroergotamine and 60% of patients on midodrine.

The sponsor suggests that the placebo effect might have been due to carryover. Of course, if this is the case, the entire study is invalid. Nevertheless, it appears from this data that no clear efficacy from midodrine for this parameter is demonstrated.

TABLE 2

PATIENT RANDOMIZATION TO
STUDY MEDICATION
(20,762-3)

PATIENT NO.	TREATMENT 1	TREATMENT 2
5101	Dihydroergotamine	Midodrine
5102	Midodrine	Dihydroergotamine
5103	Dihydroergotamine	Midodrine
5104	Dihydroergotamine	Midodrine
5105	Midodrine	Dihydroergotamine
5106	Midodrine	Dihydroergotamine
5107	Dihydroergotamin	Midodrine
5108 a	None	None
5109 b	None	None
5110	Midodrine	Dihydroergotamine
1511	Dihydroergotamine	Midodrine

a. Dropped out of study on Day 3 (pre-drug)

b. Dropped out of study on Day 2 (pre-drug)

TABLE 3

MEAN DEMOGRAPHY OF STUDY PATIENTS
(Excluding 2 Drop-outs)
(20,762-3)

VARIABLE	VALUE
Number of Patients	9
Age	
Mean	43.4 years
Range	28-72 years
Duration of Disease	
Mean	12.9 years
Range	0.5-22 years
Sex	
Males	5
Females	4
Diagnosis	
IOH	2
OH-D	7

TABLE 4

INDIVIDUAL MAINTENANCE PERIOD DOSE LEVELS
OF MIDODRINE AND DIHYDROERGOTAMINE
ACHIEVED DURING THE STUDY
(20,762-3)

PATIENT NUMBER	MIDODRINE (mg TID)	DIHYDROERGOTAMINE (mg TID)
5101	7.5	15.0
5102	5.0	15.0
5103	7.5	10.0
5104	5.0	10.0
5105	10.0	20.0
5106	7.5	5.0
5107	10.0	20.0
5108	Dropped out during placebo run-in	
5109	Dropped out during placebo run-in	
5110	5.0	5.0
5111	2.5	20.0
AVERAGE	6.7	13.3

TABLE 5

COMPARISON OF MIDODRINE (M) AND DIHYDROERGOTAMINE (DHE)
PATIENT-INABILITY-TO-STAND RESULTS
(NO. OF TIMES UNABLE TO STAND/NO. OF ATTEMPTS TO STAND; (%)a.
(20,762-3)

PATIENT NO.	BASELINE		PLACEBO		MIDODRINE TITRATION		MIDODRINE MAINTENAN		DHE TITRATION		DHE MAINTENANCE	
5101	4/17	(24)	0/55	(0)	0/45	(0)	0/67	(0)	0/35	(0)	0/59	(0)
5102	0/17	(0)	0/17	(0)	0/47	(0)	0/34	(0)	0/44	(0)	0/60	(0)
5103	0/11	(0)	0/49	(0)	0/64	(0)	0/46	(0)	0/46	(0)	0/61	(0)
5104	0/16	(0)	0/54	(0)	0/42	(0)	0/48	(0)	0/37	(0)	0/12	(0)
5105	16/16	(100)	58/58	(100)	[illegible]	(98)	40/40	(100)	61/61	(100)	44/44	(100)
5106	3/20	(15)	26/27	(96)	33/35	(94)	50/50	(100)	41/41	(100)	33/33	(100)
5107	0/15	(0)	0/52	(0)	0/56	(0)	0/34	(0)	0/42	(0)	0/37	(0)
5110	2/20	(10)	2/10	(20)	1/35	(3)	0/10	(0)	1/20	(5)	4/30	(13)
5111	2/18	(11)	0/55	(0)	0/40	(0)	0/69	(0)	0/55	(0)	1/42	(2)

a. Unable to stand/opportunities to stand
Unable to stand = no readings in standing position, but readings in supine and/or sitting

Category: Narcotic Agonist Analgesic - Synthetic Opioid Related to the Phenylpiperidines

Related IND: - Transdermal Therapeutic System (TTS) - Fentanyl
NDAs:

Marketing Indication: Prolonged control of moderate to severe pain requiring narcotic analgesia.

Each TTS (fentanyl) should be applied to non-irritated skin on the upper torso and may be worn continuously for 72 hours before applying a new system on a different skin site. For surgical use, a dose of 50-100 mcg/hr TTS (fentanyl) is applied 1 - 2 hours prior surgery. For chronic use, a recommended dosage increment is 25 mcg/hr every 72 hours. TTS (fentanyl) - 100 is approximately equivalent in analgesic activity to 60 mg morphine IM (10 mg every 4 hours) administered over a 24-hour period. Analgesia may persist 6-12 hours after TTS (fentanyl) removal.

New Preclinical Studies and Testing Laboratories

A. Pharmacology - Literature Review

B. Acute Toxicity

C. Multidose Toxicity

1. Rat

a. 2-week diet
b. 4-week i.m.
c. 4-week i.v.

2. Rabbit

a. 4-week topical
b. 13-week topical

3. Dog

a. 4-week i.m.
b. 4-week i.v.

REPRODUCTION STUDIES

Species	Group	Mode of Administration	Doses mg/kg/day	Duration of Treatment	Laboratory	Report No.
Rat	25F	Intravenous	0,0.01,0.03	Day 6-15		TRR-111
	G_1=100, 11,11, 12, 6	subcutaneous	0,0.16,0.32, 0.64,1.25,	Day 0-21 gestation, all groups		TRR-44
	G_2=50, 6,6,3		0,0.16,0.32,			
	G_3=200,3		0,0.16			
	100,5, 5,6	subcutaneous	0,0.04,0.08, 0.16	Day 0-21		TRR-44-G2
	200,20, 20,20,20	subcutaneous	0,0.16,0.32, 0.64,1.25	Day 0-21		TRR-45
	43,28, 28,28,28	subcutaneous infusion	0,0.01,0.1, 0.5	Day 14-21		1986

TABLE 6

EFFECT OF MIDODRINE, DIHYDROERGOTAMINE AND PLACEBO
ON INCIDENCE OF INABILITY TO STAND[a]
(20.762-3)

TREATMENT	NO. OF PATIENTS DEFICIENT IN STANDING ABILITY AT BASELINE	PATIENTS SHOWING IMPROVEMENT NO.	(%)	PATIENT NOS.
Midodrine	5	3	(60%)	S101, S110, S111
Placebo	5 [b]	2	(40%)	S101, S111
Dihydroergotamine	5 [c]	2-3	(40-60%)	S101, S110, S111

a. One patient became worse on all treatments.

b. There may be carry-over effects during placebo, since it followed active treatment.

c. Patients showed improvement in titration phase but not during maintenance phase.

Table 7 details the incidence of standing systolic blood pressures >80 mmHg. In one patient, 5103, there is some suggestion of mild efficacy during midodrine maintenance but not titration but in no other patient is there any demonstration of a midodrine effect. A pharmacologic effect of an increase in mean supine systolic blood pressure was shown on midodrine compared to placebo and midodrine produced a statistically significant ($p<01$) lower pulse rate in supine position than either placebo or dihydroergotamine. The sponsor believes this is a result of a reflex due to the increase in supine blood pressure.

SAFETY

Patients received midodrine for an average of 6.8 days (range 5-8 days) in this trial. Three subjects in fact continued midodrine continued midodrine for a year - patients 5102, 5103 and 5106. Table 12 details the adverse reactions to study medication and demonstrates that Patient 5103 developed syncope on midodrine, not present during placebo, and several had other symptoms expected from this agent. By removing pre-existing symptoms, 22% of the midodrine and placebo patients had symptoms.

Table 14 details the percent of incidences of systolic blood pressures >180 mmHg and this occurred 3 times more often on midodrine than on placebo but not different than dihydroergotamine. No important changes in laboratory findings were noted.

MEDICAL REVIEW OFFICER'S EVALUATION

This study provides no evidence of midodrine's efficacy in a population principally of patients with diabetic, orthostatic hypotension. Adverse effects of decreasing heart rate and increase in systolic supine blood pressure were noted and 1 patient developed syncope on midodrine compared to placebo.

TABLE 7

INCIDENCE OF STANDING SYSTOLIC BLOOD PRESSURES
GREATER THAN 80 mm Hg

PATIENT NO.	STUDY PHASE	NO. OF VALUES >80mmHg	ATTEMPTS NO.	ATTEMPTS %
5101	BL	13	13	100.0
5101	MT	45	45	100.0
5101	MM	67	67	100.0
5101	PBO	55	55	100.0
5101	DT	48	48	100.0
5101	DM	59	58	98.3
5102	BL	17	8	47.1
5102	MT	47	32	68.1
5102	MM	34	32	94.1
5102	PBO	21	19	90.5
5102	DT	43	27	62.8
5102	DM	60	49	81.7
5103	BL	11	0	0.0
5103	MT	64	1	1.6
5103	MM	46	7	15.2
5103	PBO	50	0	0.0
5103	DT	46	0	0.0
5103	DM	61	1	1.6
5104	BL	15	15	100.0
5104	MT	42	42	100.0
5104	MM	40	40	100.0
5104	PBO	65	65	100.0
5104	DT	37	37	100.0
5104	DM	12	12	100.0
5105	BL	0	0	0.0
5105	MT	1	0	0.0
5105	MM	0	0	0.0
5105	PBO	0	0	0.0
5105	DT	0	0	0.0
5105	DM	0	0	0.0
5106	BL	18	0	0.0
5106	MT	2	0	0.0
5106	MM	0	0	0.0
5106	PBO	0	0	0.0
5106	DT	0	0	0.0
5106	DM	0	0	0.0

TABLE 7 (cont'd)

INCIDENCE OF STANDING SYSTOLIC BLOOD PRESSURES
GREATER THAN 80 mm Hg

PATIENT NO.	STUDY PHASE*	NO. OF VALUES >80mmHg	ATTEMPTS NO.	ATTEMPTS %
5107	BL	15	13	86.7
5107	MT	56	55	98.2
5107	MM	34	28	82.4
5107	PBO	52	47	90.4
5107	DT	42	39	92.9
5107	DM	37	35	94.6
5110	BL	21	17	81.0
5110	MT	31	22	71.0
5110	MM	10	4	40.0
5110	PBO	9	7	77.8
5110	DT	19	17	89.5
5110	DM	28	21	75.0
5111	BL	16	13	81.2
5111	MT	53	41	77.4
5111	MM	56	42	75.0
5111	PBO	55	37	67.3
5111	DT	40	23	57.5
5111	DM	56	33	58.9

* BL=BASELINE, MT=MIDODRINE TITRATION,
MM=MIDODRINE MAINTENANCE, PBO=PLACEBO,
DT=DIHYDROERGOTAMINE TITRATION,
DM=DIHYDROERGOTAMINE MAINTENANCE

TABLE 12

ADVERSE REACTIONS TO STUDY MEDICATIONS
(20,762-3)

TREATMENT GROUP	PATIENT NUMBER	ADVERSE REACTION REPORTED: EVENT	ADVERSE REACTION REPORTED: PRE-EXISTING CONDITION
Placebo			
(Nine Patients Treated)	5102	Dizziness/Lightheadedness	Yes
	5103	Dizziness/Lightheadedness	Yes
	5103	Depression	No
	5104	Dizziness/Lightheadedness	No
	5104	Limb pain	Yes
	5106	Dizziness/Lightheadedness	Yes
	5106	Syncope	Yes
	5109*	Nausea/vomiting	Yes
Midodrine			
(Nine patients treated)	5101	Dizziness/Lightheadedness	Yes
	5101	Headache	Yes
	5102	Dizziness/Lightheadedness	Yes
	5103	Dizziness/Lightheadedness	Yes
	5103	Headache	No
	5103	Syncope	Yes
	5103	Cardiac awareness	Yes
	5103	Chest pain	Yes
	5103	Nausea/vomiting	No
	5103	Pounding in ears	Yes
	5103	Limb pain	No
	5103	Difficulty breathing	Yes
	5106	Dizziness/Lightheadedness	Yes
	5106	Supine hypertension	Yes
	5106	Nausea/vomiting	Yes
	5106	Gastroparesis	No
	5107	Supine hypertension	Yes
	5110	Dizziness/Lightheadedness	Yes
	5110	Clammy	Yes
	5110	Chills	Yes

Table 12 (Continued)

ADVERSE REACTIONS TO STUDY MEDICATIONS

TREATMENT GROUP	PATIENT NUMBER	ADVERSE REACTION REPORTED: EVENT	PRE-EXISTING CONDITION
Dihydroergotamine			
(Nine patients treated)	5101	Dizziness/Lightheadedness	Yes
	5102	Dizziness/Lightheadedness	Yes
	5102	Painful neuropathy	Yes
	5103	Dizziness/Lightheadedness	Yes
	5103	Cardiac awareness	No
	5103	Fatigue	No
	5104	Dizziness/Lightheadedness	No
	5104	Nausea/vomiting	Yes
	5106	Fever	No
	5110	Dizziness/Lightheadedness	Yes
	5110	Dizziness/Lightheadedness	Yes

*Dropped out during run-in before active medication.

TABLE 14

INSTANCES OF SUPINE SYSTOLIC BLOOD PRESSURE
READINGS GREATER THAN 180 mm Hg
(20,762-3)

TREATMENT	NO. PATIENTS TREATED	NO. PATIENTS WITH 1 OR MORE READINGS > 180 mm Hg		NO. READINGS > 180 mm Hg
		NO.	(%)	
Baseline	9	1 a.	11%	3
Midodrine	9	3 b.	33%	4
Placebo	9	1 c.	11%	1
Dihydroergotamine	9	3 d.	33%	6

a. Patient No. 5110
b. Patient No. 5102, 5106, 5110
c. Patient No. 5110
d. Patient No. 5107, 5110, 5111

DOSE RANGING EFFICACY STUDY OF ORAL MIDODRINE AND PLACEBO IN PATIENTS WITH SEVERE ORTHOSTATIC HYPOTENSION

PROTOCOL #20762-10

Investigator: Dr. Ronald Polinsky, National Institute of Health
Dr. Roy Freeman, New York Deaconess Hospital

OBJECTIVE

To define the dose of midrodrine relationship to response as well as safety using 24 hour Holter monitoring.

This protocol is dated November, 1987 and attempted to enroll 10 to 12 cases at 3 to 6 centers of patients with orthostatic hypotension with progressive autonomic failure due to the Shy-Drager or the Bradbury-Eggleston syndrome or those with Parkisonism or diabetes who had a history of syncope or near-syncope assuming the erect position. Patients excluded include those with a history of stroke, congestive heart failure, angina, cardiac arrhythmias, severe renal or hepatic impairment, pheochromocytoma, urinary retension, Meniere's Syndrome, seizure disorder, psychosis, or pregnancy. Patients with Jobst garments were excluded as well as those on Indomethacin or other NSAIDs. Florinef was allowed as background as well as digoxin, if necessary.

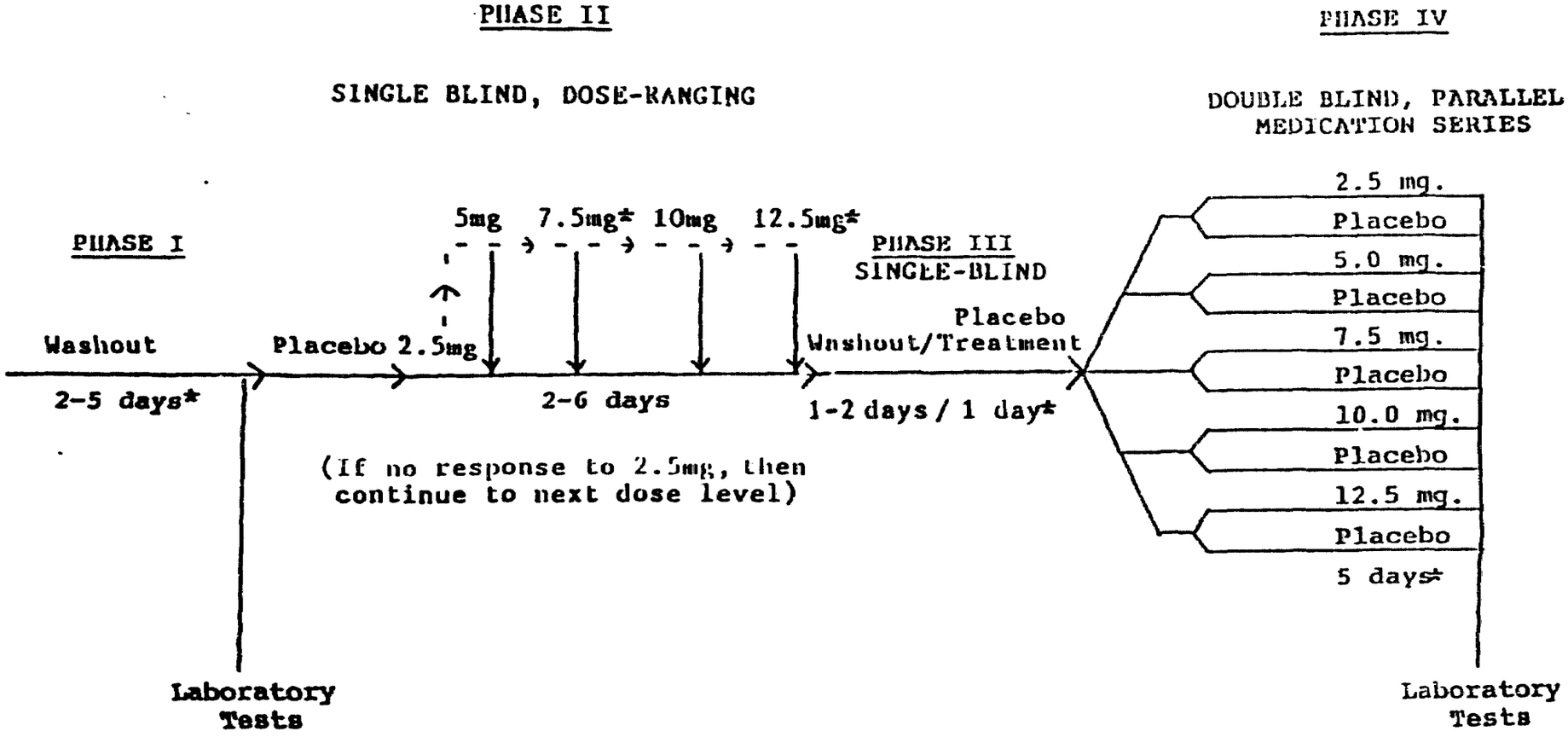
This study was divided into 4 in-hospital phases. Figure 1 details the protocol design. An amended protocol (10A) reduced Phase I to 1-2 days and Phase III placebo to 1 day and the double blind portion to 4 days. Originally, Phase I was 2-5 days, Phase II to 6 days, Phase III to 1-3 days, and Phase IV to 5 days. Matching placebo tablets were administered during Phase I which was a placebo washout baseline period. Tablets were administered in the morning before breakfast and supine and standing blood pressures and pulse were measured before and 1 hour after dosing. Sitting blood pressure was used for standing if the patient was unable to stand.

During Phase II, a single blind dose ranging use of midodrine from 2.5 up to 10 mg (in an amended protocol) on a daily basis was used (2.5, 5.0, 10.0). An automated noninvasive blood pressure monitor was used and blood pressures were taken at 1/2,1,2,4,6,8,10 and 32 hours post-dose. The first 6 patients underwent 24 hour Holtor monitoring on Day 1 of placebo and on Day 4 of midodrine. Thereafter, patients underwent Phase III which was a washout for placebo and at the end of this phase a quality of life questionnaire was utilized. In Phase IV, patients were randomized to receive placebo or midodrine therapy at a dose level and frequency based on the results of the Phase II data. Laboratory tests were performed during Phase I and Phase IV. Quality of life questionnaires were repeated at the Phase IV double blind portion.

FIGURE 1

DOSE-RANGING EFFICACY STUDY OF MIDODRINE AND PLACEBO

MIDODRINE STUDY #20,762-10



*Protocol #20,762-10A amendments: Phase I washout reduced to 1-2 days, Phase II 7.5 mg and 12.5 mg dosing days deleted, Phase III washout reduced to 1 day, and Phase IV reduced to 4 days.

Seven patients participated in this trial, 6 women and 1 man. The demographic data are shown in Tables 1 and 2.

Table 3 details prior medications in patients 101, 102 and 103 and Table 4 the concomitant medications in the 7 study patients.

RESULTS

It is important to review Tables 5 thru 11 (attached) which demonstrate the entire data obtained in this study.

Patient 101 demonstrated, to this medical reviewer, no important changes in blood pressure on midodrine compared to placebo demopnstrating no dose response relationship nor any efficacy. Patient 102 likewise demonstrated no impressive change in supine systolic blood pressure though standing systolic pressure clearly increased on midodrine but in a non-dose responsive way. The 12.5 mg systolic standing blood pressure which appears unusually out of line with the other blood pressures is difficult to interpret. During the double blind phase midodrine, at 10 mg tid, demonstrates no change in blood pressure parameters compared to the placebo Phase II data. The sponsor claims the patient noted the frequency of fainting spells was reduced under the double blind treatment with midodrine.

Patient 103 demonstrates no efficacy on midodrine and the sponsor claims that the investigator should have titrated to a higher dose.

Patient 201 demonstrates that midodrine clearly increased the standing and supine blood pressure compared to the placebo period. There was absolutely no dose responsive relationship seen, however. The second placebo phase following 5 days of titration with midodrine exhibited higher systolic blood pressures. This suggested a longer lasting effect of the drug which, if true, would suggest that a carryover effect would have to be strongly considered in trials that had only a short placebo washout prior to switching legs of a crossover design. It is important to note that no improvement in the treatment score was demonstrated in this patient's quality of life despite the fact that blood pressures were improved.

Patient 202 demonstrates an increase in supine and sitting blood pressures on midodrine with no clear dose response relationship demonstrated. This medical reviewer could not find sufficient data from this patient to confirm the author's claim that this individual had a beneficial clinical response except that on one occasion the patient could stand with a systolic blood pressure of 67 (10 mg of midodrine) but this was not true at a higher dose of midodrine with a higher supine systolic and sitting blood pressure.

TABLE 1

PROTOCOL 20,762-10
PATIENT DEMOGRAPHY

PT_NO	INVESTIGATOR	AGE	SEX	RACE
101	Polinsky	53	F	C
102	Polinsky	54	F	C
103	Polinsky	52	F	C
201	Freeman	73	F	C
202	Freeman	68	F	C
203	Freeman	77	M	B
204	Freeman	83	F	C
	Average:	66		

TABLE 2
PROTOCOL 20762-10
DIAGNOSIS

PT NO	PRIMARY	SECONDARY
101	OH/PAF*	Idiopathic
102	OH/PAF	Shy-Drager Syndrome
103	OH/PAF	Shy-Drager Syndrome
201	OH/PAF	Shy-Drager Syndrome
202	OH/PAF	Idiopathic
203	OH/PAF	Shy-Drager Syndrome
204	OH/PAF	Shy-Drager Syndrome, with Diabetes Mellitus

* Orthostatic hypotension/Progressive Autonomic Failure

TABLE 3

PROTOCOL 20.762-10
PREVIOUS MEDICATION USED TO TREAT HYPOTENSION

PT NO	PREV MED	DOSE	FREQ.	BEGAN	END-CONT	REASON DISC
101	Florinef	0.1 mg	Daily	1984	Ended 1987	Protocol
102	Florinef	0.1 mg	Daily	1983	Ended 1987	Protocol
	Motrin	800 mg	1 ID-AC	1986	Ended 9/87	Protocol
103	Florinef	0.1 mg	3 tabs qd	11/18/87	-	-
	Motrin	600 mg	AC qid	11/18/87	-	-

TABLE 4

PROTOCOL 20762-10
CONCOMITANT MEDICATION

PT NO	CONCOM MED	DOSE	FREQUENCY	BEGAN	END-CONT	REASON
102	Artane	2 mg	1 tab po qid	1985	Ongoing	Rx for rigidity
	K-Dur	20 mg	20 meq qd	1987	-	Potassium supplement
	Mandelamine	1 gm	1 gm qd	1986	Ongoing	Urinary tract infection prevention
	Vitamin C	250 mg	4 tabs qd	1986	Ongoing	Urinary tract infection prevention
103	Artane	2 mg	1.5 tab qid	11/16/87	-	Parkinsonism
	Florinef	1 mg	3 tab qd	11/16/87	-	Orthostatic hypotension
	Mandelamine	1 gm tab	1 tab po qid	11/16/87	-	Urine Acidification
	Motrin	600 mg	1 tab qid AC	11/18/87	-	Orthostatic hypotension
	Premarin	.625 mg	1 tab qd	10/87	-	s/p hysterectomy
	Vitamin C	500 mg	2 tabs qid/pc	11/16/87	-	Urine Acidification
201	Ativan	2 mg	QHS	03/87	Ongoing	Insomnia
202	Florinef	0.1 mg	QD	1982	Ongoing	Hypotension
	NACL	5.0 gms	Per Day	1982	Ongoing	Hypotension
203	Peri-colace	100 mg	PRN	1986	Ongoing	Constipation
	Tylenol	650 mg	PRN	1986	Ongoing	Pain
204	Colace	One	PRN	-	Ongoing	Constipation
	Darvocet N	100 mg	q12-PRN	-	Ongoing	Pain
	Ducolax	One	PRN	-	Ongoing	Constipation
	Serax	15 mg	q4h PRN	-	Ongoing	Anxiety
	Terbutaside	500 mg	Bid	1977	Ongoing	Diabetes

Patient 101 had no concomitant medications.

Studies in rabbits with ^{3}H-fentanyl (20 mcg/kg) have shown that the fall in plasma concentration and urinary excretion were more rapid in rabbits than in man, signifying a slower metabolism and longer biological half-life of fentanyl in humans than in rabbits.

The proposed labeling is acceptable from the standpoint of pharmacology.

Conclusion

Transdermal Therapeutic System (fentanyl) [TTS (fentanyl)] has been studied adequately in laboratory animals and has been shown to be relatively safe and efficacious. The toxicological profile which has been developed provides an adequate basis for concluding that the drug can be adequately labeled to provide assurance of its relative safe use in humans.

Clyde G Oberlander
Pharmacologist

cc: NDA 19-813
HFN-160, Doc. Rm. 160
R/D:C. Oberlander:3/11/88
R/D init. by:Dr. Inscoe:3/14/88

NDA 19-813

Alza Corporation
Palo Alto, CA 94303-0802

Type of Submission: Original NDA
Date of Submission: December 21, 1987
Date of Receipt: March 8, 1990
Date of Review: July 18, 19

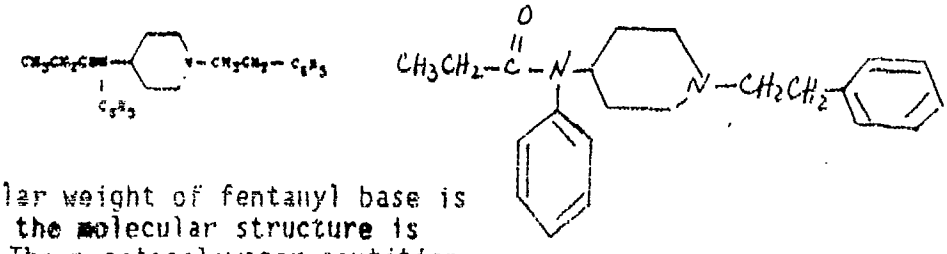
Review #2

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
ADDENDUM TO PHARMACOLOGY REVIEW OF March 11, 1988

Drug: Duragesic

Transdermal Therapeutic System (fentanyl)

DURAGESIC is a transdermal system providing continuous controlled systemic delivery of fentanyl, a potent opioid analgesic, for 72 hours. The chemical name is N-(1-phenylethyl-4-piperidyl) propionanilide. The structural formula is



The molecular weight of fentanyl base is 336.5, and the molecular structure is $C_{22}H_{28}N_2O$. The n-octanol:water partition coefficient is 860:1.

TABLE 5

MIDODRINE STUDY NO. 20,762-10
PATIENT #101

SUMMARY OF SUPINE AND STANDING PARAMETERS
DURING SINGLE-DOSE TITRATION WITH MIDODRINE
(MEAN VALUES OVER 12 HOURS POST TREATMENT)
AND TREATMENT RATING SCORES

TREATMENT (Phase)	SUPINE Sys (mm Hg)	SUPINE Dia (mm Hg)	SUPINE Pluse (Min)	STANDING Sys (mm Hg)	STANDING Dia (mm Hg)	STANDING Pulse (Min)	AVERAGE STD TIME (min)	Treatment Rating Score
Placebo (II)	138	81	60	91	57	92	5	
Placebo (III)	132	81	63	86	60	90	5	18
Placebo (Mean)	135	81	62	89	59	91	5	
Midodrine								
2.5 mg	134	80	58	103	64	86	5	
5.0 mg	142	86	58	96	62	93	5	
7.5 mg	143	86	58	96	62	93	5	
10.0 mg	135	84	57	96	62	90	5	
12.5 mg	127	76	54	84	59	86	5	
Double Blind - Mean 5 Days								
Placebo (IV)	120	71	60	86	58	83	5	15

Conclusions Midodrine, over a range of 2.5 to 10 mg, produced a non-dose related increase in standing systolic blood pressure over placebo. A modest increase in diastolic pressure was also noted. For unexplained reasons, possibly variability in the disease state, the 12.5 mg dose of midodrine did not increase these parameters over placebo. During the double-blind portion of the study, this patient was assigned to receive placebo and exhibited a treatment rating below the pre-double blind treatment placebo, 18 vs. 14.8. Thus, no benefit was achieved during DB placebo treatment either in terms of blood pressure or treatment rating.

a. Maximum score = 26.

TABLE 6

MIDODRINE STUDY NO. 20,762-10
PATIENT #102

SUMMARY OF SUPINE AND STANDING PARAMETERS
DURING SINGLE-DOSE TITRATION WITH MIDODRINE
(MEAN VALUES OVER 12 HOURS POST TREATMENT)
AND TREATMENT RATING SCORES

TREATMENT (Phase)	SUPINE Sys (mm Hg)	SUPINE Dia (mm Hg)	SUPINE Pulse (Min)	STANDING Sys (mm Hg)	STANDING Dia (mm Hg)	STANDING Pulse (Min)	AVERAGE SID_TIME (min)	Treatment Rating Score
Placebo (II)	132	76	78	77	36	88	1.0	
Placebo (III)	118	65	76	73	27	87	0.2	19
Placebo Mean	125	71	77	75	32	88	0.6	
Midodrine (II)								
2.5 mg	137	83	78	96	55	87	0.6b	
5.0 mg	135	70	78	97	42	90	0.4b	
7.5 mg	127	72	80	98	48	93	0.1b	
10.0 mg	136	53	84	83	37	98	1.9	
12.5 mg	121	77	82	136	86	74	0.1b	
Double-blind - Mean 4 Days								
Midodrine (IV) 10.0 mg tid (30 mg/day)	132	79	77	80	43	77	0.8	18

Conclusion: Midodrine increased both supine and standing, systolic and diastolic blood pressures, although a dose-response relationship was not found. This patient had difficulty standing as noted in the poor standing times. A marked improvement was noted at the 10.0 mg tid dose level. This dose level was selected for the double blind portion of the study. The blood pressure parameters were increased over placebo during the double blind portion of the study under midodrine. In addition, standing time was improved by midodrine, not reflected in the averages, but in the individual standing times. Although the overall treatment rating score does not show a great improvement over placebo, the patient noted that the frequency of fainting spells was reduced under double blind treatment with midodrine. Standing times were somewhat improved under midodrine treatment.

a. Maximum score = 26
b. Patient unable to remain standing at many observation times.

TABLE 7

PATIENT NO. 103
MIDODRINE STUDY NO. 20,762-10

SUMMARY OF SUPINE AND STANDING PARAMETERS DURING
SINGLE DOSE TITRATION WITH MIDODRINE (MEAN VALUES OVER 12 HOURS)
AND TREATMENT RATING SCORES

TREATMENT (PHASE)	SUPINE SYS (mm Hg)	SUPINE DIA (mm Hg)	SUPINE PULSE (Min)	STANDING SYS (mm Hg)	STANDING DIA (mm Hg)	STANDING PULSE (Min)	AVERAGE STD TIME (Min)	TREATMENT RATING SCORE a
Placebo (II)	128	57	73	92	57	90	5	
Placebo (III)	120	58	78	77	44	92	4	5
Placebo Mean	124	58	76	84	51	93	4.5	
Midodrine (II)								
2.5 mg	126	59	74	90	40	90	5	
5.0 mg	127	61	72	78	37	99	5	
7.5 mg	133	70	77	87	46	99	5	
10.0 mg	Not done							
12.5 mg	Not done							
Double Blind Treatment - Mean of 4 days								
Placebo (IV)	128	60	75	79	33	97	4.5	4

Conclusions: Midodrine showed a slight dose-related increase in supine systolic and diastolic blood pressure. A comparable increase was not observed in the standing parameters. It was evident the investigator did not titrate to a high enough dose of midodrine to elicit a sufficient response. During the double blind portion of the study placebo did not improve the blood pressure parameters or standing time over the pre-treatment placebo. The treatment rating score showed some deterioration from 5 to 4, since the patient stated there were more frequent fainting spells during this treatment period.

a. Maximum score = 24

TABLE 8

MIDODRINE STUDY NO. 20,762-10
PATIENT #201

SUMMARY OF SUPINE AND STANDING PARAMETERS
DURING SINGLE-DOSE TITRATION WITH MIDODRINE
(MEAN VALUES OVER 12 HOURS POST TREATMENT)
AND TREATMENT RATING SCORES

TREATMENT (Phase)	SUPINE			STANDING			SITTING			AVERAGE	TREATMENT
	Sys (mm Hg)	Dia	Pluse (Min)	Sys (mm Hg)	Dia	Pulse (Min)	Sys (mm Hg)	Dia	Pulse (Min)	STD.TIME (Min)	RATING SCOREa
Placebo (II)	112	53	67	Could not stand			84	37	76	0	
Placebo (III)	121	58	72	96 (One reading only)	46	80	82	43	86	0	5
(Following Mido. Phase II)	117	56	70				83	40	81	0	
Midodrine (II)											
2.5 mg	145	64	65	Could not stand			106	51	75	0	
5.0 mg	131	59	66	92	48	81	86	44	76	1	
7.5 mg	139	72	60	90	49	73	-	-	-	-	
10.0 mg	132	72	60	90	49	73	91	42	78	0	
12.5 mg	130	64	63	[illegible]	[illegible]	80	88	50	78	0	
Double-blind - Mean 5 Days											
Midodrine (IV) 12.5 mg tid 37.5 mg/day	136	66	67	58	24	81	79	37	84	1	5

Conclusions: Midodrine increased both supine and sitting blood pressures. In fact, this patient, who was unable to stand before midodrine, was able to stand during the midodrine titration phase of the study. Although a midodrine effect is evident, no dose-response relationship is apparent. Interestingly, the second placebo, following 5 days titration with midodrine exhibited higher supine blood pressures. Also, the patient was able to stand for one placebo observation period. This may suggest a long lasting effect of the drug. Under double blind treatment with midodrine 12.5 mg tid (37.5 mg/day), the patient showed higher values for the blood pressure parameters over placebo. No improvement in the treatment score was demonstrated in this patient, although there were objective signs of improvement.

a. Maximum score = 26

TABLE 9

MIDODRINE STUDY NO. 20,762-10
PATIENT 0202

SUMMARY OF SUPINE, SITTING AND STANDING PARAMETERS
DURING SINGLE-DOSE TITRATION WITH MIDODRINE
(MEAN VALUES OVER 12 HOURS POST TREATMENT)
AND TREATMENT RATING SCORES

TREATMENT (Phase)	SUPINE Sys (mm Hg)	SUPINE Dia (mm Hg)	SUPINE Pluse (Min)	STANDING Sys (mm Hg)	STANDING Dia (mm Hg)	STANDING Pulse (Min)	SITTING Sys (mm Hg)	SITTING Dia (mm Hg)	SITTING Pulse (Min)	AVERAGE STD.TIME (Min)	TREATMENT RATING SCORE[4]
Placebo (II)	118	71	65	Could not stand			68	48	64	0	
Placebo (III)	110	59	60	Could not stand			92	54	58	0	5
Placebo mean	114	65	63				80	51	61		
Midodrine (II)											
2.5 mg	140	77	66	Could not stand			84	59	64	0	
5.0 mg	133	76	63	Could not stand			86	52	61	0	
7.5 mg	132	76	66	Could not stand			91	55	63	0	
10.0 mg	125	70	63	67	48	59	88	54	62	0	
12.5 mg	150	77	61	Could not stand			114	63	60	0	
Double-blind - Mean 5 Days											
midodrine (IV) 12.5 mg tid 37.5 mg/day	113	66	60	79	52	59	94	55	59	0	Not done

Conclusion: Midodrine produced an increase in both supine and sitting blood pressure. Only the sitting systolic pressures suggested a dose relationship. Surprisingly, during the double blind study, under treatment with midodrine 12.5 mg tid, only a modest increase in sitting systolic blood pressure was evident. The only indication that the patient may have been feeling better is that the patient could stand at many observation points. This was not possible before midodrine. These data suggest midodrine produced a beneficial clinical response.

4. Maximum score = 26

TABLE 10

PATIENT NO. 203
MIDODRINE STUDY NO. 20.762-10

SUMMARY OF SUPINE, STANDING AND SITTING PARAMETERS
DURING SINGLE-DOSE TITRATION WITH MIDODRINE
(MEAN VALUES OVER 12 HOURS POST TREATMENT)
AND TREATMENT RATING SCORES

TREATMENT (PHASE)	SUPINE SYS (mm Hg)	SUPINE DIA (mm Hg)	SUPINE PULSE (Min)	STANDING SYS (mm Hg)	STANDING DIA (mm Hg)	STANDING PULSE (Min)	SITTING SYS (mm Hg)	SITTING DIA (mm Hg)	SITTING PULSE (Min)	AVERAGE STAND.TIME (Min)	TREATMENT RATING SCORE a
Placebo(II)	142	92	91	93	40 (one reading)	115	144	86	88	0	Not done
Placebo(III)	149	91	83	100	55	89	-	-	-	1.5	Post midodrine
Plac. Mean	146	92	87	97	48	102	144	86	88	0.8	dose ranging
Midodrine (II)											
2.5 mg	149	92	81	129	63/89(one read'g)		108	69	103	1.0	
5.0 mg	152	88	77	95	52	102	-	-	-	2.0	
7.5 mg	153	89	71	96	61	101	133	87	103	2.0	
10.0 mg	139	97	82	87	61	114	152	98	94	1.0	
12.5 mg	155	94	83	117	69	95	-	-	-	2.0	
Double Blind Study (Phase IV) - 4 average days of treatment											
Placebo	157	93	79	111	63	88	-	-	-	2.0	20

Conclusions: Midodrine caused an increase in the supine and standing blood pressures. A dose-response relationship is not evident. A marked improvement was noted in this patient since the ability to stand was restored by midodrine. The average standing time increased from 0 minutes to 1-2 minutes during the titration. For unexplained reasons, this patient maintained higher blood pressures and standing ability during the double blind placebo phase of the study. This suggests that midodrine may have a longer duration of effect than previously anticipated or that a change in disease state occured.

a. Maximum score = 26.

TABLE 11

PATIENT NO. 204
MIDODRINE STUDY NO. 20,762-10

SUMMARY OF SUPINE AND STANDING PARAMETERS
DURING SINGLE-DOSE TITRATION WITH MIDODRINE
(MEAN VALUES OVER 12 HOURS POST TREATMENT)
AND TREATMENT RATING SCORES

TREATMENT (PHASE)	SUPINE SYS (mm Hg)	SUPINE DIA (mm Hg)	SUPINE PULSE (Min)	STANDING SYS (mm Hg)	STANDING DIA (mm Hg)	STANDING PULSE (Min)	AVERAGE STAND.TIME (Min)	TREATMENT RATING SCORE a
Placebo(II)	146	59	79	106	53	94	2.1	Not done
Placebo(III)	140	77	83	114	65	93	2	
Placebo Mean	143	68	81	110	59	94	2	
MIDODRINE(II)								
2.5 mg	149	73	79	117	60	[illegible]	1.0	
5.0 mg	143	73	79	123	58	[illegible]	0.9	
10.0 mg	152	79	79	143	92	[illegible]	1.4	
12.5 mg	141	63	77	114	56	[illegible]	2.0	
Double Blind Study (Phase IV) - 4 days treatment average								
Plac-	147	74	86	129	68	93	1.9	21

Conclusion: Midodrine increased both the supine and standing systolic blood pressure. The standing systolic blood pressure suggests a dose-response relationship. Interestingly, the beneficial effect of midodrine is maintained during the double blind phase of the study while the patient received placebo.

a. Maximum score = 26

Patient 203 - This medical reviewer finds no evidence from the data on this patient that midodrine had any efficacy or any dose response relationship demonstrated.

Patient 204 - This medical reviewer concluded from this data that midodrine showed no demonstration of efficacy or dose response relationship.

SAFETY

The data from Holter monitoring in 6 patients is demonstrated in Table 14. The sponsor has noted that the abbreviation "SVT" means sinus ventricular tachycardia. I suspect this is supposed to be supraventricular tachycardia or sustained ventricular tachycardia. It is important to note that in Patient 102, that on midodrine the patient demonstrated this rhythm disturbance as well as a run of ventricular tachycardia. The sponsor states that the relationship of these events to midodrine is unknown. No other safety data of concern were noted in this study.

MEDICAL REVIEW OFFICER'S CONCLUSION

This study clearly demonstrates no efficacy of midodrine of any importance and, most disturbingly, no evidence of any dose-blood pressure response to this agent. Holter monitoring data suggests that at least in 1 patient the drug may cause, or be related to, serious atrial/ventricular arrhythmias and thus raises the potential for this problem in patients on this agent in other studies since Holter monitoring was not conducted in other protocols in this review. This medical reviewer finds this data not compatible with the statements said by the sponsor in their conclusion that midodrine appears safe and efficacious for the treatment of patients with severe orthostatic hypotension.

TABLE 14

MIDODRINE STUDY NO. 20.762-10
SUMMARY OF 24 HOUR HOLTER MONITOR RESULTS

PATIENT NO.	PRINCIPAL INVESTIGATOR	HOLTER MONITOR TREATMENT PERIOD	COMMENT
101	Polinsky	Placebo	Rare PVC's, PAC's bigeminy
		Midodrine 10 mg a	No apparent Midodrine-related changes
102*	Polinsky	Placebo	Occasional PVC's, rare PAC's
		Midodrine 2.5 mg	Rare PAC's, SVT aberrancy
		Midodrine 7.5 mg	PAC's, PVC's, SVT with AF
		Midodrine 10.0 mg	PAC's, PVC's
		Midodrine 12.5 mg	PAC's, PVC's, SVT aberrancy, possibly due to AF
		Midodrine 30.0 mg/day-day 4	PAC's, PVC's, one run of VT (3 beats)
103	Polinsky	Placebo	Rare PAC's with short runs of VT
		Midodrine 10.0 mg	No Midodrine-related abnormalities evident
201	Freeman	6 Mos. prior to Study	History of PVCs, VT
		4 days following Midodrine (37.5 mg/day)	No apparent abnormalities due to Midodrine
202	Freeman	No Holter Monitoring done	
203	Freeman	Placebo	Normal
		Midodrine 12.5 mg t.i.d. (37.5 mg/day-day 5)	No Midodrine related abnormalities evident.
204	Freeman	Midodrine 10.0 mg t.i.d. (30.0 mg/day-day 4)	No Midodrine related abnormalities evident.

*Patient 102: Showed PVC's and PAC's during placebo. The further sequelae noted during midodrine treatment are consistent with her history and the relationship to midodrine is unknown.

a. Single doses, unless otherwise stated.

PVC = Premature Ventricular Contractions
PAC = Premature Auricular Contractions
VT = Ventricular Tachycardia
SVT = Sinus Ventricular Tachycardia
AF = Auricular Fibrillation

IN-HOSPITAL COMPASSIONATE USE STUDY OF MIDODRINE ON DOSE TITRATION EFFECT ON BLOOD PRESSURE AND PULSE

PROTOCOL #20,762-5

CONDUCTED BY INVESTIGATORS DEMONSTRATED IN TABLE 1A (ATTACHED)

This is an open label compassionate use trial in which patients were admitted to hospital for 2 days of placebo given 3 times a day followed by a titration of midodrine of doses of 2.5, 5.0, 7.5, and 10 mg given tid. A minimum of 2 days was required at each dose level and vital signs were conducted before 1/2 hour, 1 and 2 hours after doses.

Sixteen patients from 9 centers were evaluable in which their mean age was 65 (range 28-78), 7 being men and 9 women. Eight had idiopathic orthostatic hypotension, 5 Shy-Drager syndrome, 1 Parkinson's disease, 1 amyloidosis and 1 diabetes.

A list of their concomitant medications is demonstrated in Table 2.

The results are demonstrated in Table 3 and show that in all 16 patients the mean systolic blood pressure of 142 on placebo was not clinically different from the range of 135-156 on midodrine without any evidence of dose responsiveness. Likewise, the systolic standing mean blood pressure of 90 on placebo was the same in the patients on 22.5 mg of midodrine per day though slightly higher at the other doses. Thus, no dose response relationship was evident.

Table 4 details the patients who received all of the dose levels possible and shows marked variability of systolic blood pressure response during the supine condition but a tendency for standing blood pressure to be increased at the highest dose levels on midodrine compared to placebo. No safety data are provided in this report.

MEDICAL REVIEW OFFICER'S EVALUATION

Again, this data demonstrates no confidence that midodrine is effective and no data on safety are provided.

TABLE 1A

(20,762-5)
INVESTIGATORS INVOLVED IN MIDODRINE IN-HOSPITAL PHASE

Bernard Tabatznik, M.D.
North Charles General Hospital
Department of Cardiology
2724 North Charles Street
Baltimore, MD 21218

James Green, M.D.
Ranch Acres Medical Center
Internal Medicine
Cardiology
3102 South Harvard
Tulsa, OK 74135

Pierre Larochelle, M.D.
The Clinical Research Institute
110 Pine Avenue West
Montreal, Quebec
Canada H2W 1R7

Charles E. Hansing, M.D.
Bellevue Cardiology Clinic,P.S.
Cascade Medical Center
1414-116th N.E.
Bellevue, WA 98004-3893

H. Cecil Coghlan, M.D.
University of Alabama at Birmingham
Department of Medicine
Division of Cardiology
Room 338 LHR, University Station
Birmingham, AL 35294

Ruben Aguilera, M.D.
Internal Medicine
12611 N. 103rd Avenue
Suite A
Sun City, AZ 85351

Fetnat Fouad-Tarazi, M.D.
The Cleveland Clinic Foundation
Department of Health and
Hypertension Research
9500 Euclid Avenue
Cleveland, OH 44106-4775

Janice Gilden, M.D.
University of Health Sciences
The Chicago Medical School
3333 Green Bay Road
N. Chicago, IL 60064

Melvin D. Yahr, M.D.
Mt. Sinai Medical Center
Department of Neurology
One Gustave Levy Place
New York, NY 10029

TABLE 2

CONCOMITANT MEDICATION
NICARDIPINE PROTOCOL 20.762-5 IN HOSPITAL PHASE

PT NO	DRUG	DOSE	FREQ	DATE BEG	DATE END	REASON FOR MEDICATION
[illegible]	Colace	[illegible] mg	[illegible]	10/11/35	Continuing	Constipation
	Florinef	0.1 mg	Bid	04/3[illegible]	Continuing	Orthostatic Hypotension
	Iron Sulfate	325 mg	Bid	10/11/35	Continuing	Anemia
	Sinemet	25/100 mg	Tid-QID	10/31/35	Continuing	Parkinson's Disease
	Slow K	8 mEq	Bid	03/35	Continuing	Hypokalemia
0[illegible]2	Florinef	0.1 mg	Bid	Unknown	Continuing	Orthostatic Hypotension
	Lasix	-	-	-	-	-
04[illegible]3	Florinef	0.1 mg	QD	04/36	Continuing	Orthostatic Hypotension
0[illegible]01	Florinef	0.3 mg	qam	-	Continuing	Orthostatic Hypotension
	Inderal	50 mg	qam	-	Continuing	-
13[illegible]5	Florinef	0.1 mg	QD	04/[illegible]/35	Continuing	IGH
	Micro K	TT	Bid	04/[illegible]/35	Continuing	Hypokalemia
	Mini Heparin	5000 USP	Q12h	04/10/35	Continuing	-
	Sodium Chloride	3 gm	Tid	04/2[illegible]/35	Continuing	IGH
1[illegible]56	Florinef	0.1 mg	Tid	1984	Continuing	IGH
	Hydralazine	25 mg	Tid	10/14/35	Continuing	Supine Hypertension
	Isordil	5 mg	Qid	08/35	Continuing	History of MI
	K-Lyte	25 mg	Tid	08/24/35	Continuing	Hypokalemia
	Sinemet	25/250	Tid	1984	Continuing	Parkinsonism
	Sodium Chloride	TT tsp	QD	08/02/35	Continuing	IGH

TABLE 2 (cont.)

CONCOMITANT MEDICATION
NIDDORINE PROTOCOL 20.782-5 IN HOSPITAL PHASE

PT NO	DRUG	DOSE	FREQ	DATE BEG	DATE END	REASON FOR MEDICATION
1[illegible]7	Florinef	.1 mg	Tid	11/21/84	Continuing	HTN
	Lasix	40	Bid	11/22/84	Continuing	Diarrhea
	Norm[illegible]	1a tab	Bid	11/22/84	Continuing	Hypocalcemia
	Potass Chloride	8 mg	Tid	12/03/84	Continuing	HTN
	Bisafac	10 mg	qAM	Unknown	Continuing	-
	Vicoxo	0.5 mg	Tid	12/14/84	Continuing	Diarrhea
	Zantac	150 mg	Bid	12/13/84	Continuing	Gastritis
1403	Florinef	0.1 mg	1	05/14/84	Continuing	Hypotension
		0.2 mgs	1	05/14/84	Continuing	Hypotension
	KCL Rougar	10 mEq	4	04/17/84	Continuing	Hypokalemia
1513	Florinef	0.3 mg	Bid	09/84	Continuing	Severe Hypotension
1701	Florinef	0.2 mg	Bid	09/85	Continuing	Hypotension
	Inderal	25 mg	Tid	03/12	Continuing	Hypotension
	NPH insulin	25 units	q AM	08/85	Continuing	Diabetes
1901	Florinef	0.1	Bid	Years ago	Continuing	-
	Nolasine	-	Bid	1984	-	Orthostatic Hypotension
2101	Clonazepam	1 mg	Qid	1993	Continuing	Parkinson's Disease
	Florinef	0.2 mg	Bid	1990	Continuing	Orthostatic Hypotension
	Lanoxin	0.25 mg	q AM	1990	Continuing	Tachycardia
	Potassium Chloride	25 mEq	Bid	1980	Continuing	Hypokalemia from Florinef
	Procardia	30 mg	q 6hr	1986	Continuing	Tachycardia

TABLE 2 (cont.)

CONCOMITANT MEDICATION
NICOTINE PROTOCOL 80,782-5 IN HOSPITAL PHASE

PT NO	DRUG	DOSE	FREQ	DATE REQ	DATE END	REASON FOR MEDICATION
2102	Calcium-Oral	[illegible]	Tid	1981-	Continuing	Postmenopausal Osteoporosis
	Estinyl	[illegible]	q AM	1981-	Continuing	Postmenopausal Osteoporosis
	Multivit	[illegible]	q AM & q PM	1981-	Continuing	Mental Health
2201	None	-	-	-	-	-
2202	Ditropan	[illegible]	qd	10/83	Continuing	Urinary Incontinence
	Florinef	[illegible]	qd	10/83	Continuing	Orthostatic Hypotension
	Sinemet	[illegible]	qd	08/84	Continuing	Parkinsonism
	Symmetrel	[illegible]	qd	10/83	Continuing	Parkinsonism
2203	Florinef	[illegible]	qd	1981	Continuing	Orthostatic Hypotension
	Potassium Chloride	[illegible]	qd	1983	Continuing	Hypokalemia
	Sinemet	[illegible]	qd	1977	Continuing	Parkinsonism
	Sodium Chloride	[illegible]	qd	-	Continuing	Orthostatic Hypotension

Results

Attached as Tables II-V are the individual subject results and supporting summary tables of the calculated pharmacokinetic values. A summary table of pharmacokinetic parameters is reproduced below:

TTS-75	AUC	Cmax	Tmax	Residual	Dose Delivered
Mean	109.0	1.83	35.3	2.86	4.54
%CV	13.3	16.3	20.3	9.2	5.7
Max					
Min					

A graphical representation of this data is presented as figure 1. The results of Wagner-Nelson analysis is presented as Table VI and figure 2.

Discussion

From the Wagner Nelson results it can be demonstrated that the release of fentanyl from the TTS system is excessive. At 24 hours, using the sponsor's fraction of drug released data, it can be calculated that 2.4mg of fentanyl has been released from the TTS-75 dosage unit. This corresponds to the proposed performance of the TTS-100 patch but not to the TTS-75 patch (the TTS-75 is designed to release 1.8mg of fentanyl over 24 hours). The individual subject results show that the range for the amount of fentanyl released at 24hrs. is from 1.76mg to 3.49mg.

The performance of the TTS-75 system over 72 hours shows that the dosage form is capable of delivering fentanyl throughout the dosing interval. Whether this amount of fentanyl would be sufficient to produce clinical analgesia without an undue amount of respiratory depression is unknown.

89-006

Study Title: Assessment of the Analgesic Efficacy of Transdermal Fentanyl by Patient Controlled Analgesia.

Investigator: G N C Kenny, FFARCS

Study Site: Glasgow Royal Infirmary
Glasgow, Scotland (U.K.)

Objective: The purpose of this study is to determine whether fentanyl, delivered transdermally, can provide a significant component of analgesia in patients after upper abdominal surgery. The dose proportionality among the three TTS(fentanly) doses are also examined.

Methods

This study was designed as a double-blind, placebo-controlled, parallel-group trial of 120 upper abdominal surgical patients. At the

present time, thirteen subjects have been enrolled in this study on active treatments; 5 on TTS-25, 5 on TTS-75, and 3 on TTS-100. The study is still underway and the investigator remains blinded as to the randomization. To be enrolled in the study the subjects have to be between the ages of 18-65, male or female, weigh 50-100kg, and be scheduled for elective upper abdominal surgery. Subjects were excluded from the study if they had any sign of hepatic or kidney dysfunction, or had significant CNS deficits. No demographic data has been provided by the sponosr on those subject currently enrolled in the study.

Two hours before the surgery, a TTS system (active or placebo) is applied to the upper anterior chest and is left in place for 72 hours unless respiratory or other clinical signs dictate earlier removal. All groups have access to additional analgesia via a patient controlled analgesia (PCA) device containing morphine. Morphine usage, as determined by the PCA record, will be one of the primary efficacy determinants in this study.

Throughout the study, blood samples for fentanyl will be collected at the following times: 0, 4, 8, 12, 24, 36, 48, 60, and 72 hours following the application of the TTS and 2, 4, 6, and 12 hours after the removal of the TTS. Optional samples could be taken at 24 and 36 hours after removal. The blood samples will be centrifuged immediately upon collection, and the resulting plasma will be frozen at -20°C. The samples will be shipped on dry ice to Dr. Hull at the University of Newcastle Upon Tyne for assay using the RIA method.

Analytical Methodology

According to the material presented by the sponsor, the plasma samples obtained in this study will be analyzed via RIA. It should be noted that in the original Fentanyl NDA (for the post-surgical indication) the sponsor provided insufficient information to address the issues of assay validation or cross-reactivity. These issues should be re-iterated to the sponsor for this study as it has a promising design with the large number of subjects proposed.

INTERIM RESULTS

Attached as Tables VII-XII are the individual subject results and supporting summary tables of the calculated pharmacokinetic values. A summary table of pharmacokinetic parameters is reproduced below:

TTS-25	AUC	Cmax	Tmax
N=5	ng*hr/ml	ng/ml	hr
Mean	37.60	0.66	47.24
%CV	66.7	53	50.4
Max			
Min			

TABLE 4

(Study No. 20762-05 In Hospital Phase)
(Mean Values)

EFFECT OF MIDODRINE ON SUPINE AND STANDING BLOOD PRESSURE (mmHg) AND PULSE (RATE/MIN)

Total Daily Dose (mg)	No. Patients	SUPINE			STANDING		
		SYS.	DIA.	PULSE	SYS.	DIA.	PULSE
0	16	142	81	77	90	62	81
7.5	16	150*	82	75*	92	62	83
0	15	140	80	78	89	61	81
7.5	15	148*	81	76*	91	61	84
15.0	15	149*	82*	76*	97*	65	83
0	9	134	79	81	88	63	84
7.5	9	141*	80	78	84	59	89
15.0	9	140*	81	78	93**	65	87
22.5	9	137	79	79	93**	63	86
0	6	132	79	81	81	60	87
7.5	6	139*	80	79	81	55	93
15.0	6	137	80	79	91	63**	90
22.5	6	135	78	79	87	60	89
30.0	6	139*	81	77*	94**	65**	89

* = statistically different from placebo (0). $p < 0.05$
** = statistically different from midodrine 7.5 mg. $p < 0.05$

RESULTS OF AN OPEN COMPASSIONATE USE STUDY OF ORAL MIDODRINE IN PATIENTS WITH SEVERE ORTHOSTATIC HYPOTENSION

PROTOCOL #20,762-5

Investigators: See Attached

Date Initiated: August 1983

Date Completed: In Progress

The objective of this study was to obtain data using oral midodrine in orthostatic hypotension in an open label compassionate use manner. Patients received oral placebo tid for up to 2 days in-hospital to obtain baseline conditions followed by in-hospital titration of midodrine given tid. An outpatient phase of long-term extended therapy was permitted. See Figure 1 for details.

Patients were allowed to have a background of fludrocortisone and/or indomethacin and/or Jobst garments. Midodrine was given starting at 2.5 mg tid up to 10 mg tid.

Thirty-five patients entered this study in which 34 received a course of midodrine. Many of the patients who were in previous protocols were transferred to this protocol in addition. Table 2 details the baseline demographic data.

Table 3 details the dose and length of therapy.

As of 2/29/88, 17 patients are ongoing in this protocol. The mean baseline and subsequent supine and standing blood pressures over 48 months of therapy is demonstrated in Table 5.

Table 6 details the mean change from baseline. It is obvious that a marked variability exists.

Table 8 details the change in heart rate over time and the mean change in heart rate in Table 9.

Standing systolic blood pressures >80 mmHg were demonstrated 45% of the time at baseline and 62-82% of the time at 6-12 months. Global response to midodrine has been evaluated by the sponsor and demonstrated in Table 12.

Table 13 demonstrates the doses used by the investigators in these 34 patients. Again, a great deal of variability is noted.

MIDODRINE COMPASSIONATE-USE
STUDY (#20.762-5)

STUDY PROFILE

INVESTIGATORS/STUDY CENTERS:

Lawrence Giroux, M.D.
Cape Coral Medical Clinic
Cape Coral, FL

Paul Seavy, M.D.
The Emory Clinic
Atlanta, GA

Bernard Tabatznik, M.D.
Department of Cardiology
North Charles General Hospital
Baltimore, MD

Mark Silverman, M.D.
Piedmont Hospital
Atlanta, GA

John Samet, M.D.
Private Practice
Clayton, MO

James Green, M.D.
Internal Medicine - Cardiology
Ranch Acres Medical Center
Tulsa, OK

Gretajo Northrup, M.D.
Rush-Presbyterian
St. Lukes Medical Center
Chicago, IL

Michael Sole, M.D.
Division of Cardiology
Toronto General Hospital
Toronto, Ontario
Canada

Irwin Klein, M.D.
Lawrence Wechsler, M.D.
University of Pittsburgh
School of Medicine
Pittsburgh, PA

Kenneth Jordan, M.D.
Loma Linda Physician's
Medical Group
Loma Linda, CA

MIDODRINE COMPASSIONATE-USE
STUDY (#20,762-5)

Fetnat Fouad-Tarazi, M.D.
The Cleveland Clinic Foundation
Heart and Hypertension Research
Cleveland, OH

John P. Finley, M.D.
The Izzak Walton Hospital
For Children
Halifax, Nova Scotia
Canada

Pierre Larochelle, M.D.
Otto Kuchel, M.D.
The Clinical Research Institute
Montreal, Quebec
Canada

H. Cecil Coghlan, M.D.
University of Alabama
School of Medicine
Birmingham, AL

Ruben Aguilera, M.D.
Internal Medicine
Private Practice
Sun City, AZ

Charles E. Hansing, M.D.
Bellevue Cardiology Clinic
Bellevue, WA

Janice Gilden, M.D.
Sant P. Singh, M.D.
Yoginder Kumar, M.D.
St. Mary of Nazareth Hospital
Chicago, IL

Melvin D. Yahr, M.D.
Mt. Sinai Medical Center
New York, NY

FIGURE 1

MIDODRINE STUDY DESIGN
(20,762-5)

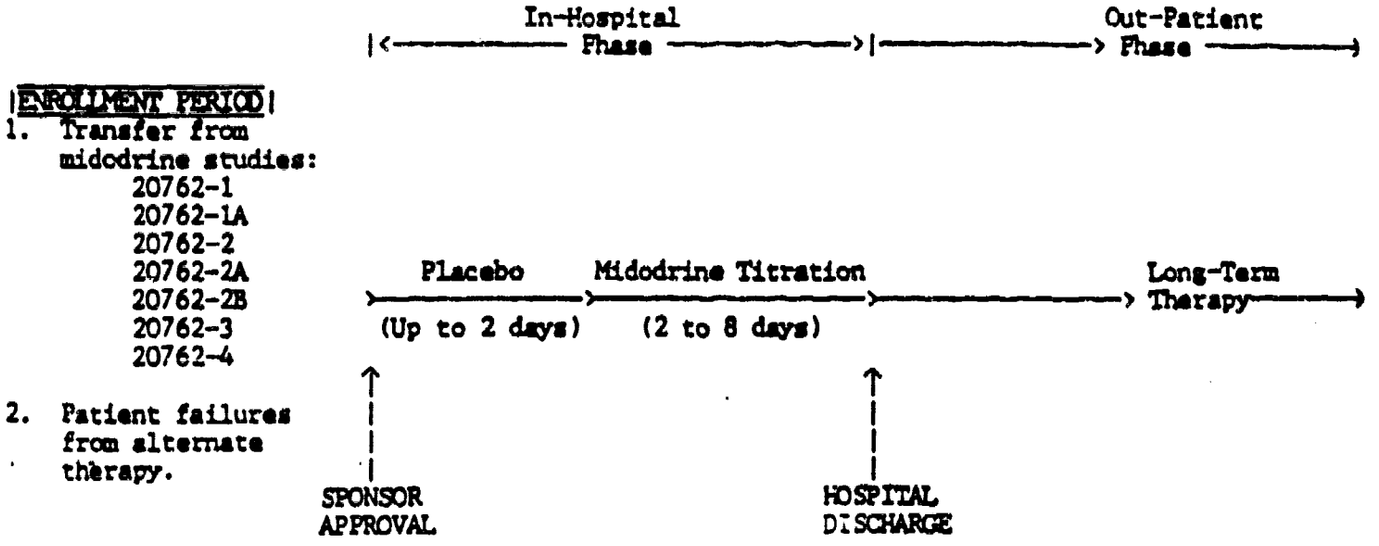


TABLE 2

MEAN BASELINE CARDIOVASCULAR PARAMETERS,
SYMPTOM INCIDENCE AND DEMOGRAPHY IN STUDY PATIENTS
(20,762-5)

VARIABLE	VALUE
Number of Patients	34
Age (Years)	60
Age Range (Years)	16-85
Duration of Disease	4.9 years
% Males	55.9
% Females	44.1
Supine Blood Pressure (mm Hg)	136/80
Standing Blood Pressure (mm Hg)	82/55
Supine Pulse Rate (bpm)	75
Standing Pulse Rate (bpm)	81
% Incidence Standing Systolic BP > 80 mm Hg	45.2
% Incidence Systolic BP > 180 mm Hg:	
Supine	0
Sitting	0
Standing	0
% Incidence Systolic BP > 200 mm Hg:	
Supine	0
Sitting	0
Standing	0

TABLE 3

DOSAGE AND LENGTH OF THERAPY AS OF LATEST RECORD*
(20,762-5)

PATIENT NUMBER	DATE	DAILY DOSAGE	TOTAL MONTHS
0101	87/05/19	30.0	58
0102	86/06/25	15.0	24
0301	86/03/23	25.0	19
0401	87/06/02	30.0	22
0402	87/07/21	30.0	13
0403	87/07/21	12.5	13
0501	86/09/24	22.5	30
0601	87/03/24	65.0	48
0701	85/11/08	22.5	1
0801	87/07/08	10.0	49
0901	85/10/07	22.5	23
0902	86/06/10	10.0	44
1001	87/03/05	30.0	56
1101	86/11/06	25.0	34
1102	85/12/13	22.5	34
1201	86/11/19	15.0	38
1202	86/10/16	22.5	36
1203	87/06/01	30.0	36
1204	87/03/16	22.5	36
1205	86/10/16	40.0	6
1206	86/11/12	10.0	4
1207	86/12/04	15.0	.75
1301	87/01/19	20.0	50
1401	85/10/20	30.0	26
1402	87/05/21	22.5	37
1403	87/05/28	15.0	14
1501	87/04/08	37.5	21
1701	86/03/15	30.0	.25
1801	86/06/19	7.5	1
2101	87/06/25	30.0	9
2102	87/06/25	15.0	5
2201	87/05/28	12.5	10
2202	85/11/01	12.5	1
2203	87/06/11	12.5	8
Average:		22.7	23.7

* Through 7/31/87.

TABLE 5

MEAN SUPINE AND STANDING BLOOD PRESSURE
IN PATIENTS WITH SEVERE ORTHOSTATIC HYPOTENSION
RECEIVING ORAL MIDODRINE FOR COMPASSIONATE PURPOSES
(20,762-5)

DURATION OF TREATMENT (Months)	NO. OF PATIENTS	MEAN BLOOD PRESSURE			
		SUPINE		STANDING	
		SYS.	DIA.	SYS.	DIA.
Baseline	34	136	80	82	55
0.5	23	155	87	106	68
1	23	147	86	95	64
2	18	149	87	95	65
3	17	145	87	89	64
6	17	135	83	88	65
12	19	154	85	107	70
24	18	144	89	95	63
36	11	139	83	101	61
48	4	148	80	75	56

TABLE 6

MEAN CHANGE FROM BASELINE
IN SUPINE AND STANDING BLOOD PRESSURE
IN PATIENTS WITH SEVERE ORTHOSTATIC HYPOTENSION
RECEIVING ORAL MIDODRINE FOR COMPASSIONATE PURPOSES
(20,762-5)

DURATION OF TREATMENT (Months)	MEAN CHANGE IN BLOOD PRESSURE (mm Hg)			
	SUPINE		STANDING	
	SYS.	DIA.	SYS.	DIA.
0.5	+19	+7	+24	+13
1	+11	+6	+13	+ 9
2	+13	+7	+13	+10
3	+ 9	+7	+ 7	+ 9
6	- 1	+3	+ 6	+10
12	+18	+5	+25	+15
24	+ 8	+9	+13	+ 8
36	+ 3	+3	+19	+ 8
48	+12	0	- 7	+ 1

TABLE 8

MEAN SUPINE AND STANDING HEART RATE
OF PATIENTS WITH SEVERE ORTHOSTATIC HYPOTENSION
RECEIVING ORAL MIDODRINE FOR COMPASSIONATE PURPOSES
(20.762-5)

DURATION OF TREATMENT (Months)	NO. OF PATIENTS	MEAN HEART RATE (bpm)	
		SUPINE	STANDING
Baseline	34	75	81
0.5	23	72	80
1	23	72	77
2	18	69	80
3	17	67	74
6	17	73	79
12	19	73	82
24	18	68	81
36	11	75	83
48	4	69	86

TABLE 9

MEAN CHANGE FROM BASELINE IN SUPINE AND STANDING HEART RATES OF PATIENTS WITH SEVERE ORTHOSTATIC HYPOTENSION RECEIVING ORAL MIDODRINE FOR COMPASSIONATE PURPOSES (20,762-5)

DURATION OF TREATMENT (Months)	MEAN CHANGE IN HEART RATE (bpm)	
	SUPINE	STANDING
0.5	-3	-1
1	-3	-4
2	-6	-1
3	-8	-7
6	-2	-2
12	-2	+1
24	-7	0
36	0	+2
48	-6	+5

TABLE 12

GLOBAL RESPONSE TO MIDODRINE THERAPY
AT FIRST AND LAST EVALUATION
(20.762-5)

RATING	NO. OF PATIENTS			
	FIRST	(%)	LAST	(%)
EXCELLENT	7	(21.9)	1	(3.1)
GOOD	13	(40.6)	22	(68.8)
FAIR	10	(31.3)	6	(18.7)
POOR	2	(6.3)	3	(9.4)

TABLE 13

INCIDENCE OF VARIOUS MIDODRINE DOSE LEVELS
ACHIEVED DURING LONG-TERM THERAPY
(20,762-5)

DAILY DOSE (mg)	INCIDENCE (N = 34)	
	No.	%
7.5	1	2.9
10.0	3	8.8
12.5	4	11.8
15.0	5	14.7
20.0	1	7.9
22.5	7	20.6
25	2	5.9
30	8	23.5
37.5	1	2.9
40	1	2.9
65	1	2.9

TABLE 14

ADVERSE EXPERIENCES

NUMBER OF PATIENTS REPORTING ADVERSE EXPERIENCES WITHIN EACH SYSTEM-ORGAN CLASS
(20,762-5)

SYSTEM-ORGAN CLASS	ADVERSE EXPERIENCE	NO. of PATIENTS
Cardiovascular	Chest Pain	2
	Flushing	1
	Palpitations	2
	Supine Hypertension	5
	Atrial Fibrillation	2
	Cardiac Failure	1
	Ventricular Arrhythmia	1
Central and Peripheral Nervous	Headache	1
	Cerebrovascular Disorder	2
	Hemiparesis	1
	Tremor	1
Gastrointestinal	Abdominal Discomfort	1
	Nausea	2
Integumentary	Psoriasis (scalp)	5
	Piloerection	1
Musculoskeletal	Night Cramps	1
Respiratory	Respiratory Arrest	3
Urinary	Frequency	2
	Dysuria	1
	Incontinence	1
	Fullness of Bladder	1
Other	Chills	1

Total number of adverse experiences reported: 38*

Number of Patients reporting one or more ADR's: 18

Number of Patients reporting no ADR's: 17

*Multiple reports of the same ADR in a single patient are counted once.

Table #

The Amount of Fentanyl Absorbed at Indicated Time Expressed as a Fraction Relative to the Total Amount Absorbed at the Last Sampling Point

TIME (hr)	Subject SCN1911	SCN1912	SCN1913	SCN1914	SCN1916	SCN1917	SCN1918	SCN1919	MEAN	SD	SE	N
0									0.049	0.062	0.023	7
1									0.015			1
2									0.060	0.063	0.026	6
4									0.205	0.216	0.088	6
6									0.231	0.061	0.043	2
8									0.249			1
12									0.350	0.137	0.052	7
18									0.473	0.207	0.078	7
24									0.529	0.134	0.051	7
32									0.607	0.088	0.033	7
40									0.664	0.078	0.029	7
48									0.773	0.106	0.040	7
52									0.871			1
56									0.820	0.098	0.037	7
64									0.892	0.056	0.021	7
72									0.981	0.125	0.047	7
76									0.976	0.043	0.016	7
80									0.986	0.044	0.017	7
84									0.982	0.045	0.017	7
88									0.995	0.050	0.019	7
96									0.995	0.052	0.019	7
108									1.007	0.041	0.018	5
120									1.000	0.000	0.000	6

a Not calculated because there is no estimate of the disappearance rate constant for this patient.

REG/TRP2/CLIN/LARJ1.11/TABLE8
12/10/87 CLM

Table VI

TABLE 15
(20,762-5)

SYSTEM-ORGAN CLASS	ADVERSE EXPERIENCE	PATIENT NO.
Cardiovascular	Chest Pain	403 701
	Flushing	2102
	Palpitations	403 701
	Supine Hypertension	1101 1201 1202 1203 1206
	Atrial Fibrillation	1201 1206
	Cardiac Failure	1201
	Ventricular Arrhythmia	1202 (death)
Central and Peripheral Nervous	Headache	403
	Cerebrovascular Disorder	501 1201
	Hemiparesis	501
	Tremor	1207
Gastrointestinal	Abdominal Discomfort	403
	Nausea	501 2102
Integumentary	Pruritus (scalp)	401 403 601 1203 2102
	Piloerection	1403
Musculoskeletal	Night Cramps	1204
Respiratory	Respiratory Arrest	102 (death) 301 (death) 1102 (death)
Urinary	Frequency	401 403
	Dysuria	1801
	Incontinence	401
	Fullness of Bladder	2102
Other	Chills	403

USE OF MIDODRINE IN 176 PATIENTS WITH PRIMARY AND SECONDARY ORTHOSTATIC HYPOTENSION BETWEEN SEPTEMBER 1979 AND FEBRUARY 1988 AT THE MAYO CLINIC

Investigator: Alexander Schirger, et al.

This report appears to be prepared by Dr. Schirger in patients who he defines as having idiopathic orthostatic hypotension without neurologic manifestations (Bradbury-Eggleston syndrome), idiopathic orthostatic hypotension with somatic neurologic manifestations (Shy-Drager syndrome) and secondary orthostatic hypotension due to diabetes mellitus, primary amyloidosis, etc. A further differentiation is made from those patients who have abnormal sympathetic function with orthostatic hypotension which are considered patients with orthostatic hypotension compared to those patients who have an intact sympathetic nervous system in which orthostatic hypotension is considered to be poor postural adjustment. The team at the Mayo Clinic using midodrine includes Dr. Sheldon Sheps of a division of hypertension and Dr. Gary Schwartz as well as Dr. Robert Fealey from the Department of Neurology as well as Drs. David Colville from the Department of Internal Medicine and Dr. Alexander Schirger of the Division of Cardiovascular Diseases.

Midodrine has been used in those patients who do not adequately respond to Ritalin 10 mg tid, Jobst garment, Florinef, and Indomethacin. Not all of the agents needed to be used if there were reasons that made them impractical or disadvantageous.

The report points out that patients with orthostatic hypotension, especially secondary, have a progressive downhill course with a reduced 5 year survival rate.

This group used midodrine 30 minutes before rising from bed, 30 minutes before lunch and at about 4:30 P.M. before supper.

These authors noted a relatively short half-life for the drug and short duration of action so they therefore would often give midodrine at 9 A.M. and 1 P.M. to some individuals. Sometimes they would give a dose 1/2 hour prior to a patient getting out of bed during the night for urination. They initiate dosing with 2.5 mg tablet size. The principal response index was the standing blood pressure elevation without orthostatic symptoms. A 1 minute standing blood pressure was used.

Figure 1 details the distribution of patients according to diagnostic categories.

FIGURE I

ALL GUTRON ONLY PATIENTS

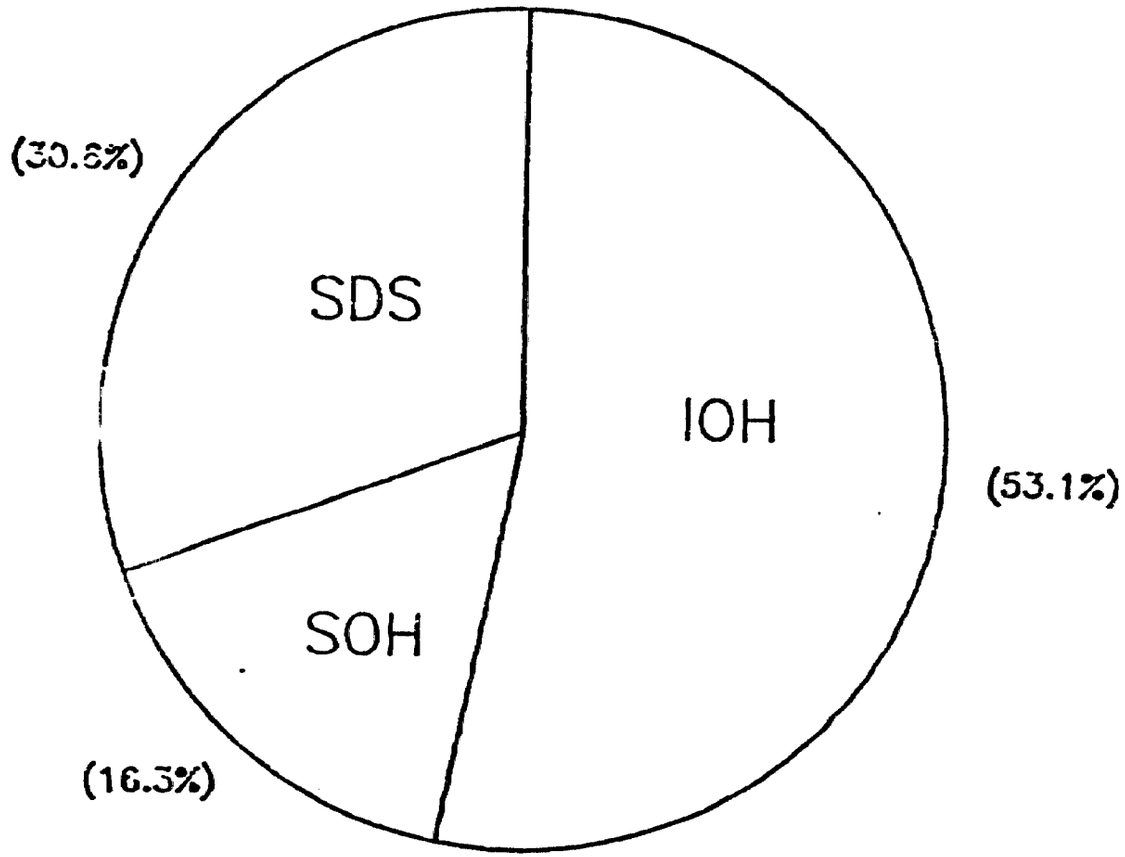


FIGURE 1 (CON'T)

CURRENT GUTRON PATIENTS

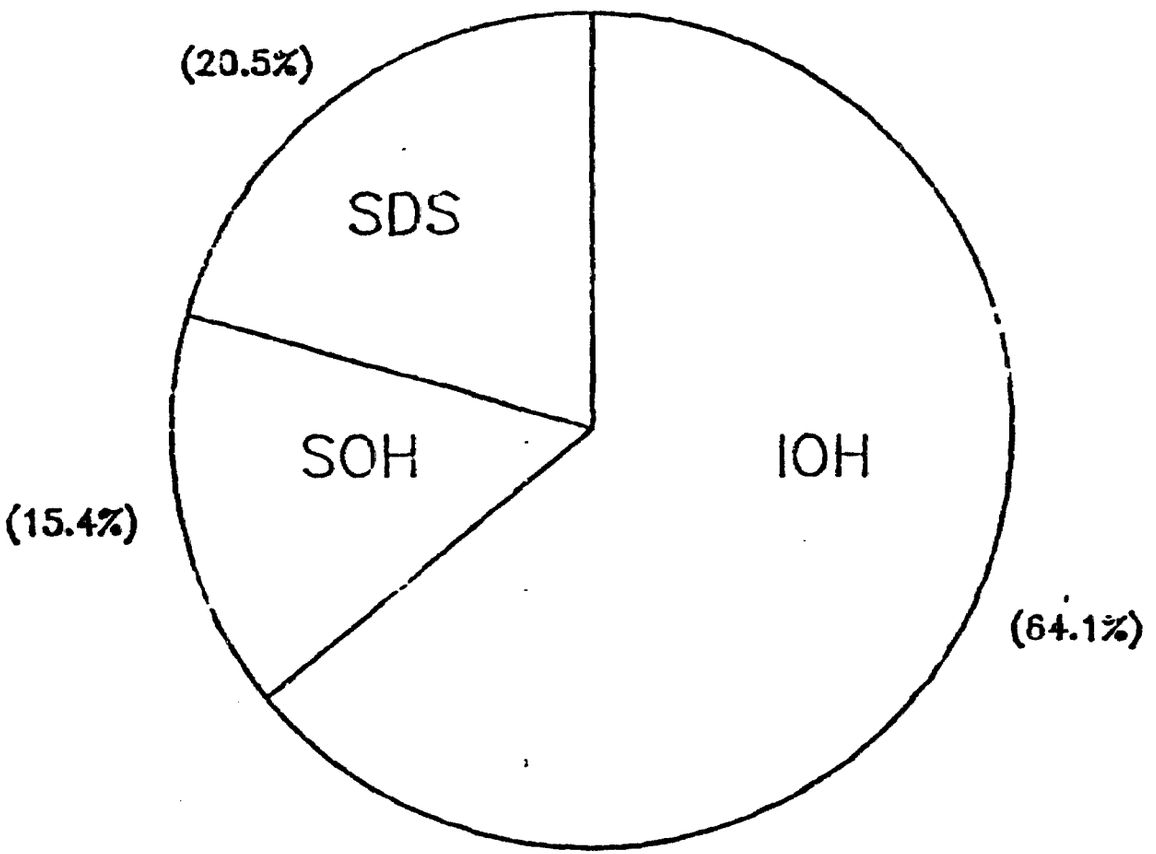


FIGURE I (CON'T)

DISCONTINUED GUTRON PATIENTS

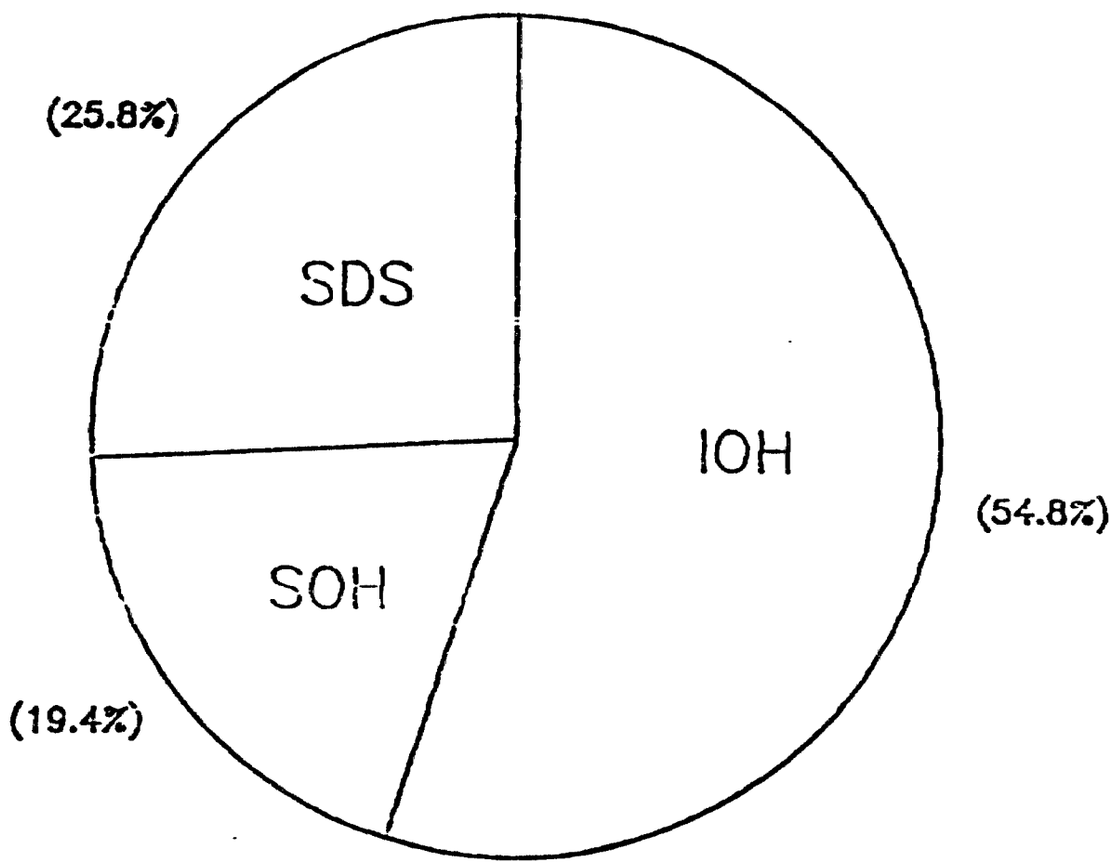


FIGURE I (CON'T)

DECEASED GUTRON PATIENTS

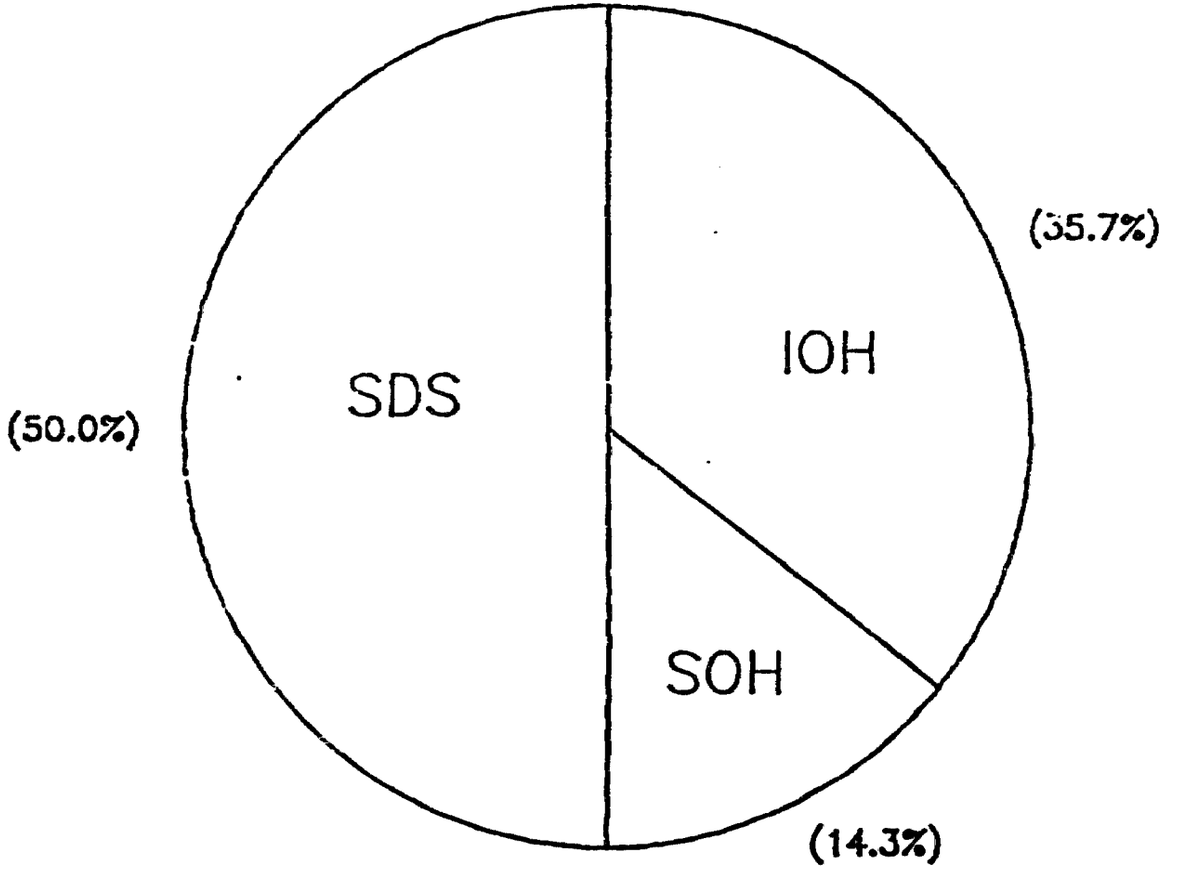


Table A details the age distribution of the patients. This group concluded from data that the baseline catecholamine pattern offered no guidelines as to the patients' response to midodrine and could not be used for any predictive value. This group also concluded that although initially patients may not show a blood pressure response they seem to show subjective improvement over time. Figure III-A details some of this information.

The ability to distinguish a trend from blood pressure/disease variability is obviously not apparent to this reviewer.

Long term observations in 74 patients treated with midodrine were provided by this group in which principally family members and/or the patient measured blood pressure. Table II-A demonstrates that some patients (7-15%) developed severe hypertension (180/110) but this incidence depended on the time of day.

Table II-C demonstrates that some patients had a marked improvement in their standing systolic blood pressure. However, some were worse. Fifty-nine patients responded to a questionnaire in which 50 felt that they had fewer fainting spells on midodrine.

In regards to side effects, in addition to supine hypertension, other common side effects included pruritis, paresthesia, piloerection, headache, urinary urgency, flushing, insomnia, nightmares, and in 1 patient biopsy proven angiitis. One patient had a sustained hemorrhagic cerebral accident.

MEDICAL REVIEW OFFICER'S EVALUATION

This open label individual investigator/center study provides no control data regarding midodrine's efficacy. Obviously, in this group's opinion, midodrine is effective in some patients. Adverse effects, however, have been documented as described above and of concern is one case of angiitis.

While in the Mayo Clinic's experience, this agent would be useful in the armamentarium in the management of patients with this disorder approvability to the general public of physicians requires careful consideration of the balance of benefit versus risk in terms of who will receive this agent, at what dose, and with what adverse effects compared to efficacy. The Mayo Clinic believes that because of the nature of the disease process that they were reluctant to particpate in placebo controlled trials so they state in their report that they would be willing to undertake a short term placebo controlled double blind crossover trial.

TABLE A

AGE AND SEX DISTRIBUTION
IN 177 PATIENTS WITH ORTHOSTATIC HYPOTENSION

	DIAGNOSIS	90 MEN							87 WOMEN						
		20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 to 89	20 to 29	30 to 39	40 to 49	50 to 59	60 to 69	70 to 79	80 to 89
	IOH			3	9	10	16	9		2	2	6	17	11	4
	SDS			1	6	12	4	2				8	12	6	2
SOH	AMYLOID			2	1	3					1				
SOH	DM				1		1	1	3	2		1	1		
SOH	OTHER	1			1	2	4	1		2	3		3	1	

IOH = Idiopathic Orthostatic Hypotension
SDS = Shy-Drager's Syndrome
SOH = Secondary Orthostatic Hypotension
DM = Diabetes Mellitus

FIGURE IIIA

A.M. SYSTOLIC STANDING BLOOD PRESSURE IN 24 PATIENTS CURRENTLY RECEIVING MIDODRINE

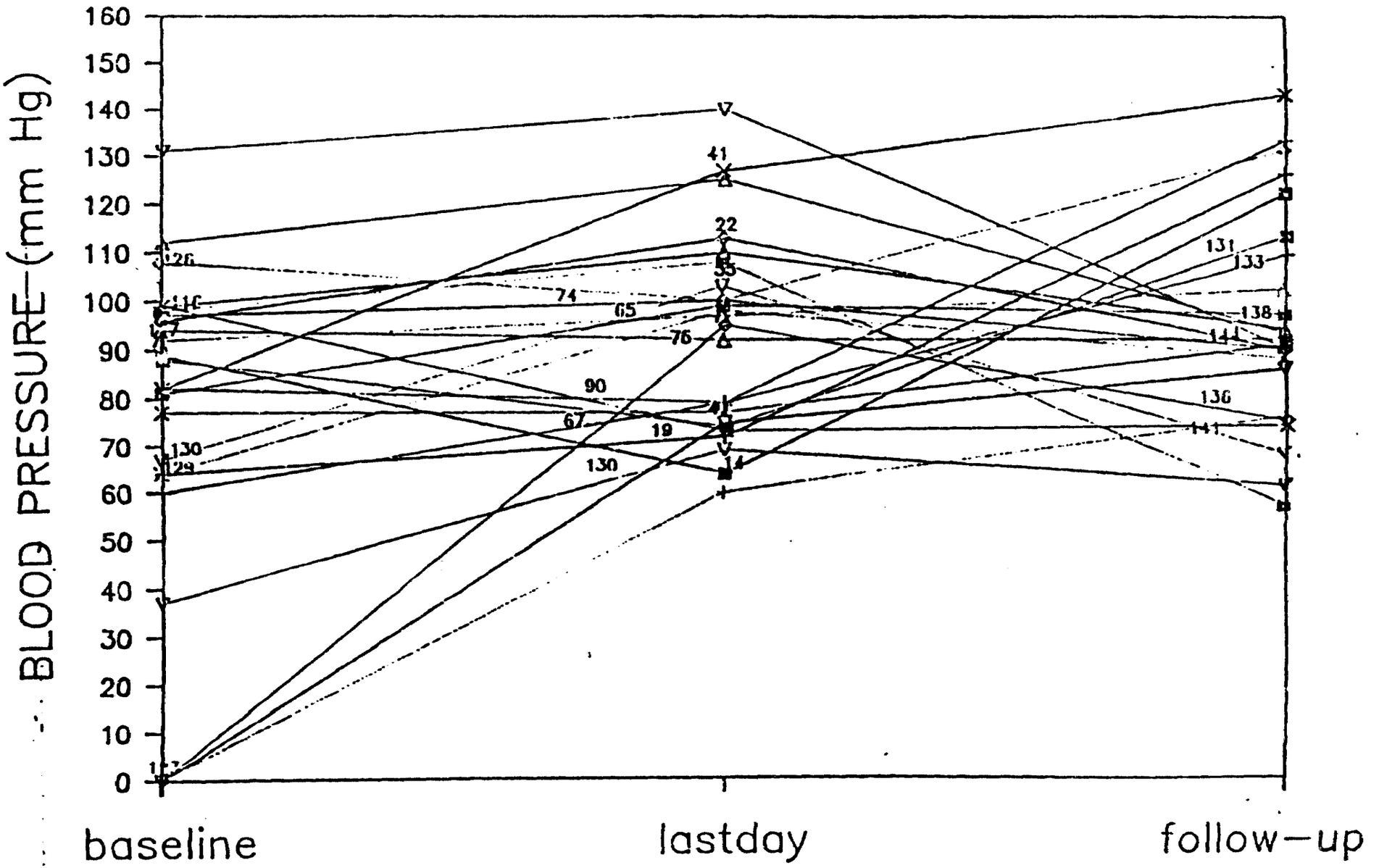


TABLE IIA

INCIDENCE OF SUPINE SYSTOLIC AND DIASTOLIC HYPERTENSION (>180 mm Hg and >110 mm Hg) IN ALL 74 PATIENTS FOLLOWED 3 TO 57 MONTHS*

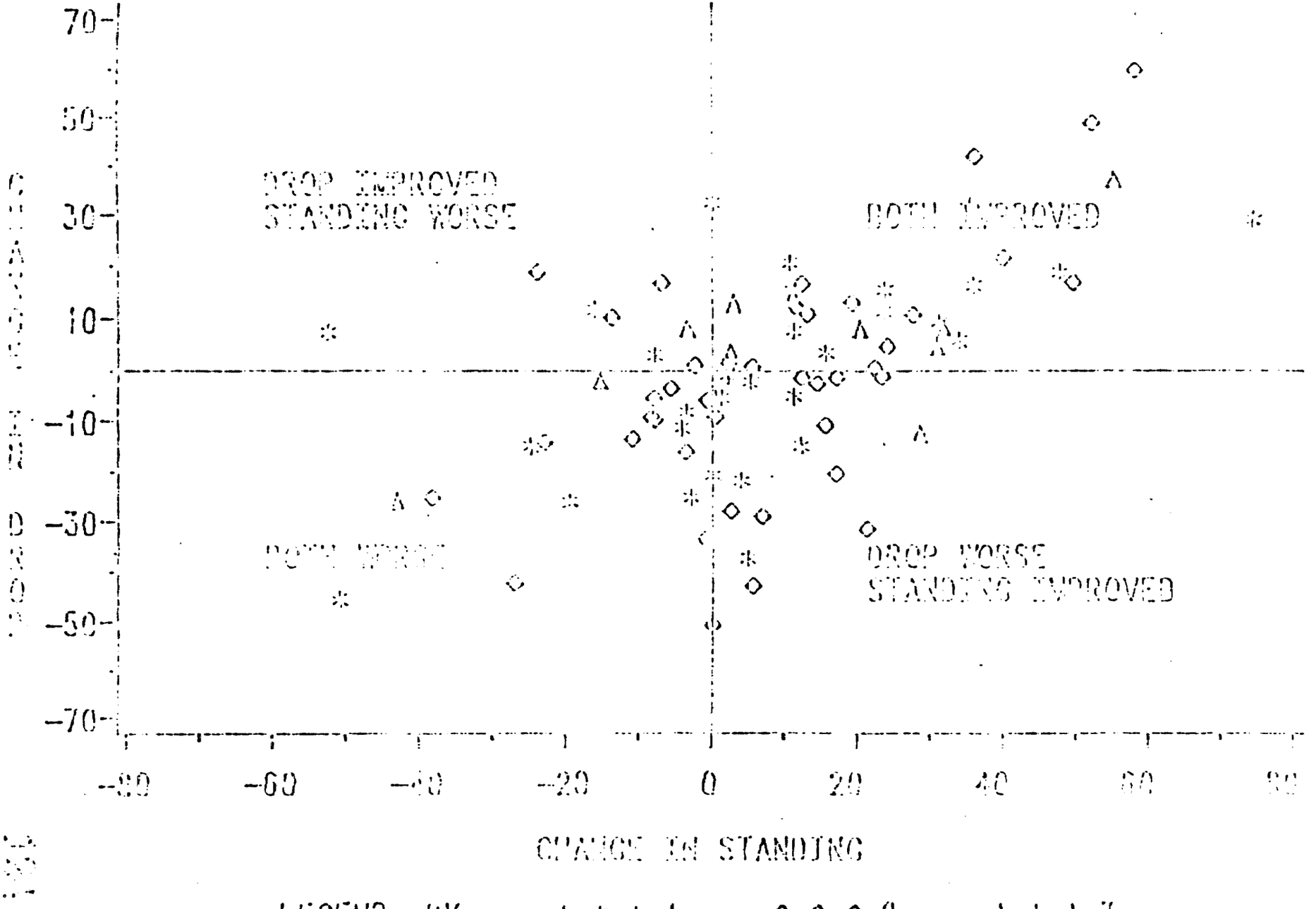
	A.M.				P.M.			
	End of follow-up		Entire period		End of follow-up		Entire period	
Blood pressure	Pt, no.	%	Pt, no.	%	Pt, no.	%	Pt, no.	%
Supine systolic	5	6.8	11	14.9	5	6.8	16	21.6
Supine diastolic	4	5.4	4	5.4	2	2.7	4	5.4

*During follow-up period those patients were included who had above noted hypertension values in more than 20% of readings

TABI 3

CHANGE IN DROP VS CHANGE IN STANDING PRESSURE

BASELINE TO LAST DAY – GROUP 3



A MULTICENTER DOUBLE BLIND PHASE III CROSSOVER COMPARISON OF THE SAFETY AND EFFICACY OF MIDODRINE AND EPHEDRINE IN PATIENTS WITH SEVERE ORTHOSTATIC HYPOTENSION

PROTOCOL #20,762-1A

Investigators: Matthew Conolly, M.D.
UCLA

Frank Douglas, M.D.
University of Chicago

Steven Higgins, M.D.
University of Colorado

David Robertson, M.D.
Vanderbilt

Stuart Selonick, M.D.
Johns Hopkins

David Streeten, M.D.
SUNY

The objective of this protocol was to evaluate midodrine compared to ephedrine in a multicenter crossover design using double blind technique.

The same protocol was followed by the Tarazi study in which - as previously stated - after a 2 day single blind placebo period patients underwent a 3-5 day titration with either midodrine or ephedrine. Midodrine was given from 2.5 to 5.0 to 7.5 to 10.0 mg tid and ephedrine from 6 to 12 to 18 to 24 tid. Thereafter, a 3-5 day maintenance therapy was used followed by a 2 day placebo period and a crossover to the other agent.

Patient selection was previously defined and included severe orthostatic hypotension on a background of Florinef and Jobst stockings. Blood pressures were obtained hourly from 8 AM to 4 PM by an automated noninvasive blood pressure monitor and criteria for effectiveness, exclusions, etc. were previously defined.

Twenty-two patients were entered by the 6 investigators and 1 (3502) did not meet study criteria. Only 8 patients were evaluated in this report from 4 centers, the other 14 being excluded because of multiple protocol violations.

Table 2 demonstrates the patient numbers and the treatments they received.

Mean blood pressure values are demonstrated in the accompanying table.

TABLE 2

PATIENT RANDOMIZATION TO
STUDY MEDICATION
(20762-1 - MULTICENTER STUDY)
PATIENTS WHO WERE ANALYZED FOR SAFETY AND EFFICACY

PATIENT NO.	TREATMENT 1	TREATMENT 2
1101	midodrine	ephedrine
1102	midodrine	ephedrine
3501	midodrine	ephedrine
3902	ephedrine	midodrine
4403	midodrine	ephedrine
4404	ephedrine	midodrine
4405	ephedrine	midodrine
4407	midodrine	ephedrine

Variable		Mean Values for Blood Pressure (mm Hg) and Pulse (bpm)			
		Baseline	Midodrine	Placebo	Ephedrine
Supine	Systolic	131.3	136.9	132.4	139.1
	Diastolic	76.4	79.5	76.9	78.5
	Pulse	71.2	71.1	73.7	77.1
Sitting	Systolic	110.9	118.0	106.4	113.2
	Diastolic	69.4	76.5	69.4	71.5
	Pulse	76.7	79.4	80.2	82.2
Standing	Systolic	95.5	96.6	96.5	99.6
	Diastolic	59.0	59.6	60.4	60.6
	Pulse	85.9	87.0	86.8	89.0

FIGURE 2

SINGLE APPLICATION TTS (fentanyl) 75 mcg/hr FOR THREE DAYS
MEAN (SE) IN-VIVO ABSORPTION and IN-VITRO DELIVERED DOSE

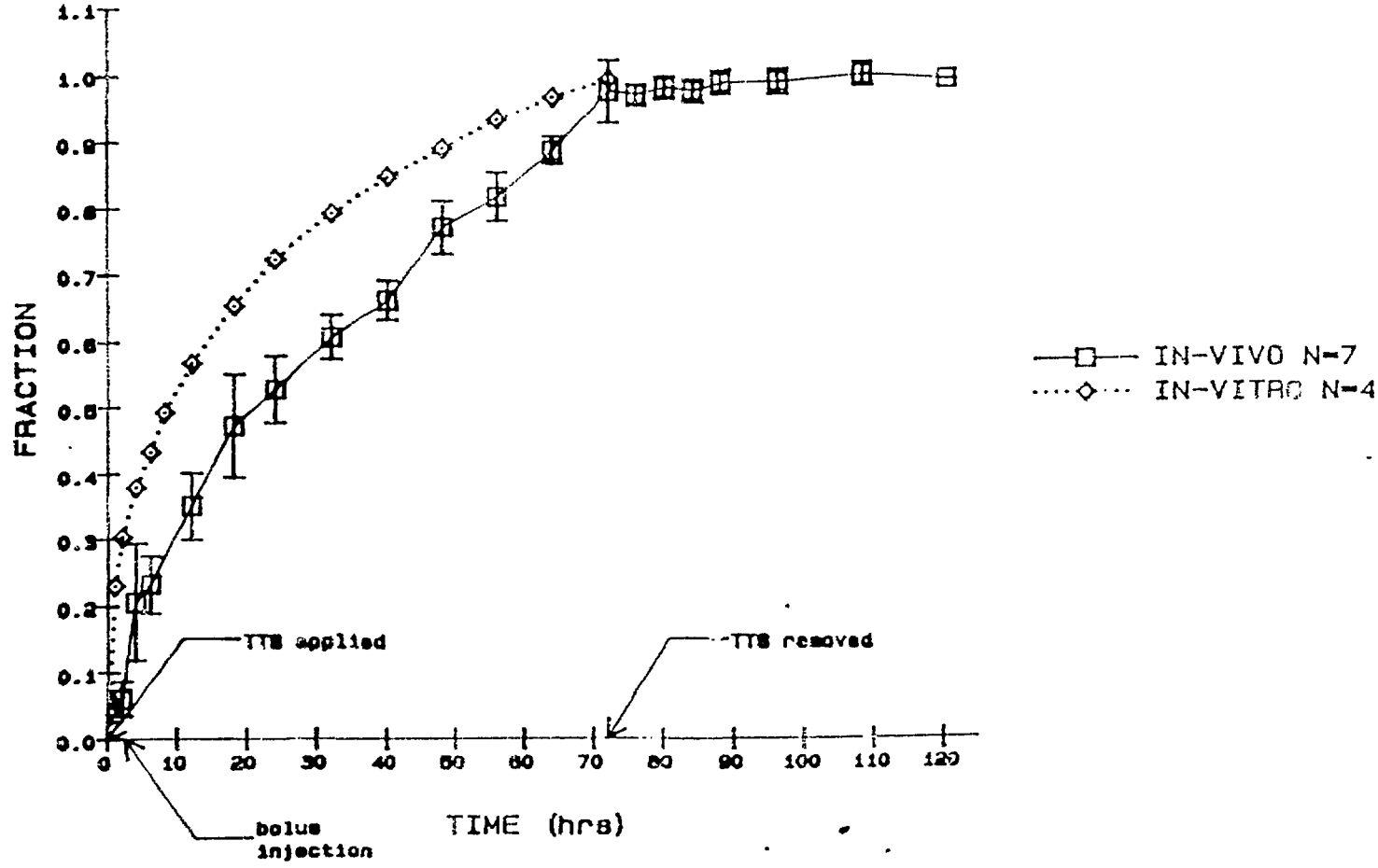


Fig 2

Note that both midodrine and ephedrine increased the blood pressure slightly compared to the placebo periods but this reviewer considers these to be extremely modest and of no clinical significance. Statistically, the sponsor claims an increase was significant for ephedrine compared to baseline and for midodrine only in the sitting systolic blood pressure. No significant changes in standing blood pressure were noted. The statistical significant factors are displayed in the accompanying table.

SAFETY

On midodrine, 2 patients had adverse effects. Patient 1407 had flushing and 3502 had supine hypertension requiring discontinuation from therapy. No clinical laboratory data of concern were noted.

MEDICAL REVIEW OFFICER'S COMMENTS

This study obviously demonstrates no supportive data for the efficacy of midodrine and again demonstrates that some patients may have to be discontinued because of hypertension. If this protocol report was combined with the Tarazi report which would have been proper - I suspect that the weak support that that trial offers for the efficacy of midodrine would have totally vanished.

The significance levels are displayed below.

	P Values for Comparison of Means				
Variable	B vs M	B vs E	P vs M	P vs E	M vs E
Supine Systolic	.11	.03	.19	.06	NS
Diastolic	.12	NS	.19	NS	NS
Pulse	NS	.02	NS	.18	.02
Sitting Systolic	.02	.07	.05	.21	NS
Diastolic	.01	.10	.04	NS	NS
Pulse	NS	NS	NS	NS	NS
Standing Systolic	NS	.18	NS	NS	NS
Diastolic	NS	NS	NS	NS	NS
Pulse	NS	NS	NS	NS	NS

REVIEW OF MIDODRINE CLINICAL LITERATURE

The sponsor reviewed and summarized the results of 56 clinical study reports which have been published or unpublished dealing with a total of 3,996 patients receiving midodrine therapy, 87% of whom suffered from hypotensive disorders. This was a markedly heterogenous group with secondary hypotension due to disease states or drug therapy or urinary or ejaculatory disorders. The duration of midodrine therapy ranged from less than 1 day to 15 months with 56% of patients receiving midodrine for 3-6 weeks. Most received a total daily dosage of either 5 mg or less (39%) and 40%, 1-3 doses of 5-10 mg.

Three thousand two hundred sixty-five patients were evaluable for adverse effects of which the incidence was 9.4% with 1.6% of the total number requiring discontinuation of midodrine due to its therapy. Most of the reactions were pilomotor. Changes in blood pressure were variable but subjective complaints were felt to be improved.

MEDICAL REVIEW OFFICER'S COMMENTS

It is this widespread use of midodrine, often with just a single dose per day, that provides this reviewer with great concern about the general release of midodrine. Subjective symptoms of autonomic dysfunction are by its definition subjective and without proper placebo controlled trials to demonstrate that such symptoms are in fact helped by the use of this agent. The benefit, which may be extremely small, must be weighed against a risk that could be considerable. The trials have demonstrated that the risks include angiitis, significant cardiac arrhythmias, bradycardia, syncope, and potentially excessive systemic hypertension leading to congestive heart failure, myocardial infarction and death.

SAFETY UPDATE

The clinical cut-off date for this NDA was set as of July 31, 1987. Two midodrine clinical trials were ongoing at that time and only 3 patients have been demonstrated to have safety concern in one of those trials. One developed supine hypertension requiring discontinuation after 5 years of therapy, another had night cramps of moderate severity and a final one, a single isolated seizure with no clear relationship to the drug with an unlikely relationship since there has been no recurrence with continuation of therapy at 30 mg per day.

Previous adverse drug effects of concern were submitted by the sponsor on FDA 1639 forms in 1982 thru 1984. These include 1 cardiac arrest resulting in death, 1 stroke ending in death, 2 myocardial infarctions ending in death, and 1 congestive heart failure ending in death. The potential relationship of these events to midodrine is uncertain but plausible.

Pharmacologist Review

NDA 19-815

REVIEW/EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA: ORAL CARCINOGENICITY STUDIES IN RATS AND MICE

W.T. Link, Ph.D.
September 19, 1995

SPONSOR: Roberts Pharmaceutical Corporation

DRUG: Midodrine (TS 701) (Amatine®)

TESTING FACILITY:

STUDY NUMBER

STUDY DATE: Study completed 11 April, 1989

GLP COMPLIANCE: The author has provided a statement that the above study was conducted in compliance with Good Laboratory Practice regulations.

ANIMALS: The study was conducted using Sprague Dawley rats, 300 males and 300 females, approximately six weeks of age at the start of dosing. Animals were housed, sex segregated, with five animals per cage (dim. 580 x 385 x 200 mm). Two weeks of acclimatization were provided prior to start of dosing.

MODE OF ADMINISTRATION OF TEST AGENT: TS 701 from two batches (M32998, received 4 March 1987 and P22150, received 17 July 1987) was used in this study. Stock dosing solutions were prepared fresh weekly using distilled water as vehicle. Analysis of dosing solutions, and validation of 7 day stability was conducted during weeks 1, 13, 26, 35, 43, 54, 61, 71, 78, 94 and 105 of dosing, under Animals received daily oral doses of TS 701 or vehicle by gavage using a steel dosing cannula at a constant volume of 5 ml dosing solution per kg body wt. Animals were weighed daily for dosage calculations.

DOSE LEVELS: Rats were randomly assigned to four Groups as follows:

	Dose Level (mg TS 701/kg/day)	number of males	number of females
Group 1	0	100	100
Group 2	1	50	50
Group 3	3	50	50
Group 4	10	100	100

OBSERVATIONS/MEASUREMENTS: All animals were checked for viability each morning and as late as practical in the evening. In addition, from Week 52 to the end of the study, animals were checked for moribundity at approximately midnight. Animals were observed for reaction to treatment during the day. The location, appearance, dimensions and progression of all visible or palpable masses was recorded. Every animal was given a detailed clinical examination weekly.

Body weight was recorded weekly, starting one week prior to treatment, until Week 13 and at four week intervals thereafter. Food consumption per cage was recorded on the same intervals as for body weight. Water consumption was verified visually but not reported.

LABORATORY INVESTIGATIONS: Differential blood smears were taken from all animals at Weeks 51, 77/78 and 102/103. Differential blood counts were performed on all Group 1 (Control) and Group 4 (High Dose, 10 mg/kg/day) for each of the indicated time intervals. During Weeks 102/103, peripheral blood red and white cell counts were performed on all Group 1 and 4 animals.

TERMINAL STUDIES: All surviving animals were sacrificed and necropsied after week 104. The gross dissection and necropsy were performed under the supervision of a pathologist. Premature decedents were necropsied at time of discovery.

The following organs were weighed:

Adrenals
Brain
Heart
Kidneys
Liver
Lungs
Ovaries (with Fallopian tubes)
Pituitary
Prostate
Seminal vesicles
Spleen
Testes
Thymus
Thyroids
Uterus

The following tissues were examined <u>in situ</u> and fixed:

Adrenals
Aortic arch
Any abnormal tissue
Bladder
Bone (sternum and rib)
Brain
Epididymides
Eyes
Femur (bone marrow)
Heart
Harderian gland
Intestine: duodenum
jejunum
ileum
caecum
colon
Kidneys
Liver
Testes (plus epididymides)
Thymus
Thyroids (with parathyroids, examined where present)
Lungs (perfused)
Mammary gland
Mesenteric lymph node
Muscle (thigh)
Nasal cavity
Oesophagus
Ovaries (with Fallopian tubes)
Pancreas
Pituitary
Prostate
Sciatic nerve
Seminal vesicles
Skin
Spinal cord
Spleen
Stomach (glandular and non-glandular)
Submaxillary salivary gland
Submandibular lymph node
Tongue
Trachea
Uterus
Vagina

HISTOPATHOLOGICAL EVALUATION: All tissues fixed, with the exception of aortic arch and nasal cavity, were processed and examined histopathologically for all animals in the Control (Group 1) and High dose (Group 4) and for all premature decedents.

STATISTICAL EVALUATION: Organ weight and body weight data were statistically analyzed for homogeneity of variance using the F-max test. If the group variances appeared homogeneous a parametric ANOVA was used and pairwise comparisons made via Student's t-test using Fisher's F-protected LSD. If the variances were heterogeneous log or square root transformations were used to attempt to normalize the variances. If they remained

heterogeneous, then a non-parametric test such as a Kruskal-Wallis ANOVA was used. Organ weights were also analyzed conditional on body weight (i.e. analysis of covariance). Histopathology data were analyzed using Fisher's Exact Probability test.

Differences in survival between the Control and groups receiving the test material were assessed graphically using Kaplan-Meier survival curve and tested formally using the Gehan-Wilcoxon test.

RESULTS

OBSERVATIONS:

Mortality: There were 277 premature deaths during the study, distributed among the four Groups as follows:

	Group 1 (Control)	Group 2 (1.0 mg/kg/day)	Group 3 (3.0 mg/kg/day)	Group 4 (10.0 mg/kg/day)
Males	42/(100)	22/(50)	25/(50)	48/(100)
Females	41/(100)	21/(50)	25/(50)	53/(100)

High dose (Group 4) females showed an increased rate of mortality in the early stages of the study (Weeks 4-24, see Fig. 1). A period of no premature deaths followed until Week 56 where, again, Group 4 females showed significantly higher mortality rates than control (Group 1) females. Mortality for male animals (see Fig. 2.) was not significantly greater than for controls.

Clinical signs: Clinical signs recorded included perigenital swellings, swollen hindlimbs and hindfeet, hunched emaciated posture, subdued behavior, pale extremities, breathing difficulties, hypothermia and ataxia. These signs were regarded as generally typical for rats of this age and strain. There were no differences in the incidence of external palpable masses.

In group 4 males there was a significant increase in the incidence of sores on the feet or limbs (23/100 in Group 4, 5/100 in Group 1).

Body weight: Group mean body weights for Groups 1 through 4, males and females, are shown in Fig. 3.

Figure 1

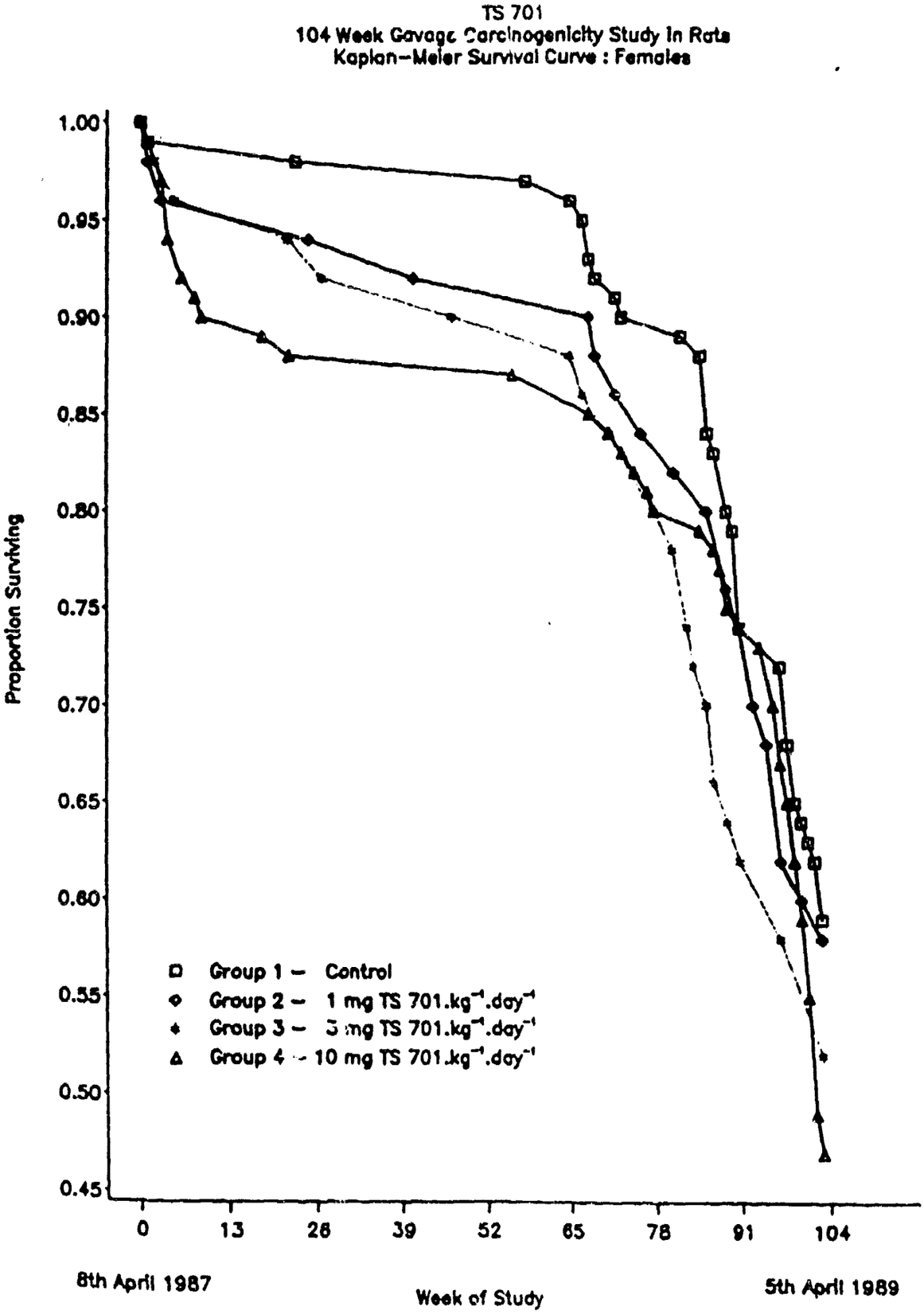
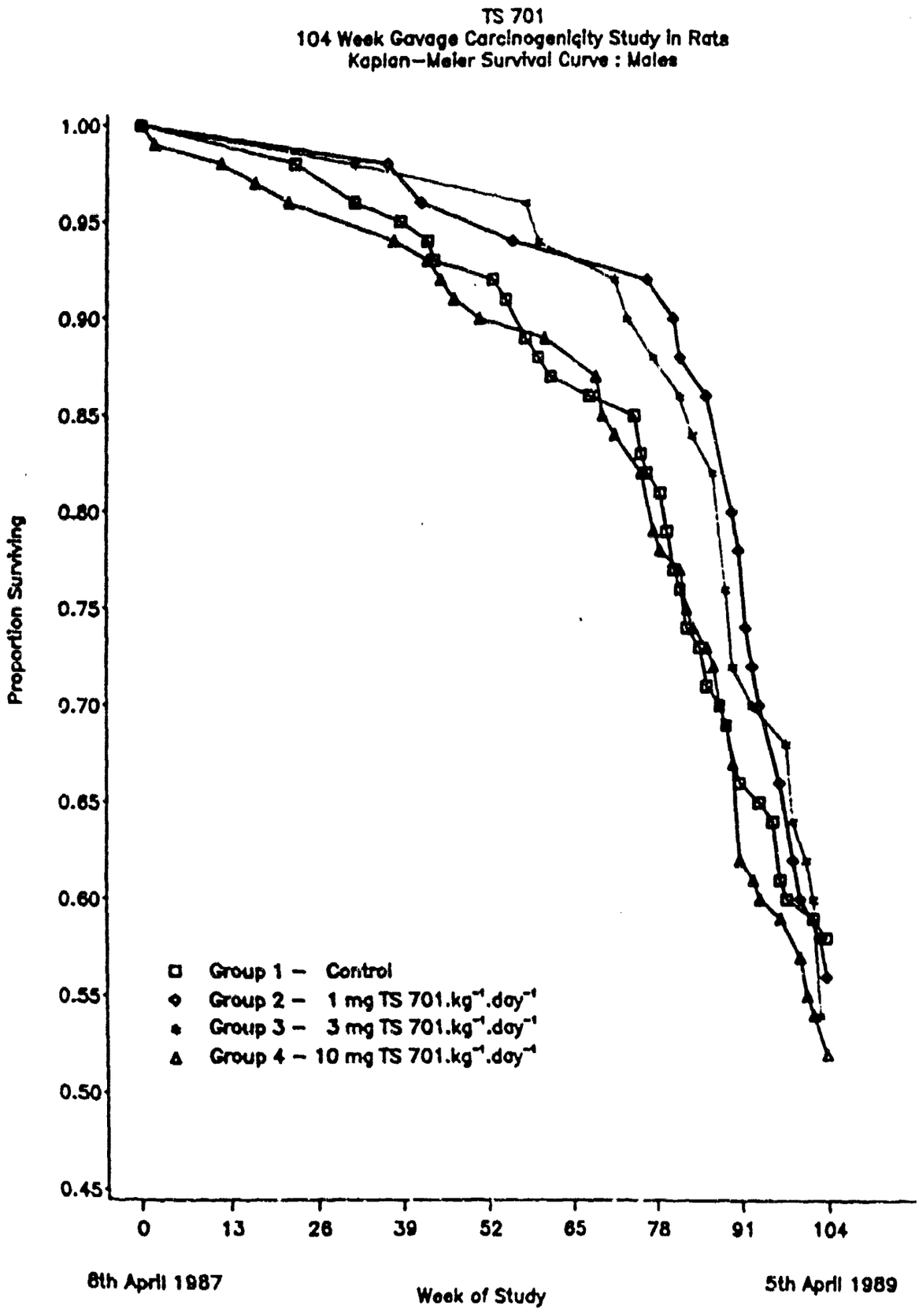

TS 701
104 Week Gavage Carcinogenicity Study In Rats
Kaplan–Meier Survival Curve : Females
Proportion Surviving
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
0
13
26
39
52
65
78
91
104
8th April 1987
Week of Study
5th April 1989
Group 1 – Control
Group 2 – 1 mg TS 701.kg⁻¹.day⁻¹
Group 3 – 3 mg TS 701.kg⁻¹.day⁻¹
Group 4 – 10 mg TS 701.kg⁻¹.day⁻¹

Figure 2


TS 701
104 Week Gavage Carcinogenicity Study in Rats
Kaplan–Meier Survival Curve : Males
Proportion Surviving
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
0.45
Group 1 – Control
Group 2 – 1 mg TS 701.kg⁻¹.day⁻¹
Group 3 – 3 mg TS 701.kg⁻¹.day⁻¹
Group 4 – 10 mg TS 701.kg⁻¹.day⁻¹
0
13
26
39
52
65
78
91
104
8th April 1987
Week of Study
5th April 1989

Attachment (1)

b. Quantitative Composition

Component Weight per Dosage Form (mg)

Nominal Delivery Rate Delivery Area (Size)	25 mcg/hr (10 cm²)	50 mcg/hr (20 cm²)	75 mcg/hr (30 cm²)	100 mcg/hr (40 cm²)
Component				
Occlusive Backing				
Drug Reservoir				
Fentanyl Base (Active Component)	2.5	5	7.5	10
Release Membrane				
Contact Adhesive				
Protective Liner				
Total Weight:	659	1255	1810	2377 mg

* Freon is a processing aid and is not a component of the final system

Figure 3

TS 701
104 Week Gavage Carcinogenicity Study in Rats
Body Weight (g): Group Mean Values

Treatment	Group/Dose Level (mg TS 701.kg^{-1}.day^{-1})							
Period (Weeks)	1♂ (0)	2♂ (1)	3♂ (3)	4♂ (10)	1♀ (0)	2♀ (1)	3♀ (3)	4♀ (10)
Pretrial	129^{100}	$*126^{50}$	128^{50}	$*127^{100}$	93^{100}	91^{50}	92^{50}	91^{100}
0	187	184	184	**182	130	128	130	**127
1	231	228	228	**225	151^{99}	149^{49}	148	***148^{99}
2	268	267	255	263^{99}	169	167	169^{49}	165
3	310	306	305	299	191	189^{48}	189	***183^{97}
4	337	337	334	327	204	203	204	198^{94}
5	358	357	357	350	214	215	217^{48}	210
6	382	383	380	373	225	225	227	220^{92}
7	405	401	400	391	235	232	234	***224
8	426	422	421	**409	242	239	241	***232^{91}
9	441	438	435	**424	247	246	247	**238^{90}
10	446	454	449	438	252	250	251	**243
11	473	470	464	**452	259	254	257	***247
12	483	478	473	**461^{98}	261	256	261	***249
13	493	486	480	**470	264	260	264	***252
16	518	515	504	**496	272	268	273	**261
20	540	540	530	520^{97}	280	278	27[illegible]	***266^{89}
24	554^{98}	557	543	534^{96}	283^{98}	281	285^{47}	***268^{88}
28	577	581	563	*553	295	292^{47}	293^{46}	***278
32	589^{96}	592	574^{49}	*563	301	302	303	**285
36	606	609	589	*579	309	307	310	***289
40	620^{95}	620^{49}	600	**585^{94}	314	312	315	***293
44	624^{93}	633^{48}	609	**591^{93}	322	320^{46}	322	***300
48	640	651	625	**605^{92}	330	323	331^{45}	***305
52	650	660	635^{48}	**614^{91}	339	328	338	***309
56	661^{91}	664^{47}	636	**617	349	339	348	***321^{87}
60	668^{88}	682	652^{47}	**629	361^{87}	346	360	***328
64	680^{87}	689	659	**632^{80}	362	350	359	***330
68	685^{86}	696	668	**636	373^{83}	359^{45}	372^{43}	***343^{85}
72	687	695	658^{46}	***627^{85}	373^{81}	361^{43}	371^{42}	**343^{84}
76	689^{83}	688	664^{45}	***632^{83}	385^{80}	373^{42}	379	**361^{82}
80	691^{79}	682^{46}	659^{44}	***628^{79}	389	381	388^{40}	366^{80}
84	694^{74}	684^{44}	657^{42}	***623^{75}	393^{69}	386^{41}	397^{36}	372
88	683^{70}	658^{43}	*641^{41}	***613^{71}	386^{63}	385^{40}	392^{33}	370^{77}
92	681^{66}	655^{37}	658^{8}	***607^{63}	398^{74}	382^{37}	402^{31}	373^{74}
96	681^{64}	661^{35}	674^{35}	**613^{60}	391	396^{34}	404	373^{70}
100	682^{60}	654^{30}	669^{32}	***599^{56}	398^{64}	392^{30}	396^{29}	368^{59}
104	664^{58}	633^{28}	662^{28}	***582^{52}	396^{59}	386^{28}	398^{26}	369^{47}
Weight Gain (g) Weeks (0-104)	477	449	478	400	266	258	268	242
% of Controls	-	94	100	84	-	97	101	91

Numbers in superscript indicate the number of survivors at that and subsequent timepoints
* = Significantly different from Control, P<0.05
** = Significantly different from Control, P<0.01
*** = Significantly different from Control, P<0.001

MALES: High dose males (Group 4) showed a 16% reduction in body weight gain relative to Group 1 controls. Analysis of group mean body weights demonstrated significant reductions at periods throughout the study for Group 4 rats relative to control. Groups 2 and 3 were not different from control in any period.

FEMALES: Group 4 females showed a 9% reduction in overall weight gain with significant differences in mean body weight from start of the study until Week 76. Group mean body weights were not different from control for the remainder of the study. Group 2 and 3 females were not significantly different from control in any time period.

Food and water consumption: There were no significant differences among Groups, male or female, with regard to food intake or water consumption.

Analyses of dosing solutions: The dosing solutions analyzed were generally within the ±10% limits of acceptability for this study. Exceptions noted were as follows:

Week 11 - solution for Group 4 was 11% high

Week 61 - solutions for Groups 3 and 4 were both low by 12%

Week 105 - solutions for Groups 2, 3 and 4 were low by 25%, 30% and 36% respectively. Reanalysis demonstrated the values were within the limits of the study.

LABORATORY INVESTIGATIONS: There were no significant differences in group mean values for differential blood counts at Weeks 51, 77/78 and 103/104 for males or females. Whole blood red and white cell counts performed on Week 102/103 demonstrated no differences from control in either sex.

TERMINAL INVESTIGATIONS:

Organ weights: Statistical comparison of organ weights among the Groups demonstrated numerous treatment-related differences. Organs, with weight differences significant at the $p<0.05$ level, are listed below by comparison of Group 4 (High dose) males and females relative to their control (Group 1).

Parameter	Change	MALES	FEMALES
I. Absolute organ wt.	increase	Adrenals Lungs	none
	decrease	Prostate Seminal vesicles	Heart
II. Normalized to average body wt.	increase	Adrenals Lungs Heart	Lungs
	decrease	Prostate Seminal vesicles	none
III. Relative (% of body wt.)	increase	Adrenals, Brain Heart, Kidneys Liver, Lungs Thyroid, Spleen	Kidneys Liver Lungs
	decrease	Prostate Seminal vesicles	none

[redacted]

GROSS PATHOLOGY: During the period of necropsy, several lesions were described which occurred exclusively or predominantly in the Groups receiving TS 701 and appear to be treatment related. Significant differences from control were only reported for Group 4, those animals receiving the highest (10 mg/kg/day) dose. The incidence of these lesions and their statistical significance are shown below:

Lesion:	Group 1 Males	Group 4 Males	Group 1 Females	Group 4 Females
Thorax: fluid/blood	1	7	1	8*
Aorta: dilated	1	9*	1	8*
Heart: atrium enlarged/mass	0	24***	1	3
Kidneys: granular	2	10*	8	5
Kidneys: cyst	3	13*	4	5
Kidneys: depressed foci	3	13*	4	4
Feet/limbs: sores	5	23**	3	7

Level of significance:
* $p<0.05$
** $p<0.01$
*** $p<0.001$

[redacted]

HISTOPATHOLOGY:

Non-neoplastic findings

AORTA: Lesions of the aorta were found in the portion of the aorta attached to the heart or in sections from aortas processed due to observed abnormalities discovered during necropsy. Aortic aneurysms occurred with high frequency in high dose (Group 4) rats. Nine males out of 21 and 13 out of 18 females observed had visible aneurysms compared to no occurrences in male or female controls. In several cases the aneurysm had ruptured causing intrathoracic hemorrhage, and deaths from this cause were reported as early as Week 4.

Mineralization of the aorta was reported in 13 of the 21 males and 7 of the 18[1] females examined, however the incidence of this finding was 4 out of 4 for males and 0 out of 1 for females among the control (Group 1) rats. It is likely that these control animals were selected for examination because of apparent gross findings, rather than selected randomly from the control population.

HEART: Numerous treatment-associated cardiac lesions were reported, with high dose males being the most severely affected. These include left atrial thrombosis (25 out of 100, $p<0.001$); left and right atrial hypertrophy with degeneration (78/100 and 19/100 respectively, $p<0.001$); left atrial calcification (13/100, $p<0.001$) and left atrial endocardial thickening (13/100, $p<0.01$).

High dose females showed significant left and right atrial hypertrophy with degeneration (56/100, $p<0.001$ and 8/100, $p<0.01$ respectively).

PULMONARY VESSELS: Significant increases in the incidence of lesions were only observed in males. These were vascular wall mineralization in high dose males (26/100, $p<0.001$) and medial muscle hypertrophy in high dose male premature decedents (10/48, compared to 1/42 controls).

LUNGS: An increased incidence of interstitial pneumonitis was seen in high dose female rats (34/98, $p<0.05$).

KIDNEYS: There was an increased incidence and severity of nephropathy in both high dose males (92/100 relative to 80/100 for control, $p<0.05$) and females (76/100 relative to 56/100, $p<0.01$).

---

[1] In the study summary, pg. 33, this value is reported as 8, not 18 as reported in Table 18, pg. 103. The correct value is 18.

ADRENALS: There was a significant increase in incidence of adrenal infarcts in high dose females (9/98, $p<0.01$).

OTHER FINDINGS: There were significant decreases in the incidence of the following lesions in high dose animals relative to control:

Liver: Males had lower incidence of portal sclerosis ($p<0.001$) and pale cell foci ($p<0.01$) than control.

Kidney: Females had lower incidence of pelvic mineral deposits ($p<0.001$).

Pancreas: Fewer treated animals showed replacement of pancreatic acini by fat cells (males - $p<0.001$, females - $p<0.05$).

Neoplastic findings:

The single significant neoplastic finding was of increased incidence of benign interstitial cell tumors of the testes (19/100 relative to control 6/100, $p<0.05$).

Comparisons that were not significant, but different and of possible borderline significance include:

malignant pheochromocytoma - 11/100 for high dose males relative to 4/100 for control

benign mammary adenoma - 5/98 for high dose females relative to 2/99 for control

DISCUSSION:

The above study was carried out to determine the carcinogenic potential of TS 701 during long term, high dose oral treatment. The features of primary interest in this review are therefore: Is the dosage as high as can be reasonably tolerated? and: Were there any significant neoplastic findings associated with treatment? Additionally, because of the profound effects of this agent on the cardiovascular and renal systems, discussion of the non-neoplastic findings is warranted.

It appears that the minimal requirements were met with regard to dosage adequacy, number of animals, duration of exposure and thoroughness

in evaluation of experimental results. Dosage adequacy is demonstrated by 1) significant or borderline increases in mortality in the high dose group; 2) decrease in body weight gain; 3) significant treatment-associated changes in organ weights especially relative to body weight and 4) widespread cardiovascular and renal pathology evident at both the gross and microscopic level. Based on these effects, it seems apparent that significantly greater mortality would be observed at dose levels much higher than the 10.0 mg/kg/day used, and is therefore at or near the maximum tolerable dose for this agent in rats.

The effects on mortality appear to be of borderline significance with one noteworthy exception: the early deaths among high dose females. The cause of death was attributable to thoracic hemorrhage secondary to rupture of aortic aneurysm in selected premature decedents. Aneurysms were a significantly observed feature among survivors in the treated groups as well. It is likely that these aneurysms and early sudden deaths are due to the pronounced cardiovascular effects of the TS 701[2]. These effects are not observed at lower doses.

The decrease in body weight gain in treated animals was greater in males and not significant in females after Week 76. This decrease was not associated with decreased food consumption or water intake. This decrease could be due to a contraction of body fluid volume secondary to the cardiovascular and renal effects of TS 701. Alternatively, it could simply reflect greater metabolism with unchanging caloric intake resulting in depletion of body fat. The effect on body weight is not apparent in the lower dose groups.

Changes in organ weight were observed in both directions and probably result from multiple factors. Regional changes in blood flow, increased metabolic load, ongoing pathology and secondary effects resulting from direct cardiovascular or renal effects and ongoing pathology in other organs probably all play a role. The increase in heart weight is undoubtedly due to hypertrophy secondary to increases in both preload (decreased venous compliance and increased venous return) and afterload (increase in stroke volume and total peripheral resistance). Increased liver weight may simply reflect an increased metabolic load due to the TS 701 per se, or be secondary to cardiovascular and renal effects of the agent.

The pronounced gross and microscopic pathology observed in the treated groups can, for the most part, be explained on the basis of the pharmacologic action of TS 701 as an alpha agonist. In most respects, the lesions observed are consistent with those observed in chronic hypertension: cardiac

---

[2] It is probably coincidental, but still worth noting, that the sudden mortality increase in females evident in Fig. 1 (weeks 1-13) ends at the same time (mid July) as the second batch (#P22150) of TS 701 arrived.

[redacted]

hypertrophy, nephropathy and adrenal infarcts. Additionally, the presence of significant sores and external lesions of the limbs are consistent with peripheral vascular perfusion deficits seen with chronic adrenergic stimulation.

While pathologic responses to persistent adrenergic stimulation can explain the observations, they do not rule out the possibility of direct or indirect cytotoxic effects on cardiac and vascular tissue independent of alpha receptors or elevated arterial pressure. Separation of such effects, if present, may not be easily demonstrated.

Neoplastic findings:

Significantly increased incidence of interstitial tumors of the testes were associated with high dose TS 701 treatment. While this was reported to be just within the natural incidence (4-20%) seen at Inveresk, the incidence shows a tendency towards dose-dependency. Incidence of this tumor type was 6% (6/100), 0% (0/22), 12% (3/25) and 19% (19/100) for Groups 1, 2, 3 and 4 respectively. In order to suggest that Group 1 controls are showing incidence on the low side of normal, would require the simultaneous claim for Group 2 as well.

Other tumors noted by this reviewer which appear to be of borderline significance were malignant pheochromocytoma and benign mammary adenoma. The occurrence of pheochromocytoma is especially worth noting in light of the cardiovascular effects of TS 701 and a significant effect (direct or indirect) on the adrenals themselves. There is no suggestion of increased incidence of these tumor types in the intermediate dosage groups.

[redacted]

NDA 19-815

REVIEW/EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA
78 WEEK ORAL CARCINOGENICITY STUDY IN MICE

William T. Link, Ph.D.
September 18, 1995

SPONSOR: Taisho Pharmaceutical Company Limited

DRUG: Midodrine (TS 701) (Amatine®)

TESTING FACILITY:

STUDY NUMBER

STUDY DATE: Study completed 21 February, 1989

GLP COMPLIANCE: The author has provided a statement that the above study was conducted in compliance with Good Laboratory Practice regulations.

ANIMALS: The study was conducted using CD-1 strain mice, 300 male and 300 female. Mice were obtained from
They were approximately 4 weeks old on arrival (males 21 ± 1, females 18 ± 1 g). Mice were allowed to acclimatize for 13 days prior to initiation of dosing.

MODE OF ADMINISTRATION OF TEST AGENT: TS 701, Batch No. P22150 (250 g. received on 17 July, 1987) was used in this study. Stock dosing solutions were prepared weekly using distilled water as vehicle. Doses were administered daily (seven days per week) for a minimum of 78 weeks, by gavage using a steel dosing cannula at a constant volume of 5 ml/kg body weight. Animals were weighed daily for dosage calculations.

DOSE LEVELS: Mice were randomly divided into four dosing Groups as follows:

	Dose Level (mg TS 701/kg/day)	number of males	number of females
Group 1	0	100	100
Group 2	1.7	50	50
Group 3	5.0	50	50
Group 4	15.0	100	100

OBSERVATIONS/MEASUREMENTS: All animals were checked for viability each morning and as late as practical in the evening. In addition, from Week 52 to the end of the study, animals were checked for moribundity at approximately midnight. Animals were observed for reaction to treatment during the day. The location, appearance, dimensions and progression of all visible or palpable masses was recorded. Every animal was given a detailed clinical examination weekly.

Body weight was recorded weekly, starting one week prior to treatment, until Week 13 and at four week intervals thereafter. Food consumption per cage was recorded on the same intervals as for body weight. Water consumption was verified visually but not reported.

LABORATORY INVESTIGATIONS: Differential blood smears were taken from all animals at Weeks 51, 77/78 and 102/103. Differential blood counts were performed on all Group 1 (Control) and Group 4 (High Dose, 15 mg/kg/day) for each of the indicated time intervals. During Week 77, peripheral blood red and white cell counts were performed on all Group 1 and 4 animals.

TERMINAL STUDIES: All surviving animals were sacrificed and necropsied after Week 78. The gross dissection and necropsy were performed under the supervision of a pathologist. Premature decedents were necropsied at time of discovery.

The following organs were weighed:

Adrenals	Prostate
Brain	Seminal vesicles
Heart	Spleen
Kidneys	Testes
Liver	Thymus
Lungs	Thyroids
Ovaries (with Fallopian tubes)	Uterus
Pituitary	

The following tissues were examined in situ and fixed:

Adrenals	Lungs (perfused)
Aortic arch	Mammary gland
Any abnormal tissue	Mesenteric lymph node
Bladder	Muscle (thigh)
Bone (sternum and rib)	Nasal cavity
Brain	Oesophagus
Epididymides	Ovaries (with Fallopian tubes)
Eyes	Pancreas
Femur (bone marrow)	Pituitary
Heart	Prostate
Harderian gland	Sciatic nerve
Intestine: duodenum	Seminal vesicles
jejunum	Skin
ileum	Spinal cord
caecum	Spleen
colon	Stomach (glandular and non-glandular)
Kidneys	Submaxillary salivary gland
Liver	Submandibular lymph node
Testes (plus epididymides)	Tongue
Thymus	Trachea
Thyroids (with parathyroids, examined where present)	Uterus
	Vagina

HISTOPATHOLOGICAL EVALUATION: All tissues fixed, with the exception of aortic arch and nasal cavity, were processed and examined histopathologically for all animals in the Control (Group 1) and High dose (Group 4) and for all premature decedents.

STATISTICAL EVALUATION: Organ weight and body weight data were statistically analyzed for homogeneity of variance using the F-max test. If the group variances appeared homogeneous a parametric ANOVA was used and pairwise comparisons made via Student's t-test using Fisher's F-protected LSD. If the variances were heterogeneous log or square root transformations were used to attempt to normalize the variances. If they remained heterogeneous, then a non-parametric test such as a Kruskal-Wallis ANOVA was used. Organ weights were also analyzed conditional on body weight (i.e.

analysis of covariance). Histopathology data were analyzed using Fisher's Exact Probability test.

Differences in survival between the Control and groups receiving the test material were assessed graphically using Kaplan-Meier survival curve and tested formally using the Gehan-Wilcoxon test.

RESULTS

OBSERVATIONS:

Mortality: There were 119 premature deaths distributed throughout the Groups as follows:

	Group 1 (Control)	Group 2 (1.7 mg/kg/day)	Group 3 (5.0 mg/kg/day)	Group 4 (15.0 mg/kg/day)
Males	14/(100)	7/(50)	13/(50)	20/(100)
Females	22/(100)	13/(50)	10/(50)	20/(100)

Kaplan-Meier Survival curves for all four Groups in males (Figure 1) and females (Figure 2) are presented below. There was some suggestion of increased mortality in Group 3 males, particularly in the latter stages of the study. This difference was not significant though, with a p value of $0.05<p<0.10$. There is no evidence of differential mortality among the four Groups of female mice.

Body weight: There were no demonstrable differences in body weight among any of the Groups in either sex. Body weights for all Groups, both male and female are presented in Table 1.

Food and water consumption: There were no notable differences in either food or water intake in either sex among the four dosing Groups.

Analyses of dosing solutions: Periodic analysis of the dosing solutions showed that acceptable accuracy (± 10%) was achieved.

Figure 1

TS 701
78 Week Gavage Carcinogenicity Study in Mice
Kaplan–Meier Survival Curve : Males

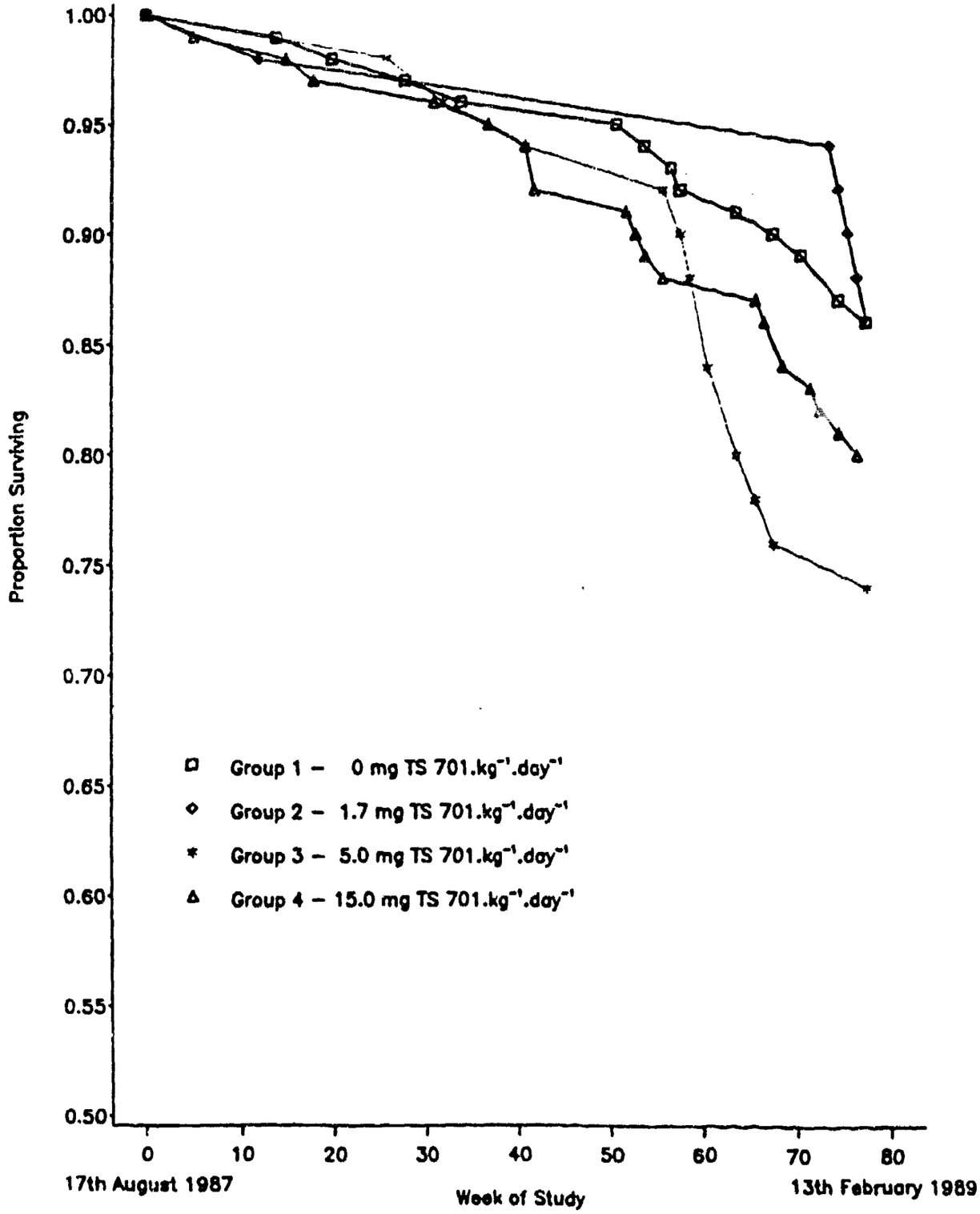


Figure 2

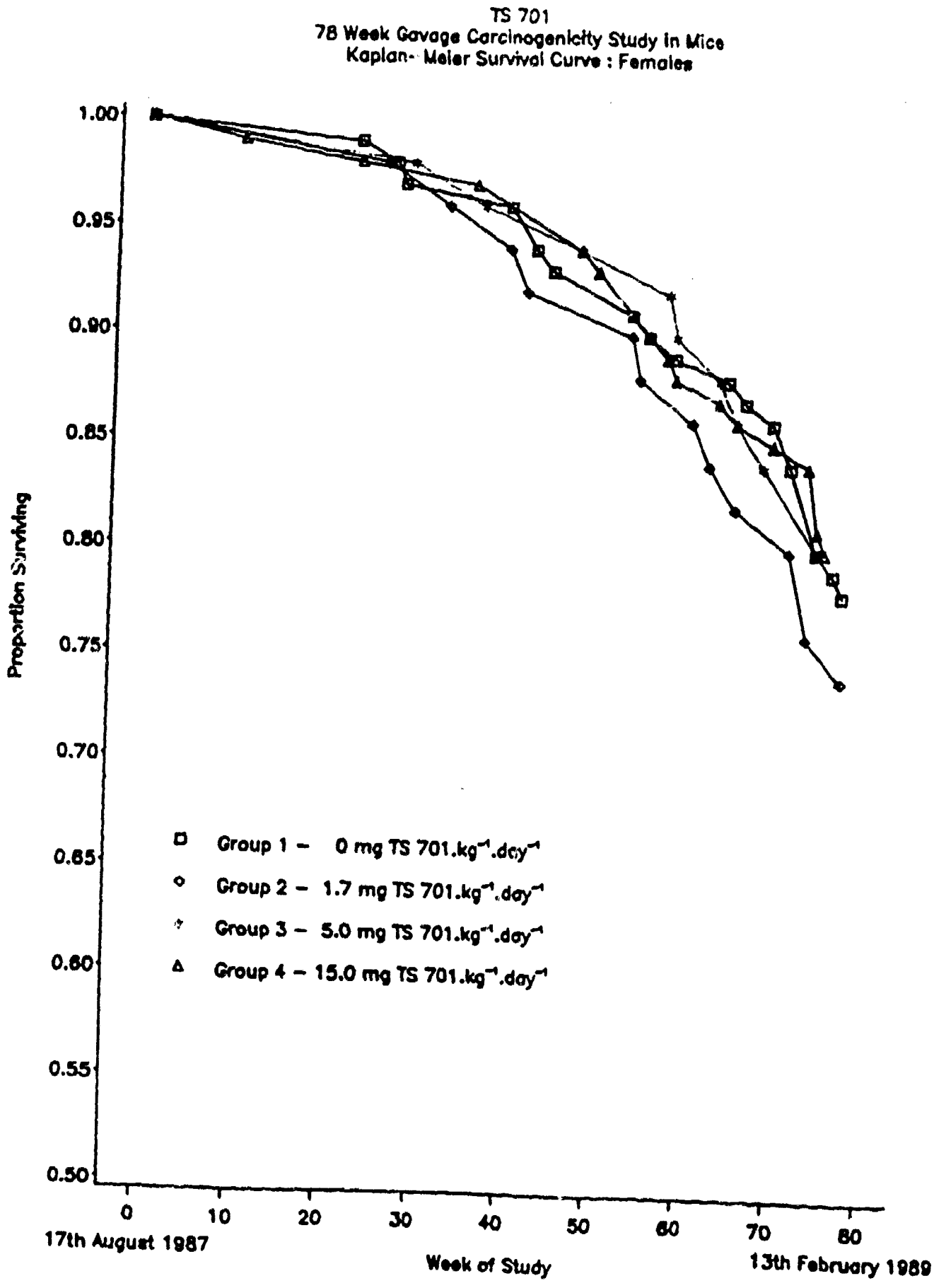
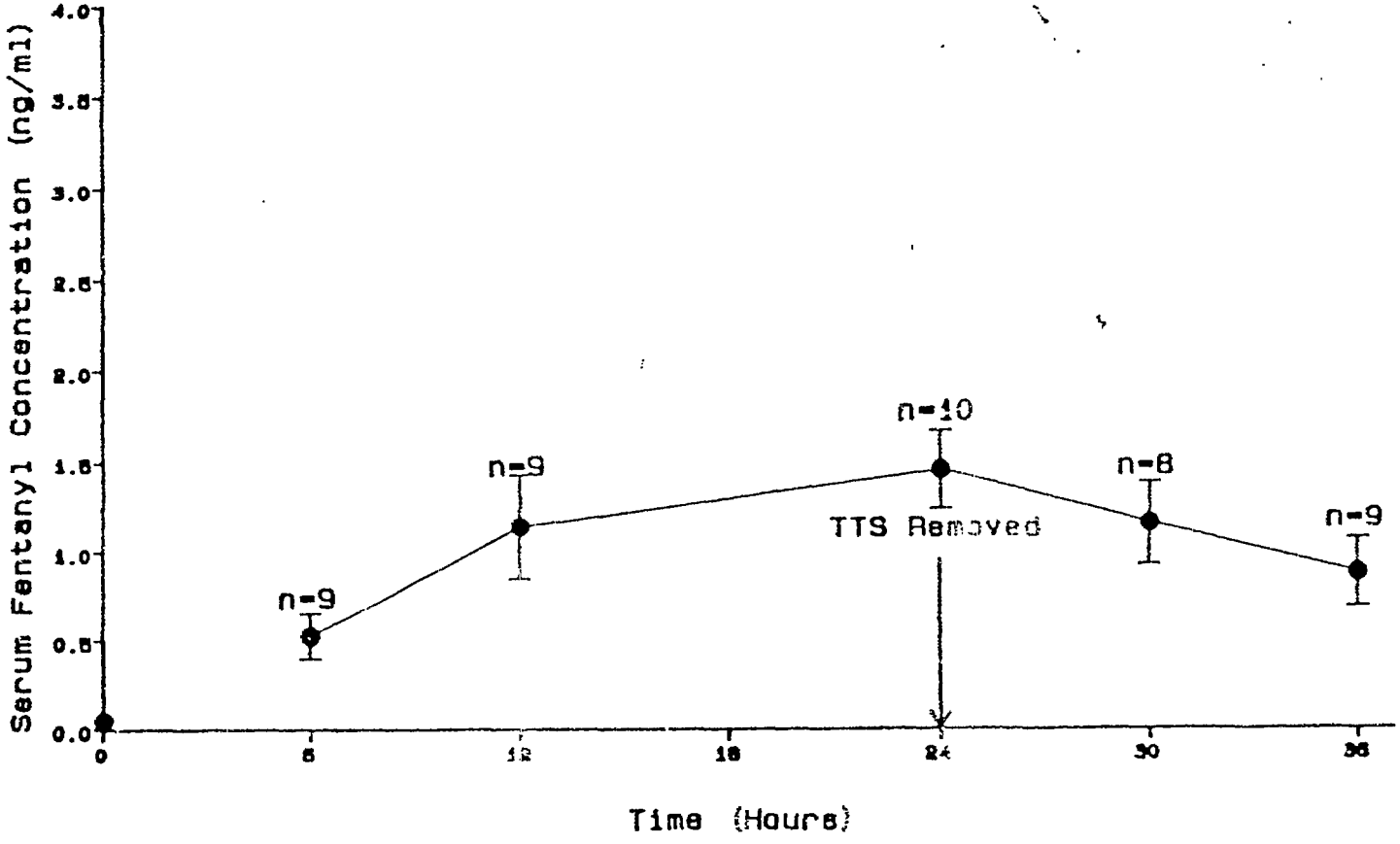

TS 701
78 Week Gavage Carcinogenicity Study in Mice
Kaplan- Meier Survival Curve : Females
Proportion Surviving
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
0.60
0.55
0.50
Group 1 – 0 mg TS 701.kg⁻¹.day⁻¹
Group 2 – 1.7 mg TS 701.kg⁻¹.day⁻¹
Group 3 – 5.0 mg TS 701.kg⁻¹.day⁻¹
Group 4 – 15.0 mg TS 701.kg⁻¹.day⁻¹
0
10
20
30
40
50
60
70
80
17th August 1987
Week of Study
13th February 1989

FIGURE 6

Mean (SE) Serum Fentanyl Concentration (ng/ml)
at Time from TTS Application*



*Values less than 0.1 ng/ml were reported as 0.05 ng/ml

Table 1

78 Week Gavage Carcinogenicity Study in Mice
Body Weight (g) Group Mean Values

Treatment Period (Weeks)	Group/Dose Level (mg TS 701 kg^{-1}.day^{-1}) 1♂ (0)	2♂ (1.7)	3♂ (5.0)	4♂ (15.0)	1♀ (0)	2♀ (1.7)	3♀ (5.0)	4♀ (15.0)
Pretrial	26.5^{100}	26.2^{50}	26.0^{50}	25.9^{100}	21.6^{100}	20.9^{50}	21.0^{50}	21.3^{100}
0	28.3	28.0	27.7	27.7	22.2	21.8	21.6	21.7
1	30.1	30.1	29.8	29.7	23.8	23.3	23.5	**24.7
2	31.6	32.0^{48a}	31.6	31.2	25.1	24.7	**24.2	25.3
3	32.3	32.1^{50}	31.6	31.4	25.4	24.8	*24.7	25.9
4	32.6	33.0	32.6	32.2	25.9	25.4	*25.?	**26.8
5	32.8	33.4	33.1	32.9^{99}	26.5	26.0	25.8	*27.1
6	33.8	33.6	33.4	33.1	26.6	26.3	25.8	27.1
7	34.2	34.1	33.8	33.5	27.3	26.8	26.7	27.6
8	34.3	34.2	34.1	33.8	27.6	27.2	*26.8	28.1
9	34.6	34.6	34.7	34.1	28.0	27.6	27.5	28.2
10	34.9	35.1	34.7	34.2	28.0	27.6	27.4	28.3^{99}
11	35.6	35.7	35.5	*34.7	28.8	28.4	28.2	29.2
12	35.8	35.7	35.4	34.9	28.5	28.2	28.2	**29.4
13	35.9	36.1^{49}	35.6	35.2	29.0	28.8	28.7	**29.9
16	35.9^{99}	36.0	35.8^{49a}	35.4^{97a}	29.1	28.9	28.7	***30.2^{97b}
18	36.3	36.6	36.0^{50}	35.7^{98}	29.5	29.0	29.2	*30.3^{99}
24	37.8^{98}	38.0	38.0	*36.8^{97}	30.7^{99}	30.5	30.4	31.2^{98}
28	37.8^{97}	37.6	37.5^{49}	37.2	30.6^{97}	30.5^{49}	30.5	31.3
32	38.1	38.1	38.1^{48}	*37.0^{96}	31.0	30.7	30.7^{49}	3)
36	38.0^{96}	38.1	38.1	37.4	31.0	31.5^{48}	31.0	**32.^{97}
40	38.2	38.2	38.1	37.2^{95}	31.5^{96}	31.2^{47}	30.6^{48}	31.4
44	38.8	38.9	38.8^{47}	**37.5^{92}	31.7^{94}	31.4^{46}	31.0	31.7
48	38.4	38.4	38.5	37.5	31.2^{93}	31.4	30.8^{47}	31.6^{94}
52	38.6^{95}	38.7	38.5	37.5^{91}	31.8	31.8	31.3	31.7^{93}
56	38.5^{94}	38.7	38.5^{46}	37.8^{88}	31.3^{90}	31.6^{44}	31.2	31.6^{90}
60	38.5^{92}	38.8	38.7^{44}	37.6	32.0^{89}	32.2	31.8^{45}	31.9^{88}
64	38.8^{91}	39.1	38.8^{40}	38.3	32.5	32.4^{42}	31.8^{44}	32.5^{87}
68	38.9^{90}	39.4	39.0^{38}	38.4^{86}	32.3^{87}	32.9^{41}	31.9^{43}	32.4^{86}
74	38.6^{89}	39.1^{47}	38.5	38.2^{82}	32.9^{84}	32.5^{38}	32.0^{42}	32.4^{84}
76	39.0^{87}	38.8^{45}	38.3	38.0^{81}	32.9^{80}	33.0	32.2^{4}	32.2
78	38.8^{86}	38.5^{43}	38.3^{37}	38.0^{80}	32.8^{78}	32.7^{37}	32.0	32.3^{80}
Weight Gain (g) (Weeks 0-78)	10.3	10.5	10.8	10.3	10.4	10.9	10.4	10.6
% of Controls	-	102	105	100	-	105	100	102

Numbers in superscript indicate number of animals data derived from at that and subsequent timepoints

a = One mouse excluded due to suspect body weight recording

b = Two mice excluded due to suspect body weight recordings

* = Significantly different from Controls, P<0.05

** = Significantly different from Controls, P<0.01

*** = Significantly different from Controls, P<0.001

LABORATORY INVESTIGATIONS:

Differential blood counts/Red and white blood cell counts: There were no significant intergroup differences in differential blood counts in either sex at Week 52 or 78, and no significant intergroup differences in red and white cell counts in either sex at Week 77.

TERMINAL STUDIES:

Organ weights: MALES: Both prostate and seminal vesicle weights were elevated in the high dose group with statistical significance achieved in absolute weight, with body weight as covariate and as percentage of body weight ($p<0.001$ in all comparisons). This trend was apparent in the intermediate dose group, suggesting dose-dependence, but not significant. Low dose mice were not different from control.

FEMALES: Thyroid weight was significantly increased, by all three methods of comparison, in the high dose group relative to control. The intermediate and low dose groups were not significantly different from control. Heart weight was slightly increased in the intermediate dose group after covariance analysis and when expressed as a percentage of body weight. Due to the lack of this observation in the high dose group, it is likely that this is a chance effect.

Gross Pathology: In males, there was an increased incidence of enlarged seminal vesicles in the high dose group (43/100 vs 14/100 for controls). There were no notable differences among other groups, male or female.

Histopathology:

NON-NEOPLASTIC FINDINGS: Changes considered to be associated with administration of TS 701 were present in the left atrium of the heart of mice of both sexes. High dose males (24/100) and high dose females (10/100) had karyomegaly and hypertrophy of myocytes in the left atrium. This finding was accompanied by some degree of interstitial fibrosis in 6/24 males and 3/10 females. These changes were not seen in any of the control mice. No morphologic changes between controls and treated mice were seen in the prostate gland or seminal vesicles.

NEOPLASTIC FINDINGS: There were no neoplastic findings which could be attributed to treatment with TS 701. The range of neoplasms observed was similar in type and frequency to that commonly seen in mice of this age. Hepatocellular, pulmonary and lymphoproliferative tumors were among the most common tumors observed.

DISCUSSION

There were no notable findings during 78 weeks of dosing with TS 701 in mice, with up to 15 mg/kg/day. Histopathologic evaluation did not demonstrate any evidence of carcinogenicity, but with doses of 15 mg/kg/day, TS 701 was considered to be associated with karyomegaly and hypertrophy of left atrial myocytes, accompanied by some interstitial fibrosis.

There were no morphologic changes in the prostate or seminal vesicles to account for the weight increase or necropsy findings. The macroscopic changes were suggested to be due to increased secretion which was not sufficiently severe to induce histologic changes.

As observed in the previous 104 week study in rats, there was no evidence of carcinogenicity. Additional findings that were similar between the studies are kayomegaly and hypertrophy of left atrial myocytes. These occurrences were confined to the high dose groups in both studies.

Summaries of the major histopathologic findings are attached.

RECOMMENDATIONS: The highest dosages administered in this study are probably 50 to 100-fold higher than the intended human dosage. At the low dose (still 5 to 10-fold higher than intended for humans), no significant cardiovascular or renal pathology was evident, and no neoplastic findings were evident. Labeling should undoubtedly include warning to those patients with cardiovascular and/or renal impairment. The likelihood of overt carcinogenicity is probably insignificant.

NOTE: The carcinogenicity data for these two studies has not yet been independently evaluated by our Biometrics division. A phone conversation with Dr. Karl Lin has confirmed that the sponsor has submitted the data in the appropriate format and that it was received on or about September 1. Gary Buehler has independently confirmed that this data is currently being reviewed by Biometrics.

William T. Link

William T. Link, Ph.D.
Pharmacologist

cc:
NDA 19-815
HFD-110
HFD-110/CSO
HFD-110/T Link
HFD-345/G James

SUMMARY OF HISTOPATHOLOGY FINDINGS - RAT CARCINOGENICITY STUDY:

TABLE 18 (continued)

FINDINGS	TREATMENT	INCIDENCE OF AETIOLOGY OF DEATH (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 mg kg-1. day-1	Grp 2 1 mg kg-1. day-1	Grp 3 3 mg kg-1. day-1	Grp 4 10 mg kg-1. day-1	Grp 1 0 mg kg-1. day-1	Grp 2 1 mg kg-1. day-1	Grp 3 3 mg kg-1. day-1	Grp 4 10 mg kg-1. day-1
CAUSE OF DEATH:		(42)	(22)	(25)	(48)	(42)	(21)	(25)	(53)
LIVER: HEPATOCELLULAR CARCINOMA(TA) [M]		0	0	0	2	0	0	0	0
LIVER: necrosis		1	0	0	2	0	0	0	0
HEART: pericarditis		0	0	0	0	0	0	1	0
HEART: myocarditis		0	0	0	0	1	0	0	0
HEART: thrombosis		0	0	0	2	0	0	0	0
HEART: hypertrophy with degeneration in atrium		0	0	1	6	0	0	0	2
AORTA: aneurysm		0	0	0	2	0	0	0	4
KIDNEYS: nephropathy		0	0	3	4	1	0	0	0
KIDNEYS: tubular necrosis		1	0	0	0	0	0	0	0
LUNGS: inflammation		1	1	1	2	4	1	0	4
ADRENALS: PHAEOCHROMOCYTOMA(TA) [M]		0	1	0	0	0	0	0	0
BRAIN: GLIOMA [M]		2	2	0	0	1	0	0	0
BRAIN: neoplasia (unspecified)		0	0	0	1	0	0	0	0
BRAIN: necrosis		0	0	0	1	0	0	0	0
SPINAL CORD: demyelination		0	0	0	0	1	0	0	0
SKELETAL MUSCLE: RHABDOMYOSARCOMA(TA) [M]		0	0	0	0	0	0	1	0
PANCREAS: ISLET ADENOCARCINOMA(TA) [M]		0	0	1	0	0	0	0	0
PANCREAS: CARCINOSARCOMA(TA) [M]		0	1	0	0	0	0	0	0
PITUITARY: ADENOCARCINOMA(TA) [M]		1	3	0	1	2	1	3	2
PITUITARY: ADENOMA(TA) [B]		14	8	7	8	29	11	15	28

Figures in brackets represent the number of animals from which this tissue was examined histologically

TABLE 18 (continued)

FINDINGS	TREATMENT	INCIDENCE OF AETIOLOGY OF DEATH (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 mg kg-1. day-1	Grp 2 1 mg kg-1. day-1	Grp 3 3 mg kg-1. day-1	Grp 4 10 mg kg-1. day-1	Grp 1 0 mg kg-1. day-1	Grp 2 1 mg kg-1. day-1	Grp 3 3 mg kg-1. day-1	Grp 4 10 mg kg-1. day-1
CAUSE OF DEATH:		(42)	(22)	(25)	(48)	(42)	(21)	(25)	(53)
SKIN/SUBCUTIS: SQUAMOUS-CELL CARCINOMA(TA) [M]		0	0	1	1	0	0	0	0
SKIN/SUBCUTIS: FIBROSARCOMA(TA) [M]		0	0	1	1	0	1	0	0
SKIN/SUBCUTIS: SARCOMA(TA) [M]		3	0	2	0	0	1	0	0
SKIN/SUBCUTIS: FIBROMA(TA) [B]		0	0	1	0	0	0	0	0
MAMMARY GLANDS: ADENOCARCINOMA(TA) [M]		0	0	0	0	1	0	0	0
MAMMARY GLANDS: FIBROADENOMA(TA) [B]		0	0	0	0	0	2	0	0
URINARY BLADDER: inflammation		2	0	0	0	0	0	0	0
TONGUE: SQUAMOUS-CELL CARCINOMA(TA) [M]		1	0	0	0	0	0	0	0
TRACHEA: possible traumatic damage		0	0	0	0	0	0	1	0
OESOPHAGUS: rupture		2	1	3	3	0	2	1	1
JEJUNUM: ADENOCARCINOMA(TA) [M]		0	0	0	1	0	0	0	0
SCIATIC NERVE: degeneration		0	0	0	1	0	0	0	0
ABDOMEN: SARCOMA(TA) [M]		0	1	0	0	0	0	0	0
LYMPHORETICULAR/HAEMOPOIETIC TISSUE: LYMPHOMA [M]		0	0	0	1	0	1	0	1
LYMPHORETICULAR/HAEMOPOIETIC TISSUE: LYMPHOCYTIC LEUKAEMIA [M]		0	0	0	1	0	0	0	0
LYMPHORETICULAR/HAEMOPOIETIC TISSUE: HISTIOCYTIC SARCOMA(TA) [M]		0	0	0	0	0	0	0	1
Lower jaw misaligned		0	0	0	0	1	0	0	0
Foot/tail lesions		2	1	0	0	0	0	0	0

Figures in brackets represent the number of animals from which this tissue was examined histologically

TABLE 18 (continued)

FINDINGS	TREATMENT	INCIDENCE OF AETIOLOGY OF DEATH (NUMERIC)							
		MALES				FEMALES			
		Grp 1 0 mg kg-1. day-1	Grp 2 1 mg kg-1. day-1	Grp 3 3 mg kg-1. day-1	Grp 4 10 mg kg-1. day-1	Grp 1 0 mg kg-1. day-1	Grp 2 1 mg kg-1. day-1	Grp 3 3 mg kg-1. day-1	Grp 4 10 mg kg-1. day-1
CAUSE OF DEATH:		(42)	(22)	(25)	(48)	(42)	(21)	(25)	(53)
Metastatic calcification		0	0	0	1	0	0	0	0
Accidental		0	0	0	0	0	1	0	3
Unknown		13	3	4	7	1	0	3	7

Figures in brackets represent the number of animals from which this tissue was examined histologically

TABLE 18 (continued)

Mode of Death	Treatment	Statistical Information: Males Grp 1 0 mg kg^{-1}. day^{-1}	Males Grp 2 1 mg kg^{-1}. day^{-1}	Males Grp 3 3 mg kg^{-1}. day^{-1}	Males Grp 4 10 mg kg^{-1}. day^{-1}	Females Grp 1 0 mg kg^{-1}. day^{-1}	Females Grp 2 1 mg kg^{-1}. day^{-1}	Females Grp 3 3 mg kg^{-1}. day^{-1}	Females Grp 4 10 mg kg^{-1}. day^{-1}
Terminal Kill		58	28	25	52	59	29	25	47
Found Dead		22	9	10	30	12	4	7	21
Killed Prematurely		20	13	15	18	29	17	18	32
Total		100	50	50	100	100	50	50	100

TABLE 18 (continued)

TABLE 18 (continued)

Week of Death	Treatment	Statistical Information: Males Grp 1 0 mg kg^{-1}. day^{-1}	Males Grp 2 1 mg kg^{-1}. day^{-1}	Males Grp 3 3 mg kg^{-1}. day^{-1}	Males Grp 4 10 mg kg^{-1}. day^{-1}	Females Grp 1 0 mg kg^{-1}. day^{-1}	Females Grp 2 1 mg kg^{-1}. day^{-1}	Females Grp 3 3 mg kg^{-1}. day^{-1}	Females Grp 4 10 mg kg^{-1}. day^{-1}
1-10		0	0	0	1	1	2	2	10
11-20		0	0	0	2	0	0	0	1
21-30		2	0	0	1	1	1	2	1
31-40		3	1	1	2	0	0	0	0
41-50		2	1	0	3	0	1	1	0
51-60		5	1	2	1	1	0	0	1
61-70		2	0	0	5	5	2	2	2
71-80		7	1	3	7	2	2	3	5
81-90		10	6	8	11	11	4	8	5
91-100		9	10	4	10	15	8	3	16
101-110		60	30	32	57	64	30	29	59
Total		100	50	50	100	100	50	50	100

TABLE 19

TS 701
104 Week Gavage Carcinogenicity Study in Rats
Overall Tumour Incidence

	TUMOUR TABLE			
	MALES		FEMALES	
TREATMENT	Grp 1 0 mg kg-1. day-1	Grp 4 10 mg kg-1. day-1	Grp 1 0 mg kg-1. day-1	Grp 4 10 mg kg-1. day-1
NUMBER OF ANIMALS:	100	100	100	100
NO. OF ANIMALS WITH TUMOURS	82	77	93	81
NO. OF ANIMALS WITH SINGLE TUMOURS	39	28	41	31
NO. OF ANIMALS WITH MULTIPLE TUMOURS	43	49	52	50
NO. OF ANIMALS WITH BENIGN TUMOURS	73	71	89	77
NO. OF ANIMALS WITH MALIGNANT TUMOURS	31	32	20	22
NO. OF ANIMALS WITH METASTASISING TUMOURS		1		2
TOTAL NUMBER OF TUMOURS	150	159	163	160
TOTAL NUMBER OF BENIGN TUMOURS	118	122	139	135
TOTAL NUMBER OF MALIGNANT TUMOURS	32	37	24	25
TOTAL NUMBER OF METASTASISING TUMOURS		1		2
% ANIMALS WITH TUMOURS	82	77	93	81
% ANIMALS WITH SINGLE TUMOUR	39	28	41	31
% ANIMALS WITH MULTIPLE TUMOURS	43	49	52	50
% ANIMALS WITH BENIGN TUMOURS	73	71	89	77
% ANIMALS WITH MALIGNANT TUMOURS	31	32	20	22
% ANIMALS WITH METASTASISING TUMOURS		1		2

Animals with more than one tumour type are recorded as having multiple tumours

SUMMARY OF HISTOPATHOLOGY FINDINGS - MOUSE CARCINOGENICITY STUDY:

Table 16 (continued)

Female

	0	1.7	5.0 mg/kg/day	15.0
number of animals	100	50	50	100
Non-protocol Organs				
FACTORS CONTRIBUTORY TO DEATH				
None identified	3	2	4	5
Malignant lymphoma	8	3	2	4
Amyloidosis	2	0	0	5
Ulcerative dermatitis	1	3	0	2
Mammary gland adenocarcinoma	2	0	0	0
Peritonitis	1	0	0	0
Intrauterine haemorrhage	2	1	1	0
Cystic endometrial hyperplasia	1	0	0	0
Probable dosing accident	1	0	0	1
Haemorrhagic ovarian cyst	2	0	0	1
Mammary gland adenoacanthoma	0	0	0	1
Malignant schwannoma	0	0	0	1
Thrombosis adjacent to pituitary	0	0	0	1
Haemorrhage within ovarian cyst	0	0	1	0
Osteosarcoma	0	0	1	0
Pituitary adenocarcinoma	0	1	1	0
Glomerulonephritis	0	3	0	0
Endometrial stromal polyp	0	1	0	1

Table 16 (continued)

Female

	0	1.7	5.0 mg/kg/day	15.0
number of animals	100	50	50	100
Non-protocol Organs				
PREDOMINANT PATHOLOGY				
Pulmonary adenoma	6	0	0	6
No significant pathology present	4	0	2	4
Pulmonary adenocarcinoma	1	0	0	0
Harderian gland adenoma	1	0	0	1
Malignant lymphoma	13	3	2	7
Hypertrophic gastritis	0	0	0	1
Amyloidosis	5	0	0	15
Ulcerative dermatitis	1	3	0	2
Ovarian follicular cyst	34	1	2	39
Cystic endometrial hyperplasia	13	0	1	9
Fibroma	1	0	0	0
Sarcoma, NOS	2	0	0	2
Basal cell adenoma	1	0	0	0
Endometrial stromal polyp	3	1	0	2
Mammary gland adenocarcinoma	2	0	0	1
Fat necrosis and acute peritonitis	1	0	0	0
Islet cell adenoma	1	0	0	1
Intrauterine haemorrhage	3	1	1	0
Luteoma	3	0	0	0
Fibrous polyp - uterine cervix	1	0	0	0

Table 16 (continued)

Female

	0	1.7	5.0 mg/kg/day	15.0
number of animals	100	50	50	100
Non-protocol Organs				
PREDOMINANT PATHOLOGY				
Fibrosarcoma	1	0	0	0
Focal hyperplasia - pituitary gland	1	0	0	0
Pituitary adenoma	1	0	0	0
Foreign body granuloma - lung	1	0	0	0
Hydrometra	1	0	0	0
Choriocarcinoma	0	0	0	1
Leiomyoma	0	0	0	3
Thymic lymphoid hyperplasia	0	0	0	2
Perioesophageal haemorrhage and fibrosis	0	0	0	1
Ovarian cystadenoma	0	0	0	2
Arteritis	0	0	0	1
Ovarian bursal cyst	0	0	0	1
Transitional cell papilloma	0	0	0	1
Mammary gland adenoacanthoma	0	0	0	1
Malignant schwannoma	0	0	0	2
Cellulitis	0	0	0	1
Endometrial stromal sarcoma	0	1	0	2
Metritis	0	0	0	1

Table 1· Randomized Controlled Clinical Study Characteristics

Investigator	fentanyl (mcg/hr)	— No. of Patients — Recruited	Evaluable	2-tail p-value [1]
McLeskey	50	(28, 26)	(26, 24) [2]	0.05
Caplan	75	(22, 20)	(20, 20)	0.06
Nimmo	75	(23, 23)	(23, 18)	0.03
Plezia	75	(22, 21)	(16, 21)	0.30
Hotchkiss	100	(25, 24)	(22, 21)	0.04
Stanski	100	(23, 23)	(19, 20)	0.60
	Total:	(143,137)	(126,124)	

[1] FDA assigned p-value based on applicant's Wilcoxon Rank Sum Tests up through 30 hours inclusive post-op.

[2] Counts are respectively (fentanyl, placebo)

Table 16 (continued)

Female

	0	1.7	5.0 mg/kg/day	15.0
number of animals	100	50	50	100
Non-protocol Organs				
Fractured femur	0	0	0	1
Osteosarcoma, primary site not identified	0	0	1	0
Pituitary adenocarcinoma	0	1	1	0
Glomerulonephritis	0	3	0	0

Table 16 (continued)

Female

	0	1.7	5.0 mg/kg/day	15.0
number of animals	100	50	50	100
Overall Tumour Incidence				
PRIMARY TUMOURS				
Focal Hyperplasia	6	1	1	2
BENIGN TUMOUR	20	1	0	16
MALIGNANT TUMOUR	19	5	4	16
MULTIPLE PRIMARY TUMOURS				
Focal Hyperplasia	2	0	0	1
BENIGN TUMOUR	6	1	0	6
MALIGNANT TUMOUR	1	0	0	0
MALIGNANT LYMPHOMA				
present	13	3	2	7

Table 16 (continued)

Female

	0	1.7	5.0 mg/kg/day	15.0
number of animals	100	50	50	100
Statistical Information				
Mode of death				
Terminal kill	78	37	40	80
Found dead	8	2	3	0
Killed prematurely	14	11	7	20
Total	100	50	50	100
Killed in study week				
1 - 10	0	0	0	1
21 - 30	3	1	1	1
31 - 40	1	2	1	1
41 - 50	3	1	1	4
51 - 60	4	2	2	5
61 - 70	3	3	3	3
71 - 80	86	41	42	85
Total	100	50	50	100

10 N Document

W.Link

NDA 19-815

JUN 12 1995

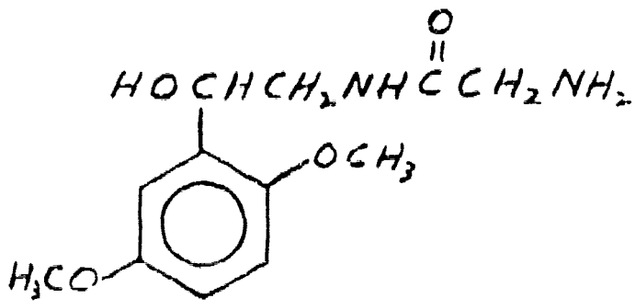
REVIEW/EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

W.T. Link, Ph.D.
May 24, 1995

SPONSOR: Roberts Pharmaceutical Corporation

DRUG: Midodrine (TS 701) (Amatine®)

STRUCTURAL FORMULA AND CHEMICAL NAME:



· HCl

Formula wt. 290.74

2-amino-N-[2-(2,5-dimethoxyphenyl)-2-hydroxyethyl]acetamide hydrochloride

or:
2-amino-N-(2,5-dimethoxy-β-hydoxyphenethyl)acetamide hydrochloride

or:
1-(2', 5'-dimethoxyphenyl)-2-glycinamidoethanol hydrochloride

PHARMACOLOGICAL CLASS: sympathomimetic, peripherally acting α-agonist

PROPOSED INVESTIGATIONAL USE: idiopathic orthostatic hypotension

PRECLINICAL PHARMACOLOGY:

The preclinical pharmacological data submitted in support of this application is extensive. A complete listing and categorizing of this data is beyond the scope of this review, and is already adequately presented in the review dated 22 Jan. 1990 by Claire Lathers. The focus here is to call attention to inconsistencies in the sponsor's interpretation of the basic receptor pharmacology of this agent, and inadequacies of study design including an

absence of validating positive standards and dose-response analyses.

Midodrine is considered a prodrug that is proteolytically cleaved at the glycyl moiety to yield ST 1059, the active metabolite. A dose-dependent pressor effect to i.v. midodrine or ST 1059 was demonstrated in intact rats, cats, dogs and in isolated rat hindlimb preparations, isolated perfused rabbit ears and isolated human veins. The metabolism of midodrine is not apparently achieved through the action of MAO or COMT, as for endogenous catechols, as inhibitors of these enzymes do not enhance the pressor effect.

Several lines of evidence argue against the conclusions drawn by the sponsors. They have interpreted the studies as demonstration of a direct acting (not causing secondary release of norepinephrine from nerve terminals), selective α-agonist which is generated from the prodrug via proteolytic cleavage. To the contrary, their data cannot rule out indirect effects on NE release; it further suggests effects on at least one other catecholamine receptor; and calls into question their hypothesis of a prodrug with only one active metabolite. These concerns are addressed, in detail, below (not in order). Copies of data from the sponsor's submission are attached.

This reviewer's first concern involves the experiments where the protease inhibitor aprotinin (Trasylol®) was used in an attempt to demonstrate that inhibition of proteolysis of midodrine would prevent its conversion to ST 1059 and therefore prevent its pressor effect. Table A (Section 4, pg. 1.3.1/8) shows the response to various treatments in the isolated perfused rat hindlimb. Midodrine (5 mg) in blood/Ringer perfused rats produced a 75.2 mmhg pressor response at 60 min. (Control). Aprotinin (12,500 K.I.U.) decreases this response to 35.6 mmhg, consistent with the hypothesis. However, identical treatment with aprotinin also blunted the response to ST 1059 (the purported active metabolite) in similar, if not greater fashion (66.0 for control vs. 24.16 mmHg). The sponsor acknowledges this discrepancy and attributes the inhibition of both midodrine and ST 1059 "other mechanisms". As can be seen in the same table, these other mechanisms do not block the pressor response to noradrenaline and, therefore suggest a direct interaction between aprotinin and midodrine or ST 1059 which prevents their binding to the α-receptor and which is independent of the receptor itself. Alternatively, this effect could suggest that ST 1059 is not the only active metabolite and that further metabolism by proteolysis of ST 1059 is required for the pressor effects. These possibilities could easily be examined by any number of available methodologies.

Additionally, only single doses of midodrine or ST 1059 were used in these analyses. Dose-response curves for these agents would have been more appropriate, and a dose-dependent shift of these curves might have shed some light on the mechanism of this inhibition. One has to question whether the threshold or maximal response were altered by aprotinin as well.

A second concern of this reviewer relates to the demonstrated enhancement of the pressor response to i.v. midodrine by pretreatment with

propranolol Table A, section 4, pg. 1.1.1/10, copy included). Intact, anesthetized rats were used in these studies. Control pressor responses to 5 mg midodrine i.v. were 48 ± 14 mmHg. The expected physiological response to a pressor substance would be reflex parasympathetic outflow via the vagus nerves, which would decrease heart rate, blunting this pressor response. Atropine would block this reflex and allow a greater pressor response as demonstrated in the table (88 ± 14mmHg, it is not clear why i.v. atropine was ineffective, but the "spinal" administration clearly demonstrates the reflex is present in controls). Intravenous propranolol also enhances the pressor effect to 62 ± 20mmHg, an apparently significant effect, which would not be expected in response to a selective, pure α-agonist. Instead, this effect suggests a role for adrenergic β receptors, namely β_2, in the response. These receptors have a distribution in skeletal muscle where their stimulation results in active vasodilation, and the large mass of this tissue can allow for a large redistribution of blood flow in response to agents that stimulate both α and β_2 receptors. Such a redistribution would blunt the expected pressor response to a purported pure α-agonist which was in reality cross-selective for both receptors. Propranolol would remove the vasodilatory component and allow the full expression of the α receptor effect. Again, the questions arising from this unexpected response can easily be addressed through receptor binding studies.

Alternatively, acute propranolol treatment could have initiated a reflexive vasoconstriction following the fall in cardiac output, which would enhance the effect of sympathomimetic agonists. This could explain the enhanced pressor response to midodrine following propranolol pretreatment. Again, this hypothesis could have easily been tested by demonstration of greater responses to other direct acting agonists such as phenylephrine following propranolol.

Thirdly, the issue of direct vs. indirect mode of action has not been adequately established. Reserpine was evaluated in both the intact rat and the isolated hindlimb preparation and did not decrease the pressor response to midodrine in either model (again using only single doses of midodrine, not dose-response curves). There is, however, reason to question the effectiveness of the reserpine treatment. For reasons of brevity, I would like to refer to Claire Lather's review (pg. 63) regarding the reserpine treatment and its limitations. Additionally, there was no demonstration that the reserpine treatment had depleted endogenous NE stores, which could have easily been performed by tyramine administration.

Similarly, attempts to rule out an indirect mode of action by using cocaine pretreatment were also inconclusive. Table 1.1.1/6 (copy provided) shows the effect of cocaine pretreatment on pressor effects induced by tyramine, midodrine or ST 1059. Cocaine blocks the reuptake of released NE and therefore blocks the action of agents that work via this uptake mechanism

and cause release of NE by displacement. Tyramine works through this uptake mechanism and its effect should be diminished by cocaine treatment. However, the lack of a significant effect on tyramine-induced pressor responses (the positive control) calls the effectiveness of the cocaine treatment into question. Clearly it would be difficult to demonstrate indirect release, under these conditions, by an agent that may work only partially through indirect mechanisms when a significant effect on tyramine-induced responses (entirely indirect) cannot be shown. Demonstration of enhanced responses to NE could also have been demonstrated to validate the effectiveness of the cocaine pretreatment, but were not performed. The small potentiation of ST 1059-induced pressor activity by cocaine is probably not real. Cocaine potentiates the effect of NE by preventing its reuptake, so unless ST 1059 is inactivated through the same uptake mechanism which inactivates NE, potentiation of a purported purely direct-acting agonist by blockade of this uptake mechanism would not be expected.

The question of direct vs. indirect effects for midodrine and ST 1059 is further complicated by the submission of a study in anesthetized dogs (1.1.2.5) where imipramine is administered (0.3 and 3.0 mg/kg i.v.) to modify the pressor response. It is not immediately clear to this reviewer why this study was even done, and what the investigators expected to find. They state "These investigations were carried out to demonstrate or rule out potentiation of the effects of midodrine and ST 1059 by imipramine." apparently because they expected imipramine to potentiate the effects of indirectly released NE if midodrine acted through this mechanism. However, above this statement they cite a reference (Sabelli and Sinay, 1960) stating that imipramine diminishes the effect of indirectly acting sympathomimetic drugs (true, because it is now known that it blocks their uptake). Their data (copies provided) demonstrate decreased pressor responses that are dose dependent on imipramine, and their interpretation is only that there was "no evidence that imipramine potentiated the pressor effects of midodrine or ST 1059". They apparently attribute the inhibition to blockade of α receptors, and cite Schaeppi (1960) in reference. However, their control blood pressure records taken after imipramine, but before midodrine or ST 1059, show imipramine dose dependent increases in pressure which would not be consistent with α blockade.

It is clear to this reviewer that the case cannot be made for claims of direct action, or pure α receptor selectivity based on the studies provided. The claim of one active metabolite generated by proteolytic cleavage is also not very convincing. Conversely, it is clear that midodrine and ST 1059 do act on α receptors and produce a prolonged pressor response which could be clinically beneficial in some cases. There is much evidence accumulated that demonstrate midodrine is relatively safe, and can be tolerated at high doses in experimental animals. Recently performed carcinogenicity studies in rats and

mice do not demonstrate any untoward effects, however our biometrics people have not given their report on this issue. I would recommend that the sponsors perform a receptor binding survey for known receptor subtypes, and do some definitive pharmacological experiments, perhaps using isolated hindquarters preparations which have been calibrated using known direct and indirect acting sympathomimetic agents, or preparations which have been sympathectomized by agents such as 6-hydroxydopamine to address the direct vs. indirect effect issue. I would also recommend that shifts in dose-response curves rather than single doses be used in these analyses.

William T. Link

William T. Link, Ph.D.

HDT 6/25/97

Orig NDA
HFD-110
HFD-110 EBuehler
HFD-110 W LINK
HFD-110 A DeFelice

Table A

Changes of perfusion pressure in the isolated perfused hindbody preparation of the rat after midodrine, ST 1059 and noradrenaline with and without pretreatments

(Mean values, standard deviations, significance data)

Substance dose	Perfusion medium	Pretreatment	n	Change of perfusion pressure in mmHg: Time after admin	$\bar{x} \pm s_x$	Significance (inhibition as % of control value)
Midodrine 1 mg	blood/Ringer	none	11	30 min	9,5 ± 5,95	
5 mg	blood/Ringer	none	15	30 min 60 min	40,33 ± 17,49 75,20 ± 24,66	(100 %) (100 %)
5 mg	blood/Ringer	2 mg/kg Reserpine s.c. 16 h before	11	30 min 60 min	40,36 ± 8,25 67,18 ± 11,12	n.s. n.s.
5 mg	blood/Ringer	Trasylol® add. 6250 K.I.U.	10	30 min 60 min	19,30 ± 7,99 42,50 ± 15,04	(47,8 %) 0,01 (56,5 %) 0,001
5 mg	blood/Ringer	Trasylol® add. 12500 K.I.U.	6	30 min 60 min	14,33 ± 10,85 35,6 ± 8,32	(35,5 %) 0,01 (47,3 %) 0,01
1 mg	Compensan®	none	6	30 min	19,08 ± 13,93	
5 mg	Compensan®	none	5	30 min	87,8 ± 30,97	(100 %)
5 mg	Compensan®	Trasylol®	6	30 min	39,66 ± 20,79	(45,2 %) 0,001
Phentolamine 1 mg, 60 min after midodrine (5 mg)	blood/Ringer	none	11		- 57,18 ± 15,61	
		2 mg/kg reserpine s.c. 15 h before	11		- 52,0 ± 11,61	
ST 1059 0,05 mg	blood/Ringer	none	9		55,89 ± 22,51	(100 %)
		Trasylol® add. 12500 K.I.U.	5		22,0 ± 9,8	(39,4 %) 0,01
ST 1059 0,2 mg	Compensan®	none	6		66,0 ± 28,2	(100 %)
		Trasylol® add. 12500 K.I.U.	6		24,16 ± 7,70	(36,6 %) 0,01
Noradrenaline 0,002 mg	blood/Ringer	none	10		29,50 ± 7,31	
		Trasylol® add. 12500 K.I.U.	8		27,12 ± 10,49	(95,1 %) n.s.
d-Midodrine 5 mg	blood/Ringer	none	5		1,6 ± 3,9	

The experiments with the various types of pretreatment showed that midodrine is a peripherally-acting and direct-acting alpha-sympathomimetic drug (i.e. it does not act by releasing catecholamines) and it is not inactivated either by transferase or by amine oxidase.

T a b l e A

Pressor potency of midodrine (5 mg/kg i.v.) in anaesthetized rats after various types of pretreatment (Mean values, standard deviation, significance)

Pretreatment Dose	n	Rise of blood pressure mm Hg $\bar{x} \pm s_x$	Significance
None	17	48 ± 14	-
Atropine (5 mg/kg i.v.)	9	44 ± 15	0,50
Spinal (5 mg/kg Atropine)	8	88 ± 14	0,001 +
Reserpine(5 mg/kg i.p. 16 h before	8	46 ± 12	0,70
Phentolamine (5 mg/kg i.v.)	6	14 ± 4	0,001 -
Propranolol (5 mg/kg i.v.)	10	62 ± 20	0,05 +
Pyrogallol (25 mg/kg i.v.)	5	50 ± 9	0,80
Iproniazid 100 mg/kg i.p. 16 h before	5	56 ± 15	0,30
Aprotinin 25,000 KIU/kg i.v.	7	29 ±, 6	0,005 -
50,000 KIU/kg i.v.	6	30 ± 5	0,005 -
Midodrine10 mg/kg p.o. 4 days	10	31 ± 6	0,001 -
2x5mg/kg/ day i.m. 4 days	8	33 ± 15	0,025 -
1 % added to feed 3 weeks	8	15 ± 7	0,001 -

n = number of tests; + = enhancement; - = diminution

In addition to the above evidence suggesting that midodrine may block beta receptors only in an *in vitro* preparation, supporting results for this concept were also obtained in the *in vivo* rat preparation. Blockade of beta receptors with propranolol 5 mg/kg, iv, in rats increased the pressor effect of midodrine. The authors never explore what these data suggest. One interpretation could be that midodrine exhibits an action to both block beta receptors and to stimulate alpha receptors and that blockade of the beta receptors by propranolol prior to the administration of midodrine would make available more molecules of midodrine to stimulate the alpha receptors.

As if the data on beta receptor interaction were not confusing enough, the NDA application also contains data to support the fact that midodrine does not block beta receptors. Isoproterenol (0.4 ug/kg, iv) was used in rats to demonstrate a mean systolic and diastolic depressor effect of 36.83 ± 21.75 and 49.25 ± 21.42 mmHg. Because midodrine 1 mg/kg, iv, or ST 1059 25 ug/kg/min, iv for 10 min, failed to alter the effect of isoproterenolol, it was concluded that these entities do not block beta receptors. One could argue that the use of this dose of isoproterenolol produced a maximum depressor effect and that if the experimental design had used lower threshold doses of isoproterenolol, midodrine or ST 1059 would have been able to exert an action on beta receptors. It may be that different doses of midodrine are capable of both stimulating and blocking beta receptors, depending on the dose used.

Reserpine depletes catecholamine stores and thus if a drug normally acts on beta receptors by releasing catecholamines, its action will not occur in a reserpinized animal. The sponsor presents evidence that reserpine pretreatment did not enhance the pressor effects of midodrine and again concludes that midodrine is not acting on beta receptors. If midodrine acts on beta receptors and if removal of the neurotransmitter norepinephrine was accomplished by pretreatment with reserpine, a supersensitive response due to upregulation of the beta receptors would have resulted in an increased pressor response induced by midodrine. In the anesthetized rat studies, reserpine 5 mg/kg was administered ip 16 hr before the administration of midodrine. Because no enhancement of the pressor effect occurred, it was concluded that these data support an alpha pressor effect of midodrine. Several comments are pertinent. First, the investigators did not do plasma and tissue catecholamine assays to verify that the reserpine did indeed deplete the catecholamines. Without this supporting evidence, one must question their conclusion about the action of midodrine. Secondly, studies have shown that the action of reserpine at a dose of 5 mg/kg, ip route requires 24 hours or longer to deplete catecholamines in anesthetized dogs and cats. Indeed, the following doses and treatment times have been utilized in studies using reserpine pretreatment in anesthetized animals: cat at 5 mg/kg, ip 24-30 hr prior (Ciofalo et al, Bri J. Pharmacol Chemotherapy 30:143-154, 1967); cat 5 mg/kg, ip, 20-36 hr prior (Levitt and Roberts Clin Res 19:622-631, 1966; J. Pharmacol Exp Therap. 156:159-165, 1966); cat 5 mg/kg, ip 24 hr prior (Lathers et al, Europ J. Pharmacol. 76:371-379, 1981); dog 10 ug/kg, im daily for 6 days prior, or 2.5 mg/kg, im 24 hr prior (Takagi et al, Am J Cardiol. 15:203-205, 1965); and dog 0.01, 0.1, or 1 mg/kg, iv 24 hr prior (Boyajy and Nash, J Pharmacol Exp Therap, 148:193-201, 1965). The study included in this NDA application only waited 16 hr after reserpine 5 mg/kg, ip to administer midodrine; this may have been an insufficient time period for reserpinazation. Inadequate time to allow reserpine to deplete catecholamine stores would negate the sponsor's conclusion that reserpine did not enhance the pressor effect of midodrine.

Table 1.1.1/6

Effects of tyramine, ST 1059 and midodrine on the blood pressure of rats with and without cocaine pretreatment

Substance	Dose (mg/kg i.v.)	Max. blood pressure rise		P (t-Test)
		without pretreat.	after cocaine (5mg/kg i.v.)	
Tyramine	0,5	+ 36 + 18 + 40 + 33	+ 23 + 12 + 16 + 30 + 36 + 15	
		31,8 ± 9,6	22 ± 9,4	0,10 < P < 0,05
ST 1059	0,1	+ 42 + 48 + 28 + 42 + 46	+ 54 + 47 + 42 + 48 + 66 + 44	
		41,2 ± 7,8	50,2 ± 8,8	0,05 *
Midodrine	5	+ 31 + 46 + 41 + 60 + 49	+ 40 + 24 + 32 + 49 + 62 + 28	
		45,4 ± 10,6	39,2 ± 14,3	0,30

1.1.2.5 Modification by imipramine of the pressor effects of midodrine and ST 1059 in anaesthetized dogs

1. Purpose of the study:

Tricyclic antidepressants modify the pharmacodynamic effects of adrenergic substances in various ways: for example, imipramine enhances the pressor effect of noradrenaline, but imipramine diminishes the effect of indirectly acting sympathomimetic drugs (H. S a b e l l i, I. S i n a y : Arzneim. Forsch. 10, (1960), 935 f.). Imipramine potentiates the effect of noradrenaline by inhibiting the neuronal uptake of noradrenaline (J. A x e l r o d et al., Science 133, (1961), 383 f.). On the other hand methoxamine, which is related chemically to ST 1059, is not a substrate for uptake into nerve endings (U. T r e n d e l e n b u r g et al., J. Pharmacol. exp. Ther. 172, (1970), 91 - 99). Higher doses of imipramine have an alpha-adrenergic blocking effect (U. S c h a e p p i , Helv. physiol. pharmacol. acta 18, (1960), 545 - 562). These investigations were carried out to demonstrate or rule out potentiation of the effects of midodrine and ST 1059 by imipramine.

2. Method:

Male and female dogs (in all 25 beagles weighing from 8 to 12 kg) were anaesthetized with a mixture of urethane (700 mg/kg) and chloralose (70 mg/kg) i.v. Blood pressure in the femoral artery was

measured electromanometrically with a Statham transducer and recorded on a Hellige Multiskriptor. Midodrine (0.9 mg/kg) was injected into the jugular vein, ST 1059 (0.025 mg/kg/min) was infused over 10 minutes into the jugular vein. Two groups each of 8 animals were pretreated with imipramine (Tofranil(R), Geigy) in doses of 0.3 or 3 mg/kg i.v. 15 minutes before administering midodrine or ST 1059.

3. Results:

Detailed results Tab. 1.1.2. and 2(

Imipramine caused a dose-related reduction of the pressor effects of midodrine and ST 1059 in anaesthetized dogs. After midodrine (0.9 mg/kg i.v.) the arterial blood pressure rose by at most 35.7 mmHg whereas the midodrine-induced rise of blood pressure after 0.3 mg/kg of imipramine was only 18.6 mmHg and after 3 mg/kg of imipramine it was only 2.1 mmHg. The rise of blood pressure after intravenous infusion of ST 1059 (0.025 mg/kg/min over 10 minutes) was reduced from 27.8 mmHg (control) to 14.4 mmHg (after 0.3 mg/kg of imipramine) and to 7.9 mmHg (after 3 mg/kg of imipramine). In these tests there was no evidence that imipramine potentiated the pressor effects of midodrine or ST 1059.

Table A

Modification by imipramine of the pressor effect of midodrine in anaesthetized dogs

(Mean values)

	Change of mean pressure in the femoral a. (mm Hg) after 0.9 mg/kg of midodrine i.v. Mean values and standard deviations from 4 - 5 tests in each case.		
Pretreatment	none	Imipramine (0,3 mg/kg i.v.)	Imipramine (3mg/kg i.v.)
Time after midodrine admin.:			
5 min	+ 31,4 ± 16,6	+ 13,8 ± 5,1	- 0,3 ± 1,8
10 min	+ 35,7 ± 18,4	+ 18,6 ± 8,8	- 2,6 ± 2,1
15 min	+ 32,5 ± 10	+ 15,5 ± 7,7	+ 2,1 ± 3,1
20 min	+ 34,5 ± 15,1	+ 15,3 ± 11,2	- 0,1 ± 3,6
30 min	+ 30,1 ± 11,7	+ 13,8 ± 12,4	- 1,25± 3,1
40 min	+ 25,9 ± 14,3	+ 12 ± 11,7	- 0,6 ± 6
50 min	+ 21,4 ± 16,6	+ 12,1 ± 10,8	- 6,1 ± 3,4
60 min	+ 19,3 ± 18,8	+ 12,1 ± 10,7	- 4,5 ± 4,1

Table 8

Modification by imipramine of the pressor effect of ST 1059 in anaesthetized dogs

(Mean values)

	Change of mean pressure in the femoral a. (mm Hg) after ST 1059 (0.025 mg/kg/min for 10 min i.v.) Mean values and standard deviations from 4 tests in each case.		
Pretreatment	none	Imipramine (0,3 mg/kg i.v.)	Imipramine (3 mg/kg i.v.)
Time after starting ST 1059 infusion:			
2 min	+ 7,6 ± 4,1	+ 6 ± 4,4	+ 1,9 ± 1,6
4 min	+ 17,5 ± 5,3	+ 10 ± 8,1	+ 3,25 ± 3,6
6 min	+ 19,1 ± 8,2	+ 13,8 ± 12,8	+ 5,25 ± 5,3
8 min	+ 24,1 ± 7,9	+ 12,4 ± 12,8	+ 7,9 ± 9
10 min (= end of infusion)	+ 25,8 ± 5	+ 14,4 ± 10,5	+ 8,8 ± 11,2
15 min	+ 27,8 ± 3,5	+ 10,9 ± 12,8	+ 4,1 ± 13,4
20 min	+ 19,6 ± 4	+ 5,3 ± 11,5	+ 2,1 ± 15,7
25 min	+ 13 ± 7	+ 4 ± 12,6	+ 1,9 ± 15,7
30 min	+ 10,3 ± 7	+ 2,4 ± 15,8	+ 1,6 ± 16,3

T a b l e 1.1.2/19

Modification by imipramine of the pressor action of midodrine in anaesthetized dogs

(Detailed results)

Pretreatment	none	Imipramine (0,3mg/kg i.v.)	Imipramine (3mg/kg i.v.)
Baseline blood pressure (mean pressure femoral a. (mm Hg))	139,5 147,5 154 150 155	170,5 150,5 195,5 194,5	155,5 180,5 214 188,5
$\bar{x}$ $s_{\bar{x}}$	149,2 6,2	177,8 21,5	184,6 24,2
Midodrine (0,9 mg/kg i.v.)			
Rise of pressure (mm Hg) after 5 min	45,5 46 38,5 12 15	10 20,5 9,5 15	- 1 1,5 - 2,5 1
$\bar{x}$ $s_{\bar{x}}$	31,4 16,6	13,8 5,1	- 0,3 1,8
after 10 min	39 43 61 20 15,5	11 27,5 11 25	0,5 - 4 - 4 - 3
$\bar{x}$ $s_{\bar{x}}$	35,7 18,4	18,6 8,8	- 2,6 2,1
after 15 min	32 43 38,5 32,5 16,5	9,5 25 9 18,5	- 1,5 4,5 0,5 5
$\bar{x}$ $s_{\bar{x}}$	32,5 10	15,5 7,7	2,1 3,1

Continuation of

Table 1.1.2/19

Pretreatment	none	Imipramine (0,3mg/kg i.v.)	Imipramine (3mg/kg i.v.)
after 20 min	29,5 43,5 51 33,5 15	5 25 6 25	0 - 5 3,5 1
$\bar{x}$ $s_{\bar{x}}$	34,5 15,1	15,3 11,2	- 0,1 3,6
after 30 min	31 42,5 39 25 13	10 25,5 - 2 21,5	0,5 - 5 2 - 2,5
$\bar{x}$ $s_{\bar{x}}$	30,1 11,7	13,8 12,4	- 1,25 3,1
after 40 min	30,5 42,5 32,5 19 5	4 21 0 23	1 - 9,5 2 4
$\bar{x}$ $s_{\bar{x}}$	25,9 14,3	12 11,7	- 0,6 6
after 50 min	30,5 34 32,5 15 - 5	6 24 0,5 18	- 1 - 8 - 7 - 8,5
$\bar{x}$ $s_{\bar{x}}$	21,4 16,6	12,1 10,8	- 6,1 3,4
after 60 min	33 37 23,5 13 - 10	10 24 - 1,5 16	0 - - 8 - 5,5
$\bar{x}$ $s_{\bar{x}}$	19,3 18,8	12,1 10,7	- 4,5 4,1

T a b l e 1.1. /20

Modification by imipramine of the pressor action of ST 1059 in anaesthetized dogs

(Detailed results)

Pretreatment	none	Imipramine (0,3mg/kg i.v.)	Imipramine (3mg/kg i.v.)
Baseline blood pressure (mean pressure femoral a. mm Hg))	153 175 162 157	204,5 173,5 175,5 154	111 163,5 177 192,5
$\bar{x}$	164,3	176,9	161
$s_{\bar{x}}$	9,2	20,8	35,4
ST 1059 (Infusion 0,025 mg/kg/min i.v. for 10 minutes			
Rise of pressure (mm Hg)			
after 2 min	4 13,5 6,5 6,5	5 1,5 5,5 12	2 3 - 0,5 2
$\bar{x}$	7,6	6	1,9
$s_{\bar{x}}$	4,1	4,4	1,6
after 4 min	24 11,5 19 15,5	9 - 1 14,5 17,5	8,5 1 2,5 1
$\bar{x}$	17,5	10	3,25
$s_{\bar{x}}$	5,3	8,1	3,6
after 6 min	24 8 26,5 18	14,5 - 4,5 24,5 20,5	11,5 6 5 - 1,5
$\bar{x}$	19,1	13,8	5,25
$s_{\bar{x}}$	8,2	12,8	5,3
after 8 min	32 15,5 29,5 19,5	5,5 - 2 26 20	17,5 13 3,5 - 2,5
$\bar{x}$	24,1	12,4	7,9
$s_{\bar{x}}$	7,9	12,8	9

Continuation of

Table 1.1.2/20

Pretreatment	none	Imipramine (0,3mg/kg i.v.)	Imipramine (3mg/kg i.v.)
after 10 min (= end of infusion)	30	8	19,5
	20	3,5	16
	30	26,5	4,5
	23	19,5	- 5
$\bar{x}$	25,8	14,4	8,8
$s_{\bar{x}}$	5	10,5	11,2
after 15 min	30	11,5	23,5
	22,5	- 7	- 2,5
	29	23	2,5
	29,5	16	- 7
$\bar{x}$	27,8	10,9	4,1
$s_{\bar{x}}$	3,5	12,8	13,4
after 20 min	18,5	10,5	24,5
	15	-11	- 9
	20,5	15,5	1,5
	24,5	6	- 8,5
$\bar{x}$	19,6	5,3	2,1
$s_{\bar{x}}$	4	11,5	15,7
after 25 min	9	10,5	24
	5,5	- 12	- 8,5
	21	17	2
	16,5	0,5	- 10
$\bar{x}$	13	4	1,9
$s_{\bar{x}}$	7	12,6	15,7
after 30 min	12	9,5	24,5
	3	-15,5	- 7
	19	20,5	1,5
	7	- 5	-12,5
$\bar{x}$	10,3	2,4	1,6
$s_{\bar{x}}$	7	15,8	16,3

PHARMACOLOGIST'S REVIEW COVERSHEET

NDA No.: 19-815
SPONSOR: Roberts Laboratories, Inc., Meridian Center III, 6 Industrial Way West, Eatontown, NJ 07724
DRUG: Amatine® Tablets; Midodrine Hydrochloride Tablets
CATEGORY: Alpha Receptor Sympathomimetic Agonist
EVALUATION: See pages 79 and 80

- The submission generally consistent with Agency's Format Guideline: Yes: (X) No: ( )

- Appropriate studies submitted: Yes: (X) No: ( )

- Primary adverse pharmacological effect:

  Humans: dizziness; lightheadedness; syncope; supine hypertension; piloerection; nausea/vomiting

  Animals: piloerection; vomiting; mild midriasis; moderate bradycardia

- Target organs in toxicity studies:

  Heart: Rat: changes characteristic of those produced by sympathomimetic agents (myocardial necroses; focal degenerations of myocardial fibers)
  Liver: Rat and Dog: (Female rats) - fatty degeneration in periphery of lobes, decrease glycogen content, accumulation of lipids; (male rats) - cellular enlargement without fatty accumulation; cells rich in glycogen; dog: small numbers of enlarged cells with subanophil inclusions
  Kidney: Rat: Some histological changes; dog: increased weight
  Spleen: Rat: Necroses in form of increased erythrocytolysis. Dog: Decreased weight

- Reproductive or developmental toxicity: Yes: (X) No: ( )

  If yes, explain briefly:
  Midodrine given to pregnant rats and rabbits. See Tables 8 and 9 on pages 43 and 44 and discussion on pg 54 and 71 of this report.

- Carcinogenicity studies: Orphan drug - Not done: see discussion page 74, 75 and 79 of this report.

  Number of studies: Rat: ( ) Mouse: ( ) Other: ( )
  Results: +, -, ± ( ) ( ) ( )

  Site of tumors:

- Sub-chronic/Chronic blood level studies:

  Rat: (X) Dog: (X) Other: ( )

- GLP Problems Yes: ( ) No: ( )

  Most of the preclinical studies were conducted between 1/70 and 7/78 and thus it was not possible for the sponsor to state that GLP Compliance, as established on 6/20/79, was followed. Newer studies did follow GLP. See discussion on p. 3 of this report.

- OTHER COMMENTS:

NDA #19-815

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

Claire M. Lathers, Ph.D.
1/22/90

ORIGINAL NDA DATED: 4/26/88
CENTER RECEIPT DATE: 4/28/88
REVIEWER RECEIPT DATE: 4/24/89

SPONSOR: Roberts Laboratories, Inc.
Meridian Center III
6 Industrial Way West
Eatontown, New Jersey 07724

DRUG:

Proprietary Name United States: Amatine® Tablets

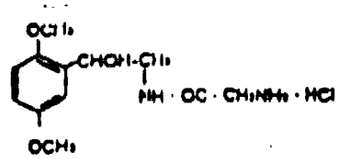
Foreign Market Name: Gutron® except for Argentina where it is called Hipertan®

Nonproprietary Name: Midodrine Hydrochloride Tablets

Code Name: ST 1085 hydrochloride

Chemical Name: d,l-alpha-(2,5-dimethoxyphenyl)-beta-glycinamidoethanol hydrochloride

STRUCTURAL FORMULA:



Molecular Weight: 290.74 $C_{12}H_{19}ClN_2O_4$

FORMULATION: Compressed tablets of 2.5 and 5.0 mg strength for oral administration.

Composition per Tablet	2 mg Tablet	5 mg Tablet
Midodrine Hydrochloride	2.50 mg	5.00 mg
Colloidal Silicon Dioxide NF		
Microcrystalline cellulose NF		
Corn Starch NF		
Talc USP		
Magnesium Stearate NF		
FD&C Yellow No. 6		

Drug product is manufactured by:

PHARMACOLOGICAL CLASS: alpha receptor sympathomimetic agonist

PROPOSED INDICATION: idiopathic orthostatic hypotension

PROPOSED DOSAGE REGIMEN: Starting recommended dose is 2.5 mg three times/day. After several days, if response is inadequate and no limiting side effects appear, a gradual escalation in increments of 2.5 mg tid at approximately weekly intervals until optimal clinical response is achieved. The maximum recommended dose is 40 mg/day.

IND'S UNDER WHICH CLINICAL TRIALS WERE CONDUCTED:

Document Number	Document Holder

INTRODUCTION: Amatine® (midodrine HCl) is a drug developed by Sponsorship of IND was transferred to Roberts Laboratories, Inc., from The latter had filed IND Amatine® is a pressor sympathomimetic agent (stimulates peripheral alpha receptors) designated by the FDA as an orphan drug product for the treatment of idiopathic orthostatic hypotension. Midodrine is a prodrug that is not metabolised by monoamine oxidase or by catechol-O-methyl transferase. It is subject to protease activity, with cleavage of a glycyl moiety to yield ST 1059, the active agent. This cleavage

occurs rapidly and completely, so that in rats only 5.7% of the urinary radioactivity derived from the tritiated midodrine was in the form of unchanged drug. The plasma half-life of ST 1059 was 1.75 and 2.5 hours in rats and dogs, respectively. Pharmacodynamic action required levels of 0.2 nmole/ml or greater in the plasma in dogs. Midodrine is marketed outside the USA under the trademark of Gutron (2.5 and 5.0 mg tablets) in 21 countries (see Table 1 this report; from Vol. 2, section 2, p. 19, 20 original NDA application) and as Hipertan in Argentina. It is also marketed in many countries in ampuls containing 5 mg/2 ml, and as 1% drops. will manufacture the bulk and finished products and perform all testing, packaging, and labeling.

Most of the preclinical studies were conducted between 1/70 and 7/78 and thus it was not possible for the sponsor to state that Good Laboratory Practice Compliance, as established on June 20, 1979, was followed. The results of the study designed to assess the effects of midodrine and metabolite ST 1059 on the rat uterus in situ, conducted by , were summarized in Report on May 1984. This report does not indicate whether the study was conducted in accordance with the Good Laboratory Practice Guidelines. Assessment of the mutagenic potential of midodrine by the back mutation test (Report) and by the micronucleus test in mice (Report) was done by

was conducted in accordance with the Good Laboratory Practice Guidelines.

Relevant clinical and nonclinical studies of midodrine have been summarized in the following tables of this report.

Table 2 Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Primary & Secondary Action

Table 3 Summary and Tabulation of Preclinical Pharmacokinetic Studies

Table 4 Summary Tabulation of Human Pharmacokinetic and Bioavailability Studies Conducted and Associated Side Effects

Table 5 Results of Acute Toxicity Studies: LD_{50}

Table 6 Subchronic/Chronic Toxicology

Table 7 Mutagenicity Studies

Table 8 Studies on Effect of ST 1085 HCl on Pregnant Rat and Fetus with Oral Application

Table 9 Studies on Effect of ST 1085 HCl on Pregnant Rabbit and Fetus with Oral Application

Table 1-1

FOREIGN MARKETING HISTORY

Midodrine is marketed outside the USA under the trademark of Gutron in the following countries and dosage forms.

GUTRON Tablets 2.5 mg

COUNTRY	REGISTRATION #	REGISTRATION DATE
Austria	15.447	2/27/74
West Germany	10792	7/15/77
Mexico	88709 S.S.A.	8/23/76
Thailand	1/2522	1979
Afghanistan		1976
Pakistan	004154	6/18/78
Hong Kong	HK-09540	9/14/79
Czechoslovakia	84/190/74-C	12/8/78
Portugal	4646	
Italy	24519	12/7/81
Luxembourg	501/80/07/0409	7/28/80
Taiwan	07377	1980
Greece	A6A/4169/11132	1981
Peru	N-13659	12/18/81
Korea	15994	1/16/82
Saudi Arabia	17/62/82 a 20	8/1/82
	18/62/82 a 50	8/1/82
Uruguay	25642	3/15/82
Poland		
Korea		6/23/86
Dubai (U.A.E.)	R/228/6034	

GUTRON Tablets 5.0 mg

COUNTRY	REGISTRATION #	REGISTRATION DATE
Austria	15.434	2/6/74
Mexico	88709 S.S.A.	8/23/76
Uruguay	23702	10/25/76
Venezuela	E.F. 19.216	9/8/76
Czechoslovakia	84/190/74-C	12/8/78
Argentina*	35.349	6/19/78

*In Argentina midodrine is marketed under the trade name HIPERTAN.

From NDA #19-815 2:2:19

Table 1-2

GUTRON Ampoules 5 mg/2 ml

COUNTRY	REGISTRATION #	REGISTRATION DATE
Austria	15.435	2/6/74
West Germany	10791	7/15/77
Mexico	88440 S.S.A.	9/10/76
Afghanistan		1976
Argentina	35.349	6/19/78
Czechoslovakia	84/189/74-C	12/8/78
Portugal	4648	
Italy	24519	12/7/81
Luxembourg	501/80/07/0410	7/28/80
Greece	A6A/4169/11132	1981
Taiwan	07378	1980
Saudi Arabia	19/62/82	8/1/82
Poland		
Rumania		
Dubai (U.A.E.)	R/228/6035	

GUTRON Drops 1%

COUNTRY	REGISTRATION #	REGISTRATION DATE
Austria	15.448	2/28/74
West Germany	10793	7/15/77
Mexico	88671 S.S.A.	8/23/76
Thailand		1975
Uruguay	23713	10/25/76
Afghanistan		1976
Egypt*	13720	1980
Venezuela	E.F. 19.882	2/6/78
Czechoslovakia	84/188/74-C	12/8/76
Portugal	4647	
Hong Kong	HK-09539	9/14/79
Italy	24519 0.25%	12/7/81
Luxembourg	501/08/07/0411	7/28/80
Argentina**	35.349	6/19/78
Greece	A6A/4169/11132	1981
Peru	N-13658	12/18/81
Poland		
Dubai (U.A.E.)	R/228/6037	

*Marketed in Egypt under trade name Midodrine
**Marketed in Argentina Hipertan

From NDA #19-815 2:2:20

Table 2-1
NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Primary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose (mg/kg) and Route	Drug	Results
PHARMACODYNAMIC EFFECTS RELATING TO PROPOSED INDICATIONS: PRESSOR EFFECT: Report #058-01; p. 1.			
URETHANE ANESTHETIZED RATS			
Table 1.1.1 - 3:4:29			
8, 8, 8, 17, 7	0.075, 0.3, 1.25, 5, 10, iv	Midodrine	Dose related increase in blood pressure 14-62 mmHg.
5	0.5, iv	l-Midodrine	Pressor effect of 20 mmHg.
8, 5	5, 50, iv	d-Midodrine	Pressor effect of 22 and 12 mmHg; l-isomer more potent than d.
17, 16	0.04, 0.10, iv	ST 1059	Pressor effect of 26 and 31 mmHg; this metabolite more potent than parent prodrug.
8	0.1, iv	Methoxamine	Pressor effect 36 mmHg.
10, 6	0.025, 0.05, iv	Norphenylephrine	Pressor effect of 24 and 36 mmHg.
8, 8	0.10, 0.20, iv	Etilefrine	Pressor effect of 30 and 30 mmHg.
50	0.002, iv	Norepinephrine	Pressor effect of 27 mmHg; pressor effect of these agonists similar to that of midodrine.
Table 1.1.2 - 3:4:31			
8, 17, 7	1.25, 5, 10, iv	Midodrine	Dose related increases in blood pressure; time to max value 8, 16.8, 21.8 min; time to 50% fall 37, 81, 127, respectively.
Table 1.1.3 - 3:4:32: 058-01, p. 14;			
9, 4	5, 10, iv	Midodrine	Did not modify pressor effect of iv NE, 0.002 mg/kg, and iv tyramine, 0.2 mg/kg; concluded alpha-agonist action is direct rather than via enhancement of availability of intrinsic biogenic amines or by elevation of receptor sensitivity.
Table 1.1.4 - 3:4:33			
4, 6	5, iv 0.5, iv	Cocaine Tyramine	Pressor effect of tyramine (0.5 mg/kg, iv) decreased from 31.8 ± 9.6 to 22 ± 9.4 mmHg after cocaine 5 mg/kg, iv.
5, 6	0.1, iv	ST 1059	Cocaine 5 mg/kg, iv, sig. increased pressor effect (41.2 ± 7.8 to 50.2 ± 8.8 mmHg); sponsor cannot explain why this action is different from prodrug.
5, 6	5, iv	Midodrine	With or without cocaine (5 mg/kg, iv) same pressor effect (45.4 ± 10.6 vs 39.2 ± 14.3 mmHg increase) cocaine blocks reuptake NE into presynaptic neuron and should not affect a directly acting amine.
Table 1.1.5 - 3:3:34			
1, 6	10, 25, im	Midodrine	Pressor effect of 0 and 22 ± 14 mmHg.
2, 4	25, 50, sc	Midodrine	Pressor effect 0 and 31 ± 22 mmHg.

Tab.. ..-2
NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Primary Action

XPERIMENT [reference] ample Size er Dose	Dose (mg/kg) and Route	Drug	Results
3	5, ip	Midodrine	Pressor effect of 40 ± 14 mmHg.
1, 15, 6, 11	2.5, 5, 10, 20, id	Midodrine	Dose-related pressor effect of 6-26 mmHg.
3, 7	2, 5, id	ST 1059	Pressor effect of 7 ± 5 and 23 ± 9 mmHg; dose ratio of id and iv less than 8:1.
3	5, id	Methoxamine	Pressor effect 17 ± 9 mmHg.
7, 4	10, 40, id	Norphenylephrine	Pressor effect of 8 ± 4 and 36 ± 22 mmHg.
3	50 id	Etilefrine	Pressor effect 12 ± 7 mmHg.
Table 1.1.6 - 3:4:35: Report 058-01			
17	5, iv	Midodrine	Pressor effect 48 ± 14 mmHg.
3	5, iv	Midodrine	Pressor effect (44 ± 15 mmHg) not enhanced by Atropine, 5 mg/kg, iv.
3	5, iv	Midodrine	Atropine, 5 mg/kg, iv & spinal increased pressor effect from 48 ± 14 to 88 ± 14 mmHg. Sponsor concludes evidence of a purely peripheral action site.
3	5, iv	Midodrine	No enhancement of pressor effect (46 ± 12 mmHg) with Reserpine, 5 mg/kg, ip 16 hr before; supports direct peripheral action for midodrine.
6	5, iv	Midodrine	Phentolamine, 5 mg/kg, iv, decreased pressor effect from 48 ± 14 to 14 ± 4 mmHg; supports alpha pressor effect of midodrine.
10	5, iv	Midodrine	Propranolol, 5 mg/kg, iv, enhanced pressor effect of midodrine from 48 ± 14 to 62 ± 20 mmHg; sponsor does not explain this action.
5	5, iv	Midodrine	Pyrogallol, 25 mg/kg, iv. Inhibits COMT; no change pressor effect midodrine (50 ± 15 mmHg); concluded no role for COMT in metabolizing midodrine.
5	5, iv	Midodrine	Iproniazid, 100 mg/kg, ip 16 h before. Inhibits MAO; did not change pressor effect of midodrine (56 ± 15 mmHg); conclude no role for MAO in metabolizing midodrine.
7, 6	5, iv	Midodrine	Aprotinin, 25,000 and 50,000 KIU/kg, iv, decreased pressor effect from 48 ± 14 to 29 ± 6 and 30 ± 5 mmHg, respectively; conclude active metabolite is produced by a proteolytic process.
10	10 mg/day, po for 4 days	Midodrine	Pressor effect of only one dose of midodrine (5 mg/kg, iv) was 48 ± 14 mmHg; pretreatment with midodrine 10 mg/day, po for 4 days sig. decreased the pressor effect to 31 ± 6 mmHg.
8	2 x 5 mg/kg/day, im	Midodrine	Pressor effect of only one dose of midodrine (5 mg/kg, iv) was 48 ± 14 mmHg; pretreatment with midodrine 2 x 5 mg/kg/day, im, sig. decreased the pressor effect to 33 ± 15 mmHg.
8	1% added to feed 3 wks, po	Midodrine	Pressor effect of only one dose of midodrine (5 mg/kg, iv) was 48 ± 14 mmHg; pretreatment with midodrine 1% added to feed 3 wks, po, sig. decreased the pressor effect to 15 ± 7 mmHg.
			Above reductions in pressor effect after multiple dosing with midodrine due to tachyphylaxis.

T. 2-3

NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.

Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Primary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose (mg/kg) and Route	Drug	Results
URETHANE/CHLORALOSE ANESTHETIZED DOGS: Report #058-01, 50 and 058-02; April 1978;			
Table 1.1.7 - 3:4:36 4 to 5 (25 in all)	0.9, iv	Midodrine	Pressor effect 31.4 ± 16.6 mmHg observed 5 min after administration; 5-30 min: same level; 40 min: 25.9 ± 14.3 mmHg; 50 and 60 min: 21.4 ± 16.6 and 19.3 ± 18.8 mmHg.
	0.9, iv	Midodrine	Imipramine, 0.3 or 3 mg/kg, iv, 15 min prior midodrine, caused dose-related reduction in pressor effect of midodrine (31 to 12.1 ± 10.7 mmHg and -4.5 ± 4.1 mmHg at 60 min, respectively); midodrine max pressor effect of 35.7 mmHg decreased to 18.6 ± 6.8 and 2.1 ± 3.1 mmHg 10 and 15 min after 0.3 and 3 mg/kg imipramine, respectively; since no potentiation, action of midodrine not mediated through release of endogenous neuronal catecholamines.
Table 1.1.8 - 3:4:37 4	0.025/min, iv for 10 min	ST 1059	4 to 6 min pressor effect was 17.5 ± 5.3 and 19.1 ± 8.2 mmHg; 8, 10, 15 min was 24.1 ± 7.9, 25.8 ± 5, 27.8 ± 3.5 mmHg; 25 and 30 min was 13 ± 7 and 10.3 ± 7 mmHg.
	0.025/min, iv for 10 min	ST 1059	Imipramine, 0.3 or 3 mg/kg, iv. Low dose 8 min pressor effect was less, only 12.4 ± 12.8 mmHg; all subsequent values lower; 3 mg/kg less pressor effect min 2 through exp. end; max pressor effect ST 1059 was 27.8 ± 3.5 mmHg 15 min and decreased to 14.4 ± 10.5 min 10 and 7.9 ± 9 mmHg 8 min after 0.3 and 3 mg/kg imipramine, respectively; since no potentiation occurred, action of midodrine (ST 1059) not mediated through release of endogenous neuronal catecholamines; sponsor does not explain why pressor effect was decreased.
URETHANE/CHLORALOSE ANESTHETIZED CATS: Report #058-01, p. 79, 84, 89;			
Table 1.1.9 - 3:4:38 9 10	1, iv 0.1, iv	Midodrine ST 1059	Isoproterenol, 0.4 ug/kg, iv, given before and 5, 15, 30 min after midodrine (n = 4 cats, respectively): Isoproterenol increased dP/dt carotid artery, heart rate, and femoral blood flow and reduced systolic and diastolic pressures; unaltered by midodrine or ST 1059.
Table 1.1.10 - 3:4:39 8	0.4 ug/kg iv	ST 1059	Isoproterenol, 0.4 ug/kg, iv, increased femoral blood flow sig. after ST 1059 although sponsors do not comment on this; they merely state that ST 1059 did not inhibit action of isoproterenol.
Table 1.1.12 - 3:4:41 9 10	0.1, iv and intravertebral	ST 1059	Mean systolic and diastolic increased 62.2 and 45.7 mmHg while mean heart rate decreased -22.2 bpm after ST 1059 administered into carotid artery; magnitude of pressor effects sig. less after intravertebral admin (22.6 and 16.2 mmHg, respectively); sig. decrease in heart rate also less (-13.4 bpm). Do not indicate at which time values collected after admin of ST 1059.
Table 1.1.13 - 3:4:42 9 10	1, iv and intravertebral	Midodrine	IV route increased mean systolic and diastolic and decreased heart rate; intravertebral route attenuated these effects; sponsor concludes involvement of CNS in activity of midodrine discounted by these data.

T. 2-4

NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Primary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose and Route	Drug	Results
ISOLATED RABBIT AORTIC STRIPS: Report #058-01, p. 124;			
3:4:6 Not Stated	10 ug 1 ug in vitro	Midodrine ST 1059	Both differed from NE in producing a contraction only after a latent period; higher the dose, the shorter the latent period; after washout, returned to baseline much more slowly than NE.
			10 ug Midodrine approx. equivalent to 0.094 ug NE. 1 ug ST 1059 approx. equivalent to 0.142 ug NE.
ISOLATED PERFUSED RABBIT EAR: Report #058-01, p. 126;			
3:4:6 10	1 ug via perfusate inj into posterior auricular artery	ST 1059	Equiv. to 0.112 NE in reducing flow but effect was more sustained.
		Midodrine	Ineffective in single inj. up to 300x dose of NE.
2	0.6 and 10 ug/min infusion rates (0.1 to 2 ml/min) perfusate	Midodrine	Latent period of minutes, caused reduction of flow.
12 8	10 ug 0.312 ug/min in perfusate	Midodrine ST 1059	10 ug Midodrine equiv. to 0.096 ug NE or 0.312 ug ST 1059.
			Response increased even after end of infusion; lasted avg. >80 min; high doses effect took longer to disappear (up to 6 hr some trials).
10	Between 0.03 and 0.15 ug/min in perfusate	ST 1059	Exhibited 1/3 potency NE; effect ST 1059 gone within 20 min.
16	.02 to 0.1 ug/min perfusate	NE	After infusion NE effect gone within 8 min.
ISOLATED RAT HIND LIMB: Report #058-01, p. 130;			
Table 1.1.14 - 3:4:45*			
	Perfusion medium: blood/Ringer		Pressure Effect min / mm/Hg
11	3.33-5 mg/kg*	Midodrine	30 / 9.5
15	15-25 mg/kg*		30 / 40.33
11	15-25 mg/kg*		60 / 75.2
11	15-25 mg/kg*	Midodrine	Reserpine, 2 mg/kg, sc 16 h before. No different from 5 mg midodrine.

*Weights of rats not given; doses in mg/kg or ug/kg estimated using rat weights of 200-300 gm since other studies used rats in these weight ranges.

Table 2-5
NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Primary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose and Route	Drug	Results
10	15-25 mg/kg* Perfusion medium: Comprensan (PVP; polyvinyl-pyrrolidine blood substitute)	Midodrine	Aprotinin (Trasylol) blocked pressor effects of midodrine.
6, 5, 6	3.33-5; 15-25; 15-25 mg/kg* in perfusate	Midodrine	Midodrine induced a 19 and 87.8 mmHg increase in perfusion pressure; aprotonin blocked effects of midodrine
11	15-25 mg/kg*, in perfusate	Midodrine	Phentolamine, 1 mg/kg, iv 60 min after midodrine alone and with Reserpine, 2 mg/kg, sc 5 hr before midodrine prevented the pressor effect of midodrine
9	Perfusion medium: Blood ringer 0.167-0.25 mg/kg*	ST 1059	Pressor effect 55.89 mmHg.
5	0.167-0.25 mg/kg*, in perfusate	ST 1059	Aprotinin reduced the pressor effect induced by ST 1059 by 22 mmHg.
6	0.665-1 mg/kg*, in perfusate	ST 1059	Perfusion: Compensan Pressor effect 66 mmHg.
6	0.665-1 mg/kg, in perfusate	ST 1059	Aprotinin reduced the pressor effect induced by ST 1059 by 24 mmHg.
10	.0067-.0145 ug/kg, in perfusate	NE	Pressor effect 28.5 ± 7.31 mmHg.
8	.0067-.0145 ug/kg, in perfusate	NE	Aprotinin did not alter pressor effect of NE (27.12 ± 10.49 mmHg). NS.
5	15-25 mg/kg, in perfusate	d-Midodrine	Pressor effect 1.6 ± 3.9 mmHg.

ISOLATED HUMAN VEINS 5:4:129: Report #058-13:

30	Preparations of saphenous vein obtained during surgery for varicose veins. Krebs Ringer					
	Threshold (M)		EDSO (M)	Max Response (unit not legible)	T1/2 of EDSO-conc (S)	
3	$0.2 \pm 1.8 \times 10^{-5}$	Midodrine	$0.5 \pm 1.4 \times 10^{-3}$	0.9	700	ST 1059 elicited
8	$7.1 \pm 5.6 \times 10^{-7}$	ST 1059	$3.3 \pm 3.2 \times 10^{-5}$	11.3	65	vasocontriction
25	$1.1 \pm 1.6 \times 10^{-8}$	NE	$4.6 \pm 1.8 \times 10^{-7}$	13.6	48	that was 80% of
9	$2.2 \pm 1.8 \times 10^{-6}$	Etilefrine	$2.3 \pm 1.1 \times 10^{-4}$	9.9	247	NE-induced con-
8	$1.0 \pm 5.1 \times 10^{-8}$	Dihydroergotamine	$4.7 \pm 3.6 \times 10^{-7}$	3.4	220	traction of veins.

*Weights of rats not given; doses in mg/kg or ug/kg estimated using rat weights of 200-300 gm since other studies used rats in these weight ranges.

2-6

NDA 19-815; AMATINE® (Midodri[illegible]olets, Roberts Laboratories, Inc.
Summary Tabulation of Results of Preclinical Pharmacology St[illegible]es of Midodrine [illegible]r Active Metabolite ST 1059: Secondary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose (mg/kg) and Route	Drug	Results
SECONDARY ACTIONS:			
ACTIVITY IN SPONTANEOUSLY BEATING GUINEA PIG ATRIA: Table 1.1.11 - 3:4:40: Report #058-01, p. 154;			
8	10^{-5}M, 3.10^{-3}M, 10^{-4}M	Midodrine	Both Midodrine and ST 1059 displaced to the right the concentration-response curve for isoproterenol (iso); midodrine exhibited only slight beta receptor blocking action (lower pA_2) and antagonism for iso; not simply competitive.
	10^{-5}M, 3.10^{-5}M, 10^{-4}M	ST 1059	ST 1059 pA_2 comparable to methoxamine and was simple competitive antagonism;
	in vitro		sponsor notes that data do not agree with cat data in which neither midodrine or ST 1059 attenuated iso-induced increases in heart rate and femoral blood flow.
ACTIVITY IN RIGHT VENTRICLE STRIPS OF RATS 3:4:7: Report #058-01, p. 37;			
2-3 mm strips	800-3200 mg/ml Oxymix bathing solution	Midodrine	800 or 1600 mg/ml - reduced force of contraction to 77% of baseline; 3200 mg/ml reduced force of contraction to 60% of baseline.
		ST 1059	Exerted no consistent effect.
ACTIVITY IN ISOLATED ELECTRICALLY-STIMULATED GUINEA PIG ATRIA 3:4:7, 47-49: Report #058-01, p. 140;			
12	10^{-8}; $3x10^{-8}$-$3x10^{-3}$M	Midodrine	Left atrium: continuous reduction of both the force (P) and rate of rise of contraction (dP/dt); sig at $3x10^{-5}$M and above; Rt atrium: only $3x10^{-3}$M sig decreased rate of contraction.
12	10^{-8}; $3x10^{-8}$-$3x10^{-3}$M	ST 1059	Left atrium: sig. reduced rate of contraction at $3x10^{-5}$M and above; sig reduction rate of increase of force at $3x10^{-4}$M and above: Rt atrium: only $3x10^{-4}$M and 10^{-3}M sig decreased
	Tyrode bathing solution		rate of contraction.
ACTIVITY IN GUINEA PIG HEART LUNG PREPARATION 3:4:8, 50			
2, 4	1, 10 mg bathing medium	Midodrine	Only 10 mg caused sig reduction of cardiac output and heart rate.
4	0.5 mg perfusion fluid	ST 1059	Slight but NS reduction of cardiac output and in heart rate.
ACTIVITY IN RABBIT LANGENDORFF HEART PREPARATION 3:4:8, 51: Report #058-01, p. 147;			
6	0.1 mg	Midodrine	Midodrine and ST 1059 sig increased inotropic and chronotropic activity; only midodrine sig increased coronary flow.
4	perfusion fluid	ST 1059	
5	0.1 ug perfusion fluid	NE	NE increased inotropic, chronotropic, and coronary flow at doses 1000 times less than midodrine.
EFFECTS ON CARDIAC CONTRACTILITY IN URETHANE/CHLORALOSE ANESTHETIZED DOG 3:4:8, 52, 53			
not given	0.6 mg/kg, iv	Midodrine	Contractile force (dP/dt) sig decreased 60 min after drug; no change in heart rate; left ventricular end diastolic pressure increased sig 15-60 min; mean flow in femoral artery decreased 60 min.
	25 ug/kg/min, iv	ST 1059	Neither heart rate nor dP/dt sig altered 10 min after drug; left ventricular systolic and end diastolic pressures and mean femoral arterial pressure elevated at end of the infusion; only LVEDP sig increased 20 min after infusion stopped.

1. 2-7

NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Secondary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose (mg/kg) and Route	Drug	Results
EFFECTS ON ECG OF CONSCIOUS STANDING DOG 3:4:8, 9: Report #058-01, p. 45;			
5	0.3 mg/kg, iv	Midodrine	Heart rate initially rose 81 to 89 bpm and then started to fall slowly; 50 and 90 min later was sig decreased; PQ and QT intervals sig prolonged 60 min
not given	1 mg/kg, po	Midodrine	Heart rate fell gradually and was sig decreased 120 min (79 to 54 bpm); PQ and QT intervals sig prolonged 120 min.
EFFECTS ON PULMONARY CIRCULATION IN CHLORALOSE/MORPHINE ANESTHETIZED DOG 3:4:9, 54-56: Report #058-01, p. 37 and #058-06, June 1974,			
5,5	0.4, 1 mg/kg, iv	Midodrine	Midodrine and ST 1059 did not alter pulmonary blood pressure or pulmonary vascular resistance; 1 mg/kg mododrine and ST 1059 elevated pulmonary blood flow; mean femoral arterial pressure,
4	25 ug/kg/min, iv	ST 1059	femoral peripheral vascular resistance were increased; heart rate and cardiac output were decreased.
4	0.4 mg/kg, iv	Midodrine	After bilateral vagotomy, 25 ug/kg/min, iv midodrine increased pulmonary arterial blood pressure; performance both ventricles increased; concluded vagal reflexes involved in protection of pulmonary circulation. Hemodyn effects Midodrine closely resembled methoxamine.
EFFECT ON GASTROINTESTINAL TRACT			
a. Intestinal Motility of Concious Mice 3:4:9, 57: Report #058-01, p. 176;			
10/dose/route	1, 4, 16 mg/kg, iv	Midodrine	Neither agent sig affected the transport of a charcoal suspension.
	3, 12, 24 mg/kg, po	Midodrine	
	1, 4 mg/kg, iv	ST 1059	
	3, 12, 24 mg/kg, po	ST 1059	
b. Intestinal Motility of Anesthetized Cats 3:4:9: Report 058-01, p. 180,			
not given	1 mg/kg, iv	Midodrine	Midodrine exhibited no effect on tone of ileum or on intestinal motility. Both ST 1059 and NE
	10 ug/kg, iv	ST 1059	reduced intestinal tone and peristalsis ceased briefly.
	2 ug/kg, iv	NE	
c. Effects on Isolated Ileum of Guinea Pig 3:4:10: Report 058-01, p. 181;			
not given	1-160 mg/ml bath solution	Midodrine	Neither 1 mg/ml of midodrine or ST 1059 had any effect and did not modify contractions induced by acetylcholine, histamine, or barium. ST 1059 80 mg/ml attenuated reflex contractions evoked by
	1-80 mg/ml	ST 1059	raised internal pressure of ileum sections; conc greater 160 mg/ml midodrine and 80 mg/ml ST 1059 reflex completely blocked; midodrine only inhibited intestinal motility at conc far above those reached in vivo, thus little likelihood of GI side effects from midodrine.

NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.

Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Secondary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose (mg/kg) and Route	Drug	Results
EFFECTS ON LIVER FUNCTION IN URETHANE ANESTHETIZED RATS 3:4:10, 59, 60: Report #058-01, p. 191;			
10, 8	2.5,5 mg/kg, iv	Midodrine	Midodrine and ST 1059 did not modify bromethalein (BSP) dye elimination when given 5 min before dye; when given 15 min after BSP only midodrine 5 mg/kg hastened elim of dye from blood and increased in the bile; neither ST 1059 1 mg/kg nor NE modified BSP excretion, sponsor concludes midodrine and ST 1059 did not impair liver function.
9	0.5 mg/kg, iv	ST 1059	
20	0.9%, iv	NaCl	
8	5 mg/kg, iv	Midodrine	
8	1 mg/kg, iv	ST 1059	
8	0.015 mg/kg, iv	NE	Midodrine 5 mg/kg did not change mg % bilirubin in blood; biliary excretion of bilirubin was increased; sponsor states that this rules out possibility of impairment of liver function and competition between midodrine and bilirubin for secretion in the bile.
8	0.9%, iv	NaCl	
EFFECTS ON KIDNEY AND URINARY BLADDER: Report #058-01			
a. Water & Electrolyte Balance of Conscious Rats 3:4:10, 61-68: Report 058-01, p. 196;			
10	1,5 mg/kg, sc	Midodrine	Both midodrine and ST 1059 decreased volume of water consumed and raised urine and electrolyte excretion; methoxamine had same effect qualitatively but was more potent; all three agents produced a dose-dependent inhibition of water retention induced by phentolamine.
10	1,5 mg/kg, sc	ST 1059	
10	1,5 mg/kg, sc	Methoxamine	
b. Urine Volume & Clearance of PAHA and Inulin in Anesthetized Rat 3:4:11, 69: Report #058-01, p. 200;			
6	5 mg/kg, iv	Midodrine	Midodrine sig decreased urine volume and PAH clearance when compared to pretest values, no sig effect on PAH or inulin clearance when compared to effect of NaCl (data hard to interpret from table).
6	0.9%, iv	NaCl	
c. Urinary Bladder Capacity in Urethane Anesthetized Guinea Pig 3:4:11, 69: Report #058-01, p. 211			
4	1 mg/kg, iv	Midodrine	No alteration of urinary bladder capacity as measured by water infusion volume required to evoke the micturation reflex.
EFFECT ON CENTRAL AND PERIPHERAL NERVOUS SYSTEMS 3:4:11, 70			
a. Chemically & Electrically Induced Convulsions in Mouse: Report #058-01, p. 228;			
PTZ or S: 10 ea	1,2,4,8,16 iv midodrine	Electroshock: 10 ea iv 1,4,16 Midodrine	Pentamethylenetetrazol (PTZ; 120 mg/kg, sc) or strychnine (S) (1.8 mg/kg, sc) 5 min after iv midodrine or ST 1059 30 min after po doses; mice still living 30 min considered protected; shock measured occurrence of tonic hindlimb spasm; neither exhibited an effect on spasms; sponsor expected results since low lipid solubility of midodrine would not expect it to cross blood brain barrier.
7,8,10,10 PTZ and 10 ea S	3,6,24,48 po midodrine	10,9, 9,10, 10 iv 3,6, 12,24, 48 Midodrine	
10 ea	1,2,4 iv ST 1059	8,10,9 iv 1,2,4 ST 1059	
10 ea	3,6,24,48 po ST 1059	10,10, 9,10, 10 po 3,6, 12,24, 48 ST 1059	

2-9

NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Secondary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose (mg/kg) and Route	Drug	Results
b. Pentobarbital Sodium Sleeping Times in Mouse 3:4:12, 72: Report #058-01, p. 237;			
10/dose	2,4,8,16 mg/kg, iv	Midodrine	Agents given po 1 hr before pentobarb (50 mg/kg, iv) or iv immediately before pentobarb; neither midodrine not ST 1059 sig modified pentobarb sleeping time.
10/control	3,12,48 mg/kg, po	Midodrine	
	2 mg/kg, iv	ST 1059	
	3,6,24 mg/kg, po	ST 1059	
c. Spontaneous Activity in Mouse 3:4:12, 73: Report #058-01, pgs. 241 & 234;			
6 ea	0.5,10 mg/kg intracerebral inj	Midodrine	Measured time required to leave a circle of radius 12 cm; 0.5 mg/kg midodrine and ST 1059 did not alter spon act; did not modify ptosis and sedation induced by reserpine (0.1 mg/kg, ip, 180 min prior); 10 mg/kg midodrine and ST 1059 decreased spon activity; produced ruffled fur, salivation; abolished only ptosis; dopamine (10 mg/kg, 180 min prior) induced sig decrease spon act only 15 min after inj only; although NS the degree of hypokinesia was greater with dopamine than with 0.9% NaCl; dopamine abolished both sedation and ptosis induced by reserpine.
	0.5,10 mg/kg	ST 1059	
2x18/dose level (18 test; 18 controls)	1,2,4,8,16, iv	Midodrine	Mice photographed every 6 min (3 sec exposure) for 3 hr; midodrine reduced activity as assessed by image blurring; effect modest when compared with effect of reserpine.
	3,6,12,24,48, po	Midodrine	
	1,2,4, iv	ST 1059	
	3,6,12,24,48, po	ST 1059	
	2,5, sc	Reserpine	
d. Hot Plate/Phenylquinone Writhing Test in Mouse 3:4:12, 75: Report #058-01, p. 247;			
10 ea	0,1,4,16 mg/kg, iv	Midodrine	Midodrine doses as high as 8 mg/kg, iv and 48 mg/kg po failed to affect reaction time for hot plate test; 16 mg/kg, iv and 48 mg/kg, po did not modify the writhing syndrome. ST 1059 sig prolonged reaction time in hot plate test and protected against the writhing syndrome.
	3,6,12,24,48 mg/kg, po	Midodrine	
	1,2,4,8,16 mg/kg, iv	ST 1059	
	3,6,12,24,48 mg/kg, po	ST 1059	
e. Morphine Analgesia in Mouse 3:14:12: Report #058-01, p. 247;			
Not given	1-16 mg/kg, iv	Midodrine	Mice placed on a heated floor; iv doses given with morphine, 15 mg/kg sc; oral doses preceded morphine by 30 min; ST 1059 sig enhanced morphine analgesia at all doses in plateau effect mode; in contrast, midodrine did not enhance analgesia when given iv but did after po doses of 6 mg/kg or greater but there was no evidence of a dose-response curve.
	1-8 mg/kg, iv	ST 1059	
	3,4,48, po	Midodrine and ST 1059	
			In tail flick test, radiant heat focused on mouse tail, enhancement of morphine analgesia occurred after both midodrine and ST 1059 in a non dose-dependent manner; authors conclude that an alteration of morphine metabolism rather than a central nervous system action of midodrine may be responsible.

Ta. 2-10

NDA 19-815; AMATINE[R] (Midodrine) Tablets, Roberts Laboratories, Inc.

Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Secondary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose (mg/kg) and Route	Drug	Results
EFFECTS ON THE EYE: Report #058-01			
a. Conjunctival Hyperemia Induced by Nicotinic Acid in Rabbit 3:14:13: Report #058-01, p. 9			
eye drops	1%	Midodrine	ST 1059 but not midodrine given 15 h later reduced redness; effect lasted for 30 min.
eye drops	1%	ST 1059	
eye drops	0.1%	Naphazoline	Naphazoline reduced redness for more than 90 min; sponsor concluded midodrine was not an effective vasocontrictor agent in this model.
b. Penetration of Sulfamethizole into Aqueous Humor of Rabbit 3:4:1,13,76: Report #058-01, p. 103;			
5,6,8	0,1,2 mg/kg, iv	Midodrine	Markedly reduced penetration of sulfamethizole; concluded midodrine reduces amount of fluid passing from blood into aqueous humor.
c. Smooth Dilator Muscle of Pupil of Mouse 3:4:13,77,78: Report #058-01, p. 276;			
3 ea group	10 mg/kg, iv	Midodrine	Only iv and po midodrine produced 40% and 33% pupil dilation; no effect other routes.
	10 mg/kg, ip	Midodrine	
	25 mg/kg, sc	Midodrine	
	100 mg/kg, po	Midodrine	
	0.4 mg/kg, iv	ST 1059	IV, po ST 1059 produced minimal midriasis; no effect other routes.
	1 mg/kg, ip	ST 1059	
	5 mg/kg, sc	ST 1059	
	10 mg/kg, po	ST 1059	
d. Intraoccular Pressure in Urethane/Chloralose Anesthetized Rabbit 3:4:13,79: Report #058-01, p. 281,			
5	0.1 mg/kg, iv	ST 1059	Only increased intraocular press from 16 to 19.5 mmHg (NS); in contrast, much greater effects on cardiovascular parameters (systolic and diastolic pressures increased 39.4 ± 16.7 and 44.5 ± 14.8 mmHg; heart rate decreased 44.0 ± 17 bpm).
4,4,6,5	0.07,0.3,1,2.5 mg/kg, iv	Midodrine	Produced similar effect to that induced by 0.1 mg/kg, iv ST 1059.
e. Contraction of Nictitating Membrane in Urethane/Chloralose Anesthetized Cats 3:4:14: Report #058-01, p. 287,			
Not given	1 mg/kg, iv	NE	NE produced a contraction that was enhanced if chronically denervated (removed superior cervical ganglion 10 d prior) or if pretreated with reserpine 16 hr prior.
Not given	10 mg/kg, iv	ST 1059	Produced enhanced contraction in denervated and reserpine groups.
	1 mg/kg, iv	Midodrine	Produced contraction of slow onset but long duration (90% max 4 h) in unpretreated cats similar to that induced by supramaximal electrical stimulation; denervation or reserpine hastened onset of midodrine action but did not affect the degree or duration of effect.

Table 2-11
NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Secondary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose (mg/kg) and Route	Drug	Results
EFFECTS ON THE UTERUS: Report #058-01			
a. Isolated Rat Uteri 3:4:14: Report #058-01, p. 214;			
Not given	0.75 mg/ml	Carbamycholine	Induced contractions.
	0.25-4 mg/ml	Isoproterenol	Reduced contractions.
	$3x10^{-5}$ M	Midodrine	Midodrine and ST 1059 were only weak competitive inhibitors of iso in uterus and were much weaker than propranolol, nonselective beta-blocker, or practolol, beta-one selective blocker.
	10^{-10}M	ST 1059	
b. Rat Uteri In Situ 3:4:14: Report #058-03; May 1984;			
31	1, 5 mg/kg, iv	Midodrine	At low doses neither affected spontaneous uterine contractions, although blood pressure was increased and heart rate was decreased; higher doses midodrine and ST 1059 increased uterine motility 46 and 24%, respectively while also increasing blood pressure by 16 and 48% and decreasing heart rate by 19 and 14%, respectively. Concluded that unlikely midodrine at therapeutic doses would sig alter uterine activity.
	0.1, 0.3 mg/kg, iv	ST 1059	
EFFECTS ON THE RESPIRATORY TRACT			
a. Urethane Anesthetized, Vagotomized Guinea Pigs 3:4:14, 80: Report #058-01, p. 220, 6/76			
not given	5 mg/kg, iv	Midodrine	*Produced gradual, minimal bronchoconstriction.*
not given	0.5 mg/kg, iv	ST 1059	*Produced minimal bronchoconstriction of short duration.*

b. Urethane/Chloralose Anesthetized Dogs 3:4:15, p. 220, 6/76

			Tidal Vol	Minute Vol	Max Resp Flow Rate
4	0.6 mg/kg, iv	Midodrine	NE	small decreases	rise
	25 mg/kg/min, iv	ST 1059	slight fall	NE	slight fall
			No sig diff.		
			NE = no effect		

ANTIINFLAMMATORY EFFECTS 3:4:15, 81: Report #058-01

a. Formalin (1%) or Carrageenin (2%) Induced Edema in Rat: Report #058-01, p. 111;

6/dose/ route	1,3,10, 0.3,1,3 mg/kg, im	Midodrine	Formalin 1% caused paw volumes to increase about 30% over 3 h; catecholamines may suppress acute inflammation and indeed, midodrine reduced the swelling 50% in dose related manner.
	1,4,8,16 mg/kg, iv	Midodrine	4 mg/kg and greater sig reduced edema formation induced by carrageenin 2%; lower doses sig. only at 4, 5 h.
	1,2 mg/kg, iv	ST 1059	Also effective decreasing edema formation; higher doses required oral route.
	50 mg/kg, po	Phenylbutazone	Equivalent to 4 mg/kg, iv or 12 mg/kg po of midodrine.
	0.9%, iv	Saline	No effect.

Ta. .-12

NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.

Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Secondary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose (mg/kg) and Route	Drug	Results
b. Injection of Acetic Acid in Mouse 3:4:15, 82: Report #058-01, p. 105;			
15,15,10, 15,10	1,2,4,8,16 mg/kg iv	Midodrine	Both sig reduced the transfer of Evans blue dye, iv from blood into peritoneal fluid; suggests effect on capillary permeability component of the inflammatory process.
15,15,7,15	3,5,12,24 mg/kg,po	Midodrine	
10,10	1,2 mg/kg, iv	ST 1059	
9,10,9,9, 10	1.5,3,6,12,24 mg/kg, po	ST 1059	
METABOLIC EFFECTS: Report #058-01			
a. Oxygen Consumption in Rat 3:4:15: Report #058-01, p. 243,			
not given	4 up to 8.0 mg/kg, iv	Midodrine	Midodrine unlike many other sympathomimetic amines, reduced O_2 consumption for only first 30 min after 8 mg/kg, iv and greater.
	0.4, 0.8 mg/kg and up, iv	ST 1059	ST 1059 reduced O_2 consumption only after 0.8 mg/kg iv and greater for first 30 min.
	0.1 mg/kg, iv	Hexopenaline	Beta sympathomimetic amine more typical in that it increased O_2 consumption; midodrine 16 mg/kg and ST 1059 0.4 mg/kg inhibited action of hexoprenaline although effect of ST 1059 briefer due to its shorter duration of action.
b. Blood Glucose Levels in Mouse 3:4:16, 83: Report #058-01, p. 303;			
15/group 30 controls	0.25,0.75,2.5 mg/kg, ip	Midodrine	High doses inhibited rise in blood glucose level.
	3, 10 mg/kg, po	Midodrine	reduced blood glucose level.
	0.1,0.3,1 mg/kg, iv	ST 1059	reduced blood glucose level.
	0.1,0.3,1 mg/kg, ip	Methoxamine	High doses reduced blood glucose level.
	0.1 mg/kg, ip	NE	No effect on blood glucose level.
	0.03,0.1 mg/kg, ip	Epi	Increased blood glucose level.
c. Blood Glucose, Lactate, and Fatty Acid Levels in Rat 3:4:16, 84			
20,19,20		Control	Lactate, glucose, fatty acid measurement.
10,10,9	15 mg/kg, ip	Midodrine	Increased blood glucose and inhibited increase in blood lactate and free fatty acids induced by isoproterenol (0.5 mg/kg, ip).
d. Blood Glucose, Lactate, and Fatty Acid Levels In Dog 3:4:16, 84			
5	1 mg/kg, iv	Midodrine	Small, sig fall bd glucose 30-240 min after midodrine and in free fatty acids 15 min after midodrine; ST 1059 did not show these effects. There were no sig changes in blood lactate, pyruvate, triglyceride, phospholipid, cholesterol, K+ levels, thromboplastin time, hematocrit, creatinine kinase.
5	0.05 mg/kg, iv	ST 1059	
6	0.9%, iv	Saline	
e. Rat Epididymal Adipose Tissue *In Vitro* 3:4:16: Report #058-01, p. 324;			
3,5	10^{-5}, 10^{-4} M	Midodrine	Unphysiological conc midodrine slightly increased free fatty acid production by lypolysis; ST 1059 one order magnitude more potent; midodrine less effective in inhibiting non-selective beta agents such as isoproterenol (10 M) than of the predominantly beta-2 receptor drug hexoprenaline.
3,6	10^{-5}, 5×10^{-6} M	ST 1059	
6	Control *in vitro*	-	

Table 2-13

NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.

Summary Tabulation of Results of Preclinical Pharmacology Studies of Midodrine or Active Metabolite ST 1059: Secondary Action

EXPERIMENT [reference] Sample Size Per Dose	Dose (mg/kg) and Route	Drug	Results
f. Histamine Release from Rat Mast Cells 3:4:16, 85: Report #058-01, p. 331;			
3 ea	4, 20 ug	Midodrine	Sig lowered mast cell histamine content.
	20 ug	ST 1059	
	Control suspension		
6,8	1,5 mg/kg, iv	Midodrine	1 mg/kg no alteration in blood or lung histamine content within 15 mins; 5 mg/kg was loss of
12	control		histamine from lung tissue without change in blood conc.
13	control, iv		5 mg/kg elevated brain epinephrine.
7	5 mg/kg	Midodrine	10 mg/kg increased spleen epinephrine and decreased brain NE.
13	10 mg/kg	Midodrine	
6	30 mg/kg/d for 3 d, po	Midodrine	Adrenal epinephrine content increased, small increase spleen levels; minor fall brain conc NE.
g. Guinea Pig Liver Homogenates 3:4:17: Report 058-01, p. 340;			
11	control		Neither midodrine nor ST 1059 were substrates or inhibitors of MAO.
23	$3x10^{-3}$M	Midodrine	
8	$3x10^{-3}$ M	ST 1059	
10	control homogenate		

Table 3-1
NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Summary and Tabulation of Preclinical Pharmacokinetic Studies

Single Dose Study

3:4:17,86: Report #058-31; July 1972:

Species Strain	No/ Group	Study Duration	Dose	Plasma t1/2 h	Urinary Recovery % of Dose per 56 h	30 min after Midodrine iv Metabolites Conc			Metabolites of Midodrine After IV Dosing		Inactive and Deaminated Metabolites at All Experiment Times	
							ST 1059	Inactive Deaminated & Conjugated				
Rat M Wistar	4/route/ experi- mental time	sacrificed 0.5, 1, 2, 4 and 8 h post drug	Midodrine 0.916-1.143 mg/kg, iv, po	1.0	97.6-99.9	plasma	33%	36%	Unchanged	5.7%	Liver	57-70%
									ST 1059	53.9%	Kidney	38-64%
									Conjugated and Uncoupled Metabolites	40.4%	Heart	42-62%
											Lung	73-86%
			ST 1059 0.5696 mg/kg, po	1.75	95.7-97.1				[See Table 3-2 (Table 1.1.49; 8:4:87)]			

Results
-Plasma clearance curves essentially identical from 1 hour on after iv or po, indicating that rapid and complete absorption of midodrine occurs.
-Radioactivity all tissues but liver and sm and lg intestines higher after iv than po 0.5-2 h.
-IV and po slopes of clearance curves all organs similar after 2 hr.
-Kidney-only 30 min was sig diff iv>po (3:4:17).
-Clearance curves (all organs except liver and brain) biphasic after iv; liver was mono-exponential; same pattern after po; brain pattern reflects blood/brain barrier (BBB).
-Kinetic profiles in some organs from rats given iv ST 1059 (55.37 uCi vs 49.25 uCi of midodrine) followed similar patterns. However, whereas at early times plasma and all tissue conc except brain close to iv midodrine, slopes for clearance curves indicated a much longer retention for ST 1059, a reflection of the longer plasma t1/2.
-Total radioactivity brain 2x higher with ST 1059 than midodrine; indicates ST 1059 crosses BBB more easily than midodrine.
-For midodrine, the metabolic pathway followed its initial hydrolysis with splitting of glycol residue to give ST 1059, demethylation to ST 1062, followed by deamination or glucuronidation. Biliary excretion is minor process.

Note: Plasma level of inactive and deaminated metabolites was 36% at 30 minutes and quickly rose to approximately 50% (3:4:18).

Table 3-2

Distribution of metabolites in the collected urine of rats after i.v. administration of midodrine (ST 1050

	Mean percent distribution (x±s, n=4)		
	Free	Conjugated	Total
Amines	61,80	7,42	69,30
ST 1085	5,71±0,49		5,71±0,49
ST 1059	53,9 ±1,63		53,9 ±1,63
ST 1061/62	2,26±0,30	7,42	9,68±0,51
Glycoles	2,34±0,06	19,76	22,10±1,45
2,5-MHPG	(2,1)	19,76±1,41	
2,5-DHPG	(0,2)		
Acids	4,93±0,31		4,93±0,31
2,5-MHHA	(4,8)		
2,5-DHMA	(0,5)		
acid7	(1,6)		
TOTAL	71,15	27,18	98,33±0,51

The parenthesised values were obtained after paper chromatographic separation of extraction fractions of collected urines.

Original Table 1:1:49 in 3:4:87 of NDA 19-815.

1-3

NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Summary and Tabulation of Preclinical Pharmacokinetic Studies

3:4:17,86: Report #058-04:

Species Strain	No/ Group	Study Duration	Dose	Plasma t1/2 h	Urinary Recovery % of Dose per 48 h	Metabolites Conc	Results		
Dog M Beagle	4	0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6 h post drug	Midodrine 0.1, 0.4, 1.6 mg/kg, iv	2	57.4%, 87.6%, 99.2%, 102.7%	The po administraton of midodrine to dogs was absorbed quickly and in most cases completely. The temporal time course of the plasma concentration of midodrine and ST 1059 was (5:#058-04:34):	Time	% Midodrine	% ST 1059
							15 min	40	22
							30 min	22	30-35
			ST 1059 0.8 mg/kg, po (gastric intubation)	2.5	(mean 89.2)		45 min	10	Not Given
							2 h	3	Not Given
							3-6 h	0-2.3	Not Given

Results:

Close correlation of hemodynamic changes (increased blood pressure and decreased heart rate) with plasma conc of midodrine metabolite ST 1059 for 6 hr post dosing with midodrine. Maximum pharmacodynamic action and plasma levels in dogs (0.3-1.0 N mole/ml) of ST 1059 achieved 0.75-2 h post drug. 6 h ST 1059 conc in plasma had returned to those seen at 15 min; neither BP nor HR at baseline values. Plasma levels of 0.2 N mole/ml ST 1059 needed for pharmacodynamic activity; above this level was a linear relationship between plasma conc and the decrease in heart rate for po and iv.

Summary section (3:4:18) indicates that in Report #058-04, in which the pharmacokinetic data were correlated with the pharmacodynamic data, midodrine was given by gastric intubation (0.8 mg/kg) or intravenously (0.1, 0.4, 1.6 mg/kg). The report (vol 5) contains pharmacokinetic and pharmacodynamic data for the gastric intubation experiments but only pharmacodynamic data for the intravenous doses.

NDA 19-815; AMATINE[R] (Midodrine Hydrochloride) Tablets, Roberts Laboratories, Inc.
Summary Tabulation of Human Pharmacokinetic and Bioavailability Studies Conducted and Associated Side Effects

M	Age yrs	Wt (kg) Ht (cm)	Mode of Admin	Dose Form	Avg Dose ug/kg	Study Duration	Mean % of Midodrine Excreted in Urine as Active Metabolite Desylymidodrine	Time Period of Excret.	& Mean Urinary Elim. Desylymidodrine (ug)	Results	Side Effects
SINGLE ORAL DOSE URINARY EXCRETION NORMAL VOLUNTEERS - 9:5:8; 28-37:058-37;											
6M+	27-59	68-90 Not given	po	one 5 mg tablet	66.9	12 h	30%	0-2 hr 2-4 hr 4-8 hr 8-12 hr	526 320 179 0	Midodrine rapidly absorbed from tablet; rapidly metabolized	Chills, formication 6/6 (sensation of small insects crawling over the skin; a form of piloerection) about 1 hr post dose, formication of scalp, shoulders, back; about 4 hrs symptoms wane; time course of appearance of metabolite correlates well with subjective effects.
MULTIPLE ORAL DOSE URINARY EXCRETION NORMAL VOLUNTEERS - 9:5:9; 38-48: 058-38;											
6M+	27-59	68-90 Not given	po	3x5 mg tab q4 h	166.5	24 h	44.9%	0-4 hr 4-8 hr 8-12 hr 12-24 hr	968 1476 1445 685	Midodrine is rapidly metabolized; no accumulation of metabolite since amount excreted similar for intervals 0-4, 4-8, and 8-12 h, dosing interval 4 h is appropriate	6/6: about 1 h after 1st tablet, formication of scalp appeared, spreading to shoulders and back; 1/2 h after 2nd tablet, formication and chills covers practically whole body; after 3rd, a moderate reddening of skin of face; all symptoms present until 20-30 h; temporary course of the total excretion correlates approx with duration of subjective effects.

+same test subjects

4-2

NDA 19-815; AMATINE® (Midodri blets, Roberts Laboratories, Inc.

Summary Tabulation of Human Pharmacokinetic and Bioavailabity Studies Conducted and Associated Side Effects

N	Age yrs	Wt (kg) Ht (cm)	Mode of Admin	Dose Form	Avg Dose ug/kg	Study Duration	Mean % of Midodrine Excreted in Urine as Active Metabolite Desylymidodrine	Mean Urinary Elimination Desylymidodrine ug	Results	Side Effects
SINGLE INTRAVENOUS DOSE URINARY EXCRETION NORMAL VOLUNTEERS - 9:5:9; 49-81: 058-39;										
1M	43	85 186	iv	5.11 mg in 2 gm of 0.9% NaCl	60.1	168 h	92.9%	Triphasic Plasma Clearance Curve Duration / t1/2 Elimin Initial 30 min 5-6 h Subsequent 48 h >160 h	Midodrine disappears rapidly from plasma as it is metabolized to desylymidodrine (ST 1059) which has a longer plasma t1/2, is amply present in urine and is responsible for pharmacol actions of midodrine	1.5-4 h after shivers on whole body with piloerection, esp. lower arms; 0-2 and 2-4 h marked increase desire to urinate with concomitant slight micturition difficulties; effects and time course corresponded with course of action of ST 1059 in plasma and urine

1. - 4-3

NDA 19-815; AMATINE[R] (Midodrine) Tablets, Roberts Laboratories, Inc.
Summary Tabulation of Human Pharmacokinetic and Bioavailabity Studies Conducted and Associated Side Effects

SINGLE DOSE INTRAVENOUS/ORAL, 2-WAY CROSSOVER METABOLIC STUDY NORMAL VOLUNTEERS - 9:5:11, 82-110: 058-40;

N	Age yrs.	Mode of Admin.	Dose Form	Study Dates
3 M & 3 F	20-27	iv	5 mg	2/9/81 &
		po (gelatin capsule of 0-4 ml of drug in soln.)	5.3 mg	2/23/81

058-40a; 10/81: , Samples from study 053-40

Mean Plasma Level ng/ml

	h	1	2	4	8	12	24	48	72
Midodrine	iv	36.87	33.64	24.00	11.71	4.88	0.65	0	0
	po	50.12	47.54	31.43	14.92	5.95	0.65	0	0

Mean Excretion Midodrine in Urine and Feces after Intravenous Administration of 5 mg, in percentage of the dose given

	Urine											Feces					
	0-2 h	2-4	4-6	6-12	12-24	2d	3	4	5	6	7	1	2	3	4	Total Urine	Total Feces
Midodrine iv	34.49	18.60	13.85	6.77	7.02	1.17	0.17	0.01	0	0	0	0.04	0.32	0.35	0.07	82.08	0.78
po	26.46	20.61	12.38	7.90	7.82	1.17	0.18	0.04	.01	0	0	0.42	0.69	0.83	0.17	76.57	2.11

	t max h	Cmax ng/ml	mean t1/2 h	AUC ng.h/ml	Total Clearance ml/min	Volume Distrib. ml	Results
iv	-	-	3.87	268.67	25.03	101.60	Experimentally obtained plasma level results were adjusted to a two-compartment model (iv) or to a one-compartment model (po). Mean absorption rate after po was calculated to be 109%; sponsor states this value means that drug was completely absorbed after po route; after iv and po only very small amts excreted in the feces.
po	0.66	53.91	3.58	307.93	-	93.83	

Three-Way Crossover Study Comparing Bioavailability of 2.5 mg Midodrine 9:150-166; Report #058-133b

N	Age yrs.	Dose Form	Study Dates
12 healthy male volunteers	21-26 yr (23 yr mean)	2.5 mg	Prior to 1987 since published in Drug Res 37 (1) No. 4, 1987.

	tmax min	Cmax ng/ml	t1/2 h	AUC ngxh/ml	Excretion 24 h urine % of dose (9:165)	Cl ml/min	V (l)	Results
Midodrine								
iv	-	-	0.41	14.6	3.6			Midodrine was absorbed very rapidly both from the drinkable solution and from table formulation; all three formulations were regarded as equivalent with respect to the active metabolite.
oral soln	23	10.9	0.45	8.71	2.2			
tablet	27	11.2	0.49	9.46	2.2			
ST 1059								
iv	-	-	3.1	28.7	39.8	1200	319	
oral soln	1.1	4.6	3.0	25.7	34.4	1392	355	
tablet	1.1	5.0	3.0	25.6	34.4	1378	353	

NDA 19-815; AMATINE® (Midodrine Hydrochloride) Tablets, Roberts Laboratories, Inc.

Summary Tabulation of Human Pharmacokinetic and Bioavailabity Studies Conducted and Associated Side Effects

SINGLE DOSE 3 WAY CROSSOVER BIOAVAILABILITY - 9:5:14, 150-166: 058-133a,b; 12/87

N	Age yrs	Wt (kg) Ht (cm)	Mode of Admin	Dose Form	
12M	21-26	63-88	iv	2.5 mg	Midodrine
		175-190	po	2.5 mg soln	Midodrine
			po	2.5 mg tablet	Midodrine

	tmax	Mean Plasma Conc ng/ml	t1/2 Plasma	AUC ST 1059 ngxh/ml		Absolute Bioavailability*		Plasma Conc Midodrine - ng/ml	5'	30'	1h	2h
Midodrine	20-30 min	10	0.5 h	iv	28.7	-		iv	56.6	7.6	3.2	Not detectable
ST 1059	1 h	5	3 h	oral soln	25.7	oral soln	90%	oral soln	3.4	8.0	3.5	1.1
				tablet	25.6	tablet	93%	tablet	4.9	9.9	4.0	1.3

*Relative bioavailability $\frac{\text{tablet}}{\text{oral soln}}$ = 109%

Table 4-5

Adverse Reaction	% Patients in Controlled Trials			
	MIDODRINE (N=17)	DHE* (N=9)	EPHEDRINE (N=8)	PBO* (N=17)
Dizzy/Lightheaded/ Dysequilibrium	35.3	66.7	25.0	23.5
Pruritis/Tingling of Scalp	5.9	0	0	5.9
Cardiac Awareness	5.9	0	0	0
Photosensitivity	0	0	12.5	0
Pounding in Ears	5.9	0	12.5	0
Fever	0	11.1	12.5	0
Neuropathy/Limb Pain	5.9	11.1	0	5.9
Fatigue	0	11.1	0	5.9
Nausea/Vomiting	5.9	11.1	0	5.9
Hypokalemia	5.9	0	0	5.9
Breathing Difficulty	5.9	0	0	0
Supine Hypertension	5.9	0	0	0
Headache	5.9	0	0	0
Gastroparesis	5.9	0	0	0
Syncope	5.9	0	0	5.9
Chest Pain	5.9	0	0	0
Depression	0	0	0	5.9

*DHE=Dihydroergotamine; PBO=Placebo

Clinical adverse experiences which occurred in 0.5 to 2.0% of patients in controlled and uncontrolled trials included:

Cardiovascular: Palpitations

Integumentary: Tingling of the scalp, piloerection

Gastrointestinal: Abdominal discomfort

Genitourinary: Dysuria, fullness of bladder, urinary retention, incontinence

Other: Chills

Side Effect	Patients (%)	
Pruritis/Scalp Itching	44	(30)
Supine Hypertension		
Before and after Rx	43	(29)
Only after Rx	36	(25)
Piloerection	37	(25)
Headache	26	(18)
Tingling	23	(16)
Nausea	15	(10)
Urinary Urgency	12	(8)
Flushed Extremities	8	(5)
Bradycardia	6	(4)
Palpitations	5	(3)
Rash	5	(3)
Arrhythmia	5	(3)
Swelling in Extremities	4	(3)
Sweating	4	(3)
Insomnia & Nervousness	3	(2)
Nightmares	3	(2)
Aggravation of Prostatism	2	(1)
Angiitis	1	(1)
Other	7	(5)

Sponsor's table found in 2:2:145,146

NDA 19-815; AMATINE® (Midodrine Hydrochloride) 5-mg Tablets, Roberts Laboratories, Inc.
Results of Acute Toxicity Studies: LD_{50}

EXPERIMENT [reference; report #]

Species	Strain	N/Group	Route	Midodrine Dose mg/kg	Study Duration	Death Rate	LD_{50} mg/kg (with deviation range)	
SINGLE DOSE STUDIES 3:4:20, 89: Report #058-17;								
Mouse	NMRI	10 M	po	300, 450, 675, 1013	48 h	0/10; 1/10; 4/10; 10/10	675	(578-788)
		6 M	sc	100, 150, 225, 338	48 h	0/6; 1/6; 4/6; 6/6	196.6	(158.1-244.4)
		10 M	ip	133, 200, 300	48 h	2/10; 4/10; 10/10	199.9	(167.2-239.1)
		6 M	iv	80, 100, 156	48 h	2/6; 3/6; 5/6	107.7	(78.79-147.3)
Rat	Sprague-Dawley	6 F	po	21.9, 32.9, 49.4	72 h	0/6; 3/6; 6/6	32.9	(27.4-39.38)
		6 F	sc	25.7, 38.5, 57.8, 86.5	72 h	1/6; 5/6; 6/6; 6/6	30.18	(22.22-40.98)
		6 F	ip	13, 19.5, 29.2, 43.8	72 h	1/6; 3/6; 3/6; 4/6	25.55	(14.47-45.11)
		6 F	iv	14.8, 18.5, 23.2, 29.0	72 h	1/6; 4/6; 5/6; 6/6	17.69	(14.79-21.17)
3:4:20, 90: Report #058-18,								
Mouse	Swiss	10 F	iv	40, 60, 90, 135	48 h	0/10; 2/10; 6/10; 10/10	79.7	(67.2-94.6)
		10 M	iv	40, 60, 90, 135	48 h	1/10; 6/10; 10/10; 10/10	54.8	(45.6-65.9)
		10 F	ip	88.7, 133.3, 200, 300	48 h	1/10; 5/10; 8/10; 9/10	140	(110.8-176.9)
		10 M	ip	88.7, 133.3, 200, 300	48 h	2/10; 2/10; 6/10; 6/10	220.9	(121.4-401.7)
		10 F	sc	66.6, 100, 150, 225, 338	48 h	not; 0/10; 1/10; 10/10; 10/10 given	169.4	(152.1-188.7)
		10 M	sc	66.6, 100, 150, 225, 338	48 h	0/10; 3/10; 4/10; 10/10; 10/10	139.2	(115.3-165.7)
		10 F	po	133.3, 200, 300, 450	48 h	0/10; 1/10; 5/10; 10/10	288	(246.2-337.2)
		10 M	po	133.3, 200, 300, 450	48 h	2/10; 6/10; 4/10; 8/10	244.9	(174.8-343.1)
Rat	Sprague-Dawley	10 F	iv	6.56, 10.25, 16, 25	72 h	0/10; 8/10; 8/10; 10/10	9.8	(8.3-11.6)
		10 M	iv	6.56, 10.25, 16, 25	72 h	0/10; 8/10; 8/10; 10/10	10.2	(8.6-13.3)
		10 F	ip	10, 15, 22.5, 33.75	72 h	0/10; 7/10; 8/10; 10/10	15	(12.7-17.7)
		10 M	ip	10, 15, 22.5, 33.75	72 h	0/10; 1/10; 5/10; 10/10	21.6	(18.5-25.3)
		10 F	sc	10, 20, 40, 80	72 h	0/10; 3/10; 7/10; 10/10	28.3	(21-38.2)
		10 M	sc	10, 20, 40, 80	72 h	0/10; 4/10; 9/10; 10/10	23.1	(17.6-30)
		10 F	po	20, 30, 45, 67.5, 101.25	72 h	0/10; 3/10; 6/10; 8/10, -	46.9	(39.5-55.6)
		10 M	po	20, 30, 45, 67.5, 101.25	72 h	-; 0/10; 6/10; 8/10; 10/10	40.7	(31.7-52.1)

5-2

NDA 19-815; AMATINE^{R} (Midodrine) Tablets, Roberts Laboratories, Inc.
Results of Acute Toxicity Studies: LD_{50}

EXPERIMENT [reference; report #] Species	Strain	N/Group	Route	Midodrine Dose mg/kg	Study Duration	Death Rate	LD_{50} mg/kg (with deviation range)
3:4:20, 92: Report #058-19;							
Dog	Mongrel	1/sex/dose	po	1.59, 2, 2.52, 10, 12.6, 100, 126, 159	2 wk	Females: one at 126, one at 159; Males: one at 159	not determined

Other Observations:

Symptoms preceding death in mice after the intravenous administration of midodrine were convulsions, ruffled coat, dyspnea, and exophthalmus. Symptoms observed after the intraperitoneal administration were extension spasms, ruffled coat, and exophthalmus. Symptoms observed after subcutaneous dosing included ruffled coat, heavy breathing, and hypersalivation while symptoms of ruffled coat, heavy breathing, and death in convulsions were noted after oral dosing.

In rats, the symptoms preceding death were ruffled coats, exophthalmus, and heavy breathing after intravenous dosing with midodrine. Symptoms of ruffled coat, exophthalmus, and heavy breathing followed intraperitoneal dosing while ruffled coat, exophthalmus, heavy breathing and hypersalivation were noted after subcutaneous dosing. Symptoms of ruffled coat, exophthalmus, heavy breathing, and hypersalivation were associated with death following oral doses of midodrine.

Ophthalmic exams and monitoring of the electrocardiogram, heart rate, an blood pressures were not done in the mouse and rat.

In dogs, anorexia occurred at a dose of 10 mg/kg, po or greater and at these doses the fecal matter was thin and pasty. Piloerection occurred at a dose of 12.6 mg/kg, po or greater. Tremors were noted at doses greater than 12.6 mg/kg, po. All dogs exhibited ataxia at doses at or greater than 100 mg/kg, po. Sedation was noted at 126 mg/kg, po while salivation occurred at all doses greater than 2 mg/kg, po for the first two to 10 hours post dosing. Vomiting was noted at a dose of 10 mg/kg, po or greater. Changes in blood pressure, respiration, an' heart rate were noted after all doses; dyspnea occurred 15-60 min after 12.6 mg/kg, po or greater and exhibited a duration between 3 to 5 hours. A strong mydriasis was noted 20 to 60 min after a dose of 10 mg/kg, po or greater and lasted for 2 to 8 hours. Pupil reaction was generally normal except at very high doses.

A total of three dogs exhibited attacks of tonic-clonic spasms and became comatose 110 min to 10 hr post drug; all died after a convulsive fit. One female dog died at 120 min after 126 mg/kg, po. One male died at 150 min after 159 mg/kg, po while one female dog died 10 hr after 159 mg/kg, po. All doses slightly prolonged the PQ and QT intervals. The dogs which died exhibited bradycardia 10 to 15 min post drug. All animals died in cardiac standstill in diastole.

Table 6-1
NDA 19-815; AMATINE^{R} (Midodrine) Tablets, Roberts Laboratories, Inc.
Subchronic/Chronic Toxicology

10 or 20 Day Administration by Stomach Tube of Midodrine in Rat

Testing Facility:

Study Number: 058-20

Study Date: 1/70

GLP Compliance: Not done.

Animals: Rat Sprague-Dawley

Mode of Administration of Test Agent: Stomach tube

Dose Levels: 0, 5, 10, 20 mg/kg/d, 5/sex/group for 10 d; 10/sex/group for 20 d

Observations/Measurements:

Body Weight	Daily
Hematology	Pt, 10 or 20 d
Clinical Biochemistry:	
a. Liver Chemistry	Pt, 10 or 20 d
b. Plasma Chemistry	Pt, 10 or 20 d
Appearance/Behavior Changes	Daily
Autopsy:	
a. Gross	10 or 20 d
b. Microscopic	10 or 20 d
c. Organ Weights	10 or 20 d

Mortality: 1 female in the dosing regimen of 20 mg/kg 20 d, po, died on day 5; organs not examined due to advanced decomposition.

Drug Associated Findings: 5:058:20; p. 229

Body Weight	No significant effect on wt gain; F slight decrease during first 5 d 20, 20 mg/kg, compensated later; assumed to be in connection with changes in the liver.
Clinical Biochemistry a. Liver Chemistry	All changes listed below are statistically significant. Liver sorbitol dehydrogenase decreased F: 10, 20 mg/kg/10 d decreased M: 5, 20 mg/kg/10 d increased F: 5, 20 mg/kg/20 d decreased M: 5, 10, 20 mg/kg/20 d

Table 6-2
NDA 19-815; AMATINE^{R} (Midodrine) Tablets, Roberts Laboratories, Inc.
Subchronic/Chronic Toxicology

a. Liver Chemistry (cont)	Glutamic Pyruvic Transaminase		
	decreased M:	5, 10	mg/kg/20 d
	Alkaline Phosphatase		
	decreased F:	20	mg/kg/10 d
	increased M:	5, 20	mg/kg/10 d
	decreased M:	10	mg/kg/10 d
	decreased F:	5	mg/kg/20 d
	Triglyceride		
	increased F:	5, 10, 20	mg/kg/10 d
	increased F:	10, 20	mg/kg/20 d
	decreased M:	10	mg/kg/20 d
	Liver Total Cholesterol		
	increased F:	5, 10, 20	mg/kg/10 d
	decreased M:	5, 20	mg/kg/10 d
	increased F:	5, 10, 20	mg/kg/20 d
	decreased M:	10, 20	mg/kg/20 d
	Phospholipids		
	increased F:	5, 20	mg/kg/10 d
	increased F:	5, 10, 20	mg/kg/20 d
	decreased M:	5, 10, 20	mg/kg/20 d
	Nonesterified Fatty Acids		
	increased F:	5, 20	mg/kg/10 d
	decreased M:	10	mg/kg/10 d
	increased F:	10	mg/kg/10 d
	increased M:	10	mg/kg/10 d
	Sulphydryl Groups		
	increased M:	5, 10, 20	mg/kg/10 d
	decreased F:	10	mg/kg/10 d
	decreased M:	20	mg/kg/20 d
	decreased F:	5, 20	mg/kg/20 d
b. Plasma Chemistry	All changes listed below are statistically significant.		
	Plasma Sorbitol Dehydrogenase Activity		
	increased M:	10, 20	mg/kg/10 d
	Glutamic Pyruvic Transaminase		
	decreased F:	5, 10, 20	mg/kg/10 d
	increased M:	5, 10, 20	mg/kg/10 d

Table 6-3
NDA 19-815; AMATINE^{R} (Midodrine) Tablets, Roberts Laboratories, Inc.
Subchronic/Chronic Toxicology

b. Plasma Chemistry (cont)	decreased F:	5, 10	mg/kg/20 d
	increased F:	10	mg/kg/20 d
	increased M:	10, 20	mg/kg/20 d
	Alkaline Phosphatase		
	decreased F:	5, 10, 20	mg/kg/10 d
	increased M:	20	mg/kg/10 d
	decreased F:	5, 20	mg/kg/20 d
	increased M:	5	mg/kg/20 d
	Triglycerides		
	decreased F:	5	mg/kg/10 d
	decreased F:	5	mg/kg/20 d
	decreased M:	5	mg/kg/20 d
	Plasma Total Cholesterol		
	decreased F:	5, 10	mg/kg/10 d
	decreased M:	5	mg/kg/10 d
	increased F:	20	mg/kg/20 d
	decreased M:	5, 10	mg/kg/20 d
	Plasma Phospholipids		
	decreased F:	10	mg/kg/10 d
	decreased M:	20	mg/kg/10 d
	decreased F:	5	mg/kg/20 d
	decreased M:	5, 10, 20	mg/kg/20 d
	increased F:	10, 20	mg/kg/20 d
	Nonesterified Fatty Acids		
	increased F:	5	mg/kg/10 d
	Total Protein		
	decreased F:	5, 10	mg/kg/10 d
Autopsy	<u>Heart</u>: Changes in the heart were characteristic of those produced by sympathomimetic agents, i.e., Ht weight increased and focal degenerations of myocardial fibers occur; not dose dependent; not particularly pronounced. Intensified foci of degeneration; myocardial fibers replaced with connective tissue and accumulation of increased numbers of round cells.		

Table 6-4
NDA 19-815; AMATINE^{R} (Midodrine) Tablets, Roberts Laboratories, Inc.
Subchronic/Chronic Toxicology

Autopsy (cont)	<u>Liver</u>: More marked than cardiac; sex. diff. a. F-fatty degeneration in periphery of lobes b. F-decrease of glycogen content c. F-accumulation of lipids d. M-cellular enlargement without fatty accumulation e. M-cells were rich in glycogen

Table 6-5
NDA 19-815; AMATINE^{R} (Midodrine) Tablets, Roberts Laboratories, Inc.
Subchronic/Chronic Toxicology

6 Month Adminstration Orally by Stomach Tube of Midodrine or ST 1059 in Rat

Testing Facility:

Study Number: 058-21

Study Date: 2/72

GLP Compliance: Not done.

Animals: Rat Sprague-Dawley

Mode of Administration of Test Agent: Orally by Stomach tube

Dose Levels: 0, 1, 5, 20 mg/kg/day, po Midodrine and 0.3, 1 mg/kg/day, po ST 1059; 10/sex/group

Observations/Measurements:

Body Weight	weekly
Hematology	Pt, 3, 6 mon
Clinical Biochemistry:	
a. Liver Chemistry	6 mon
b. Plasma Chemistry	6 mon
Urinalysis	12 hr urines in prelim period; then every 6 wks: renal function Pt, 12 wk, 25 wk.
Appearance/Behavior Changes	Daily
Autopsy	
a. Gross	6 mon
b. Microscopic	6 mon
c. Organ Weights	6 mon

Mortality: Initial test affected by infection (severe kidney damage) since independent of the dose deaths occurred; 2 animals died in control group, 7 @ 1 mg/kg, 4 @ 5 mg/kg, and only 2 at 20 mg/kg. In comparison, 2 deaths occurred in control group in a second test, one after 0.3 mg/kg and 3 after 1.0 mg/kg (6:4:7).

Table 6-6
NDA 19-815; AMATINE^{R} (Midodrine) Tablets, Roberts Laboratories, Inc.
Subchronic/Chronic Toxicology

Drug Associated Findings:

Body Weight	No effect on wt gain when F compared to controls but in males wt gain was less in 20 mg/kg from the 21st week on. However, the same effect was also observed in the controls from the 20th week (6:4:11, 123, 130).
Clinical Biochemistry a. Liver Chemistry	5 mg/kg midodrine 6 mo minimal increase triglycerides F 5.98 ± 4.05 to 8.54 ± 2.70 mg % M 5.49 ± 1.99 to 9.42 ± 3.05 mg %
Sponsor states that the "lipid fractions in plasma and liver showed significant differences but there was no dose-dependence and no conformity of the direction of action with the two tests". 6:4:6	Other liver lipids no change. Decrease heptic free fatty acids. Male 0.5, 2.5 mg/kg increased glutamic oxaloacetic transaminase associated with occurrence of enlarged cells; no evidence fatty infiltration of liver. 0.3 and 1 mg/kg increase in liver triglycerides and cholesterol F only; no change hepatic glutamic oxaloacetic transaminase .
b. Plasma Chemistry	Increase plasma alkaline phosphatase 5, 20 mg/kg. No change in plasma lipids. 20 mg/kg decrease in plasma free fatty acids. M & F 1 mg/kg decrease albumin; smaller decrease after 5 mg/kg and no change after 20 mg/kg. Plasma Na, K, urea not altered. Supplementary study of 0.3 and 1 mg/kg 6 mon showed no changes in plasma albumin function; no changess in plasma glutamic oxaloacetic transaminase.
Autopsy	Heart: Myocardial necroses 1. Only single degenerative changes in myocardial fibers near endocardium = Symptom A. 2. Only short chains of round cells scattered between myocardial fibers, esp. near endocardium; little rows of fibrocytes threaded like a string of pearls arranged around cells here and there in myocardium = Symptom B. 3. Symptom A+B

Table 6-7
NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Subchronic/Chronic Toxicology

Autopsy (cont)

4. Small scars of connective tissue in papillary muscle = Symptom C and symptoms of A+B = A+B+C.
5. Total # of rats in which myocardial changes were seen.
6. Total # of rats in which no myocardial changes were observed.

mg/kg, po	1	2	3	4	5	6
0	3/20	0/20	0/20	0/20	3/20	17/20
1	0/20	0/20	2/20	3/20	5/10	15/20
5	0/16	0/20	4/16	4/16	8/16	8/16
20*	2/18	0/18	2/18	7/18	11/18	7/18
or	2/20	0/20	2/20	7/20	11/20	9/20
Supplementary Study						
0	2/20	0/20	1/20+	0/20	3/20	17/20
0.3	0/20	1/20	3/20**	1/20	5/20	15/20
1***	1/17	0/17	2/17	1/17	4/17	13/17

Kidney: 20 mg/kg/day - histological changes.

Spleen: Necroses in form of an increased erythrocytolysis.

*Cannot decipher whether total N is 18 or 20 (6:4:42).
**One animal also exhibited slight thickening of lt. ventricle.
***Sponsor states that 20 animals were in group, but data for only 17 rats given.
+Small accumulation of basophil round cells found one area under the endocardium in a papillary muscle. Little roads of round cells found in myocardium in the direct surroundings.

Table 6-8
NDA 19-815; AMATINE^{R} (Midodrine) Tablets, Roberts Laboratories, Inc.
Subchronic/Chronic Toxicology

6 Month Oral Administration of Midodrine in Dog

Testing Facility:

Study Number: 058-22

Study Date: 4/71

GLP Compliance: Not done.

Animals: Mongrel dog; 6-9 mon.

Mode of Administration of Test Agent: po

Dose Levels: 0, 0.5, 2.5, 12.5 mg/kg/day; 8/sex/group

Observations/Measurements:

Body Weight	weekly
Hematology	Pt, monthly
Clinical Biochemistry:	
a. Liver Chemistry	
-Phenylbutazone Test	Pt, 1, 3, 6 mon
-BSP Excretion	Pt, 2, 4, 6 mon
b. Plasma Chemistry	Pt, 1, 2, 4, 6 mon
Feces (Stool Character)	Daily
Physical Examination	Weekly
Appearance/Behavior Changes	Daily
Blood Pressure, Respiration and Heart Rate	Weekly
Body Temp	Weekly
Autopsy	
a. Gross	6 mon
b. Microscopic	1, 6 mon
c. Organ Weights	6 mon

Interim Sacrifice: Two additional male animals receiving Midodrine 0.5 mg/kg were sacrificed after 1 month for histological exam of hearts.

Mortality: All survived.

[redacted]

Table 6-9
NDA 19-815; AMATINE^{R} (Midodrine) Tablets, Roberts Laboratories, Inc.
Subchronic/Chronic Toxicology

Drug Associated Findings:

Clinical Biochemistry
a. Liver Chemistry — No suggestion of induction of liver enzymes.

b. Plasma Chemistry — Sporadic changes in plasma transaminases, not dose-related.

Autopsy

Heart: 0.5 mg/kg-1mo - papillary muscle Lt ventricle, myocardial fibers noted with loss of fibrils and one vacuolated fiber; not considered abnormal.

At highest dose (equivalent to 50X that suggested for daily use in humans), only sporadic degenerated myocardial fiber (endocardium): bands connective tissue missing in myocardium; little rows of fibrocytes threaded like a string of pearls in the myocardium; no sig defects.
1. Myocardium in area papillary muscle of Lt. ventricle. Loss of fibrils and vacuolated fiber = Symptom A.
2. Isolated degenerating myocardial fibers in endocardium = Symptom B.
3. Symptom B + some thickening of endocardium bands connective tissue missing is myocardium as recent or older scars = Symptom C.
4. Symptom B and C - short rows of myofibrils threaded like strings of pearls.
5. Symptom B + short rows myofibrils like pearls.
6. # Dogs changes in myocardium.
7. # Dogs no changes in myocardium.

Duration mon	mg/kg, po	1	2	3	4	5	6	7
	0	0/4	0/4	0/4	0/4	0/4	0/4	0/4
6	.5	0/4	1/4	1/4	0/4	0/4	2/4	2/4
6	2.5	0/4	1/4	0/4	1/4	0/4	2/4	2/4
6	12.5	0/4	0/4	0/4	0/4	4/4	4/4	0/4
1	0.5	1/2	0/2	0/2	0/2	0/2	1/2	1/2

Liver: Small numbers of enlarged cells with subanophil inclusions.

Table 6-10
NDA 19-815; AMATINE^{R} (Midodrine) Tablets, Roberts Laboratories, Inc.
Subchronic/Chronic Toxicology

6 Month Oral Administration of Midodrine in Dog

Testing Facility:

Study Number: 058-23

Study Dates: 12/75-8/76

GLP Compliance: Not done.

Animals: Beagle dog; 8 mon

Mode of Administration of Test Agent: po

Dose Levels: 0, 3, 9, 27 mg/kg/d; 6/sex/group

Observations/Measurements:

Body Weight	weekly
Hematology	Pt, 6, 13, 18, 26 wk
Clinical Biochemistry:	
a. Liver Chemistry	Pt, 6, 13, 18, 26 wk
b. Plasma Chemistry	Pt, 6, 13, 18, 26 wk
Urinalysis	Pt, 6, 13, 18, 26 wk
Feces (Stool Character)	Daily
Physical Examination	Daily
Appearance/Behavior Changes	Daily
Blood Pressure	BP tested 26 wk
Electrocardiogram	Pt 6, 13, 18, 26 wk before and 2 hr drug
Ophthalmology	Day 1, 6, 13, 18, 26 wk
Autopsy	
a. Gross	26 wk
b. Microscopic	26 wk
c. Organ Weights	26 wk

Mortality: All survived.

Table 6-11
NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Subchronic/Chronic Toxicology

Drug Associated Findings:

Body Weight	27 mg/kg sig decrease from wk 1; sig at wk 6; 22.2% decrease wk 26.
Food Intake	27 mg/kg decreased intake from wk 1.
Clinical Biochemistry a. Liver Chemistry	No change.
b. Plasma Chemistry	No change plasma lipids. 20 mg/kg decrease in plasma free fatty acids. 1 mg/kg decrease albumin; smaller decrease after 5 mg/kg and no change after 20 mg/kg. Plasma Na, K, urea not altered.
Opthalmology	3 mg/kg/d: Mild midriasis 6/6, lasted 8-14 h, none after 13-18 wk. 9 mg/kg/d: Medium degree midriasis: time frame as above.
Piloerection	3 mg/kg/d: Mild piloerection 4/6, gone in 14-35 d. 9 mg/kg/d: Time frame as above.
Vomiting	3 mg/kg/d: Vomiting in 5/6 dogs 1 hr post drug. Vomiting was mild, occurring only in the first and second week and lasted for a total of 1 to 5 days. 9 mg/kg/d: Mild vomiting 6/6 dogs.
Blood Pressure	BP-24 hrs after the final administration of midodrine was lowered.
Electrocardiogram	The reaction to the administration of NE was diminished. Sponsor suggests that this reflects an acquired tolerance to sympathomimetics and an alteration of sympathetic tone. Moderate bradycardia (prolonged PQ, QT int). 25 mg/kg: toxic symptoms above more pronounced, mild to moderate sedation; BP further depressed.
Autopsy	Heart: 27 mg/kg/d, po; one dog with large flattened thickening of endocardium with proliferation of fiber-poor connective tissue (high degree fibrosis); no inflammatory infiltrations.
Organ Weights	Decreased wt Ht and spleen after 27 mg/kg; increased wt lung, liver, kidney.

Table
NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Mutagenicity Studies

Salmonella typhimurium Back-Mutation Test (Ames Test):

Reference: 3:4:25: Report #058-25; 5/85;

Methods:

Midodrine Dose: 10, 30, 100, 300, 1000 ug/dish. Each concentration was tested on 3 Petri dishes; two independent tests were done.

Strains: TA 1000 and TA 1535: Sensitive to induction of mutation by base-pair substitution.
TA 98, TA 1537, TA 1538: Used to detect frame-shift mutations.

Substance considered to be a positive mutagen if double the number of spontaneous mutants observed with at least one strain and there was concentration-dependency of this effect. All 5 strains exhibit both nfa (loss of lipopolysaccaride coat) and UV+B mutations. Measurements of rate of reversion in histidine-auxotrophic strains.

Results: No evidence of back-mutation whether or not metabolic activation system (S 9 mix) from rat liver was present.

Mouse Micronucleus Test:

Reference: 3:4:25: Report #058-26; 5/85;

Methods: Detects *in vivo* chromosomal fractures and anomalies of the spindle fibers; acentric fragments and chromosomes cast adrift persist in polychromatic erythrocytes as micronuclei after expulsion of the main nuclei.

Species: Mouse [Ico:OFI (IoPsCAW)]

N: 10/group

Route: iv

Midodrine Dose: 0.25, 2.5, 25 mg/kg 24 hr intervals with 2 doses.

Clinical Observation: Sacrificed 6 hr after second dose; took bone marrow smears (femoral).

Results: Among 10,000 normochromatic and 10,000 polychromatic RBC per group, actually more micronuclei in control animals than in any midodrine group.

NOTE: The treatment used in the control group was not defined. Was it vehicle for midodrine or the "water controls" used in the rat studies described below?

Triethylenemelamine (known mutagen): Greatly increased the incidence of micronuclei.

Normochromatic cells: No change in numbers of micronuclei after any treatment.

Range of values ea mouse: Treated: 0-3/500 Control: 0-4/500

Table
NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Mutagenicity Studies

Rat Micronucleus Test:

Reference: 3:4:26: Report #058-127; 4/71;

Methods:

Species: Rat (CFHB-Wistar)

N: 5/group

Route: Oral, gavage

Midodrine Dose: Two doses at 6.25, 12.5, 25 mg/kg, 24 hr intervals.

Results: Micronucleated Cells/2000 Polychromatic RBC

	Mean	(Range)
water controls	2.2	(1-5)
2 x 6.25 mg/kg	2.7	(1-7)
2 x 12.5 mg/kg	3.2	(2-6)
2 x 25 mg/kg	3.2	(2-6)

Sponsor concludes that "In view of the small number of animals (5/group vs 10/group in the mouse study), and the negative findings in the mice, the slight excess of micronuclei in the treated rats is unlikely to have any signficance."

Mouse Dominant Lethal Test:

Reference: 3:4:26; Report #058-24; 11/76;

Methods: Preliminary toxicology to assess tolerable dose range. Doses of Midodrine administered ranged from 15-400 mg/kg, po. Two days after the end of treatment, the mice were paired for 1 week on a one to one basis with untreated females. Thirteen days after the mid-week pairing, or 14 days after discovery of a copulation plug, the females were killed, and the uteri examined for implantations, viable embryos, and early and late embryonic deaths.

Species: Mouse, CFLP, Male

Midodrine Dose: 15-400 mg/kg

Route: Oral

N: Not given

Results: The results of this study caused sponsor to decide to administer midodrine orally for 5 consecutive days at daily doses of 9, 27, and 81 mg/kg to groups of 20 male mice each.

Table 7-3
NDA 19-815; AMATINE® (Midodrine) Tablets, Roberts Laboratories, Inc.
Mutagenicity Studies

Mouse Dominant Lethal Test:

Reference: 3:4:36; Report #058-24; 11/76;

Methods: 2 d after end of treatment male mice were paired for 1 week on a one to one basis with untreated females; 13 d after midweek pairing or 14 d after discovery of a copulation plug, females sacrificed and uteri examined for implantation, viable embryos and early and late embryonic deaths.

Species: Mouse, CFLP

Midodrine Dose: 9, 27, 81 mg/kg/d

Route: Oral

N: 20/group

Results: Male mice showed suppression of weight gain, some retardation in growth @ 81 mg/kg/day; other doses reduced weight gain only during treatment period of 5 consecutive days.

Higher proportion of nonpregnant females (did not define higher) after first mating period, in non-dose related fashion. In second pairing, all males that failed to induce pregnancy the first time mated successfully.

Implantation rate, litter size, post implantation loss unaffected by treatment of male parent at any dose.

Conclusion: Dominant lethal assay provided no evidence of activity for midodrine.

Table 8
NDA 19-815; AMATINE® (Midodrir [illegible]lets, Roberts Laboratories, Inc.
Studies on Effect of ST 1085 HCl on [illegible]nt Rat and Fetus with Oral Application

	Methods	Results
Reference/Report #	8:4:155;	
Dose	0, 0.1, 1.5, and 20 mg/kg/day, po, by stomach tube from 6th to 15th day of pregnancy	
Control	Solvent (1% aqueous tylose mush/100 gm body wt)	
Strain and Age	Sprague-Dawley, 11-17 weeks	
N	10 M and 10 F/test and control group; M not treated	
Body Weight and Food Consumption	Pt - 109-256 gm; determined daily (AM) to calculate daily dose of substance	-Food consumption @ 20 mg/kg/day reduced during whole treatment period; from 2nd day treatment (8th d preg) weight curve began to flatten; body wt sig reduced compared to controls.
Clinical Observation/ Mortality	behavior pattern, appearance, character of stools daily	-No maternal deaths. -20 mg/kg/day: mild ataxia 20-30 min after drug for 1/2 to 1 1/2 hr from first day of treatment on; animals somewhat shy (more so than prior to drug)
Fertilization	1 F and 1 M put together for 15 hr; if no success in mating, trial repeated with another partner on the following day, up to 14 d altogether; positive proof of spermatoza considered as time of conception (day 0) (Note: 8:162 uses "term" instead of "time".)	
Embroytoxic/Fetotoxic Effects	On d 20 of pregnancy rats were etherized and laparotomised; uterus taken and prepared. Inner organs dissected with macroscopic exam; fetuses taken and: 1. # fetuses counted 2. Sex and viability of fetuses determined (spontaneous respiration and movability) 3. Number of resorption sites determined 4. No. of corpora lutea and position of fetuses in uterus determined 5. Weighed; runts defined as those with weight lower than 70% of the mean weight of the litter 6. Outer appearance of the fetuses inspected, esp. for malformations 7. Number and kind of possible variations (retardations)/ maternal animal 8. Sections, macroscopic exam of position and condition of organs; skeletal system stained with Alizarine by DAWSON method (8:4:163)* 9. Number and weight of placenta 10. # live fetuses/maternal animal 11. # implantations/maternal animal 12. Pre-implantation loss 13. Post-implantation loss	-Sectioning after laparatomy did not show any pathological changes 1. A relatively lower number of fetuses @ 20 mg/kg/day 2. No dead fetuses were found at any doses 3. Resorption rate significantly increased @ 20 mg/kg/day 4. No findings given 5. Sig. reduction body weight @ 20 mg/kg/day and postimplantation loss was increased (35.9% vs 10.5% for controls) 6. Development of fetus was normal 7. Variations reported were retardation of ossification: phalanges, sternebrae; hypoplasia of skull or aplasia of the 13th pair of ribs; dislocation of testicle; Note: text does not clearly indicate that these findings are significant 8:4:174 8. No malformations noted 9. Tendency for wt of placenta to decrease at 20 mg/kg/day 10. No dead fetuses found. # Live fetuses/litter were decreased 11. Not given 12. Not given 13. 35.9% @ 20 mg/kg ST-1085 vs 10.5% with control. 0.1 and 1.5 mg/kg - no effect prenatal development

*Alizarin red S solution is a method used to demonstrate calcium (Putt FA: Manual of Histopathological Staining Methods. John Wiley & Sons, NY, 1972, p 205-206). It has been used to stain the osseous of the skeletons of rat and hamster embryos obtained from pregnant females with B1-hypovitaminosis (Bandazhevskii YI: Arkh Anat Gistol Embriol 87:88-92, 1984); study morphogenesis in parietal bones in mice with ages from 1-81 days (Guihard-Costa AM and Sakka M: Mammalia. 47:257-264, 1983); and identify the loci of ossification in the bones of the thoracic limb of neonatal Harianha calves (Dhingra et al. Indian J Anim Sci. 45:837-842, 1975). Dawson's Alizarin staining method has been used to study the morphogenesis and appearance of ossification centers in the lower end of the developing tibiotarsus procured from chick embryos (Navagir SS and Dubey PN: Z Mikrosk Anat Forsch 90:360-367, 1976). Dawson's method has also been used to study teratogenic effects of chloramphenicol on chick embryos (Cilievici, O, Triaistaru T: Morphol Embryol 24:27-33, 1978).

NDA 19-815; AMATINE^{R} (Midodrine) Tablets, Roberts Laboratories, Inc.
Studies on Effect of ST 1085 HCl on Pregnant Rabbit and Fetus with Oral Application

	Methods	Results
Reference/Report #	8:4:124; 'Report #U58-127; 5/71	
Dose	0.1, 1.5, and 20 mg/kg/day, po, from 6th to 18th day of pregnancy 0.1 mg/kg/day=the lowest dose, about the therapeutic dose recommended for humans; 1.5 mg/kg/day=15-fold the human therapeutic dose; 20 mg/kg/day=the maximum dose tolerated by rabbits and rats in preliminary tests designed to determine a lethal effect in fetus or in the maternal animal	
Control	Solvent, 0.5 ml 1% tylose mush/kg body weight	
Strain and Age	New Zealand White, age not given	
N	10 mated females/dose	
Body Weight and Food Consumption	Daily, always in morning at same time of day. This measurement used for calculating the daily dose of the substance. Daily by re-weighing the quantities of food which were not eaten.	Sig. reduction in food intake @ 20 mg/kg/day, po. The development of weight was inhibited and the body weight was significantly reduced on the 18th day of pregnancy.
Clinical Observation/ Mortality	Daily - maternal behavior patterns, appearance and character of stools.	Maternal rabbits were ataxic @ 20 mg/kg/day shortly after. administration and were slightly sedated for 1-3 hr during the whole duration of treatment.
Embryotoxic/Fetotoxic Effects	On 29 day of pregnancy rabbits were stunned by a blow behind the neck. The uterus was taken and prepared. The inner organs were dissected with macroscopic examination. The fetuses were taken and executed and the following determinations were done:	
	1. Location of corpora lutea and position of fetuses in the uterus. Counting and weighing of fetuses.	At 20 mg/kg/day, po: 1. & 2. Sponsor concluded this dose may be lethal for fetuses since a total of only 14 full grown fetuses found, including 6 runts and 4 dead; body weight of fetuses sig reduced.
	2. Determination of sex and viability of fetuses. Animals considered viable if found alive after a 5 hr stay in the incubator at 37°C (criteria were spontaneous respiration, spontaneous movability).	
	3. Number of resorptions.	3. Resorption rate was considerably increased. Post-implantation loss rate of 88.2% occurred after 20 mg/kg/day, po in comparison with 12.3% in the controls. Concluded (1) that the lowest toxic dose for fetus and maternal animal lies between 1.5 and 20 mg/kg/day when midodrine is given by stomach tube and (2) 20 mg/kg day by stomach tube may be lethal for fetuses.
	4. Fetal inspection for gross, visceral, and skeletal abnormalities	4. Development of fetuses was normal; no malformed fetuses were found at any of doses tested.

LABELING:

Toxicity, Mutagenesis and Fertility (Volume 2, section 2, page 8):

This heading needs to be changed in accordance with regulations on Content and Format for Labeling of Human Prescription Drugs (21 CFR 201.57) to Carcinogenesis, Mutagenesis, Impairment of Fertility, and the following statement included: "No long-term studies in animals have been performed to evaluate carcinogenic potential."

In submission volume 3:4:26, the sponsor concludes that "In view of the small number of animals (5/group vs 10/group in the mouse study), and the negative findings in the mice, the slight excess of micronuclei in the treated rats is unlikely to have any significance." The increase either is or is not significant and this should be determined statistically rather than to state "unlikely to have any significance." If the change is significant, the proposed mutagenesis labeling section (volume 2, section 2, page 9) will have to be rewritten. If the sponsor actually meant that the slight excess of micronuclei in the treated rats is unlikely to have any biological significance, then they should state this.

The dominant lethal assay test should be added to this section so the text 2:2:9 reads "In the Ames test, using 5 strains of Salmonella typhimurium, the micronucleus test in rodents, and the dominant lethal assay test in mice, there was no evidence that midodrine was mutagenic." Finally, the Mutagenesis section should be deleted from page 9 and its revised text incorporated under Carcinogenesis, Mutagenesis, Impairment of Fertility on page 8. The relocated mutagenesis statement should be followed by the following sentence: "Other than the dominant lethal assay in male mice, there have been no studies of the potential of midodrine to adversely affect fertility."

The information currently located under Toxicity, Mutagenesis and Fertility and under Chronic Toxicity needs to be combined and placed in a separate Animal Toxicology section located prior to Carcinogenesis, Mutagenesis, Impairment of Fertility. Extensive editing will be needed to limit text to clearly drug-related pathology of the kind not readily identifiable in clinical trials.

Pregnancy (Volume 2, section 2, page 10):

Proposed statement incorrectly uses Pregnancy Category B code and incorrectly states that there was "no evidence of impaired fertility or harm to the fetus due to midodrine administration." The section should read: Pregnancy Category C: Midodrine has been shown to produce a significant increase in the resorption rate and body weight of rat and rabbit fetuses at maternally toxic doses of 20 mg/kg/day (reduced food intake and body weight gain). There was no evidence of harm to the fetus at doses up to 1.5 mg/kg/day or 2.63 times the maximum recommended human dose of 40 mg/day (0.5714 mg/kg in a 70 kg patient). There are no adequate and well-controlled studies in pregnant women. Midodrine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

[redacted]

Reproduction Studies: This section may now be deleted. The information has been incorporated into our revised Pregnancy section (see our recommendation under Pregnancy above).

On page 7, 4 lines from the bottom, "phenylephrine" is misspelled.

OVERALL SUMMARY AND EVALUATION:

Midodrine, a substituted phenylethanolamide, is an alpha receptor sympathomimetic agonist. The pressor activity resides in the l-isomer of midodrine. Midodrine is a prodrug converted into the active metabolite des-gly-midodrine (ST 1059). The existence of this metabolite is thought to explain why there is a gradual onset of action of midodrine.

However, to evaluate whether midodrine itself has pressor activity, one must compare hemodynamic and pharmacokinetic data obtained after oral and intravenous dosing. In the first 15 min after the po administration of 0.8 mg/kg midodrine, the blood pressure increased and the heart rate fell in 2 of 4 dogs (Fig. 1; 5:40). The blood pressure showed a slight decrease in the other 2 dogs at this time; the heart rate increased in one of these dogs and showed little or no change in one dog. For these four dogs the mean arterial blood pressure increased and the mean heart rate decreased 15 min after 0.8 mg/kg, po midodrine (Fig. 2; 5:41). The mean percentage of unchanged midodrine in the plasma was 40% 15 min after its administration (0.33 M/ml plasma). This value was greater than the plasma value obtained for the metabolite ST 1059 (0.235 M/ml). The midodrine values in the plasma were the highest 15 min after the administration in 3 of the 4 dogs. One dog exhibited a delayed absorption, with the maximum plasma level being reached only after 90 min. The presence of the metabolite of midodrine, ST 1059 in the plasma could be 15 min after the administration of midodrine and was 22% (0.235 M/ml plasma). The maximum increase in blood pressure occurred around 1 hr (between 45-60 min) and coincided with approximately 0.135 M/ml plasma midodrine and 0.65 M/ml plasma ST 1059. The onset of the decrease in the mean heart rate was somewhat delayed with a maximum at 75 min after po administration of midodrine. These data and the intravenous administration of 0.9 mg/kg midodrine to anesthetized dogs (Report #058-01) to produce a 31.4 $\pm$ 16.6 mmHg pressor effect 5 min after its administration suggest that the parent compound may have a pressor effect. However, when the sponsor compared the results obtained after oral dosing in dogs with those obtained after intravenous administration, they concluded that the formation of the metabolite ST 1059 is the cause of the alpha sympathomimetic effect (2:178) since the course of the ST 1059 plasma level is in close temporal correlation with the hemodynamic changes. The sponsor does not conclusively confirm that the early pressor action (15 min) resides primarily in the metabolite product of midodrine.

The sponsor indicates that midodrine acts exclusively to stimulate peripheral alpha sympathomimetic receptors to increase the tone in both arteriolar and venous blood vessels, resulting in an increase in the blood pressure and a decrease in venous pooling. The action of midodrine is thought to be that of a direct acting amine since the pressor effects of norepinephrine and tyramine were not enhanced by midodrine. Thus, the sponsor concluded that the alpha agonist action of midodrine is direct rather than being due to an enhancement of the availability of intrinsic biogenic amines or by elevation of receptor

Figure 1

Abb. 1
Fig. 1

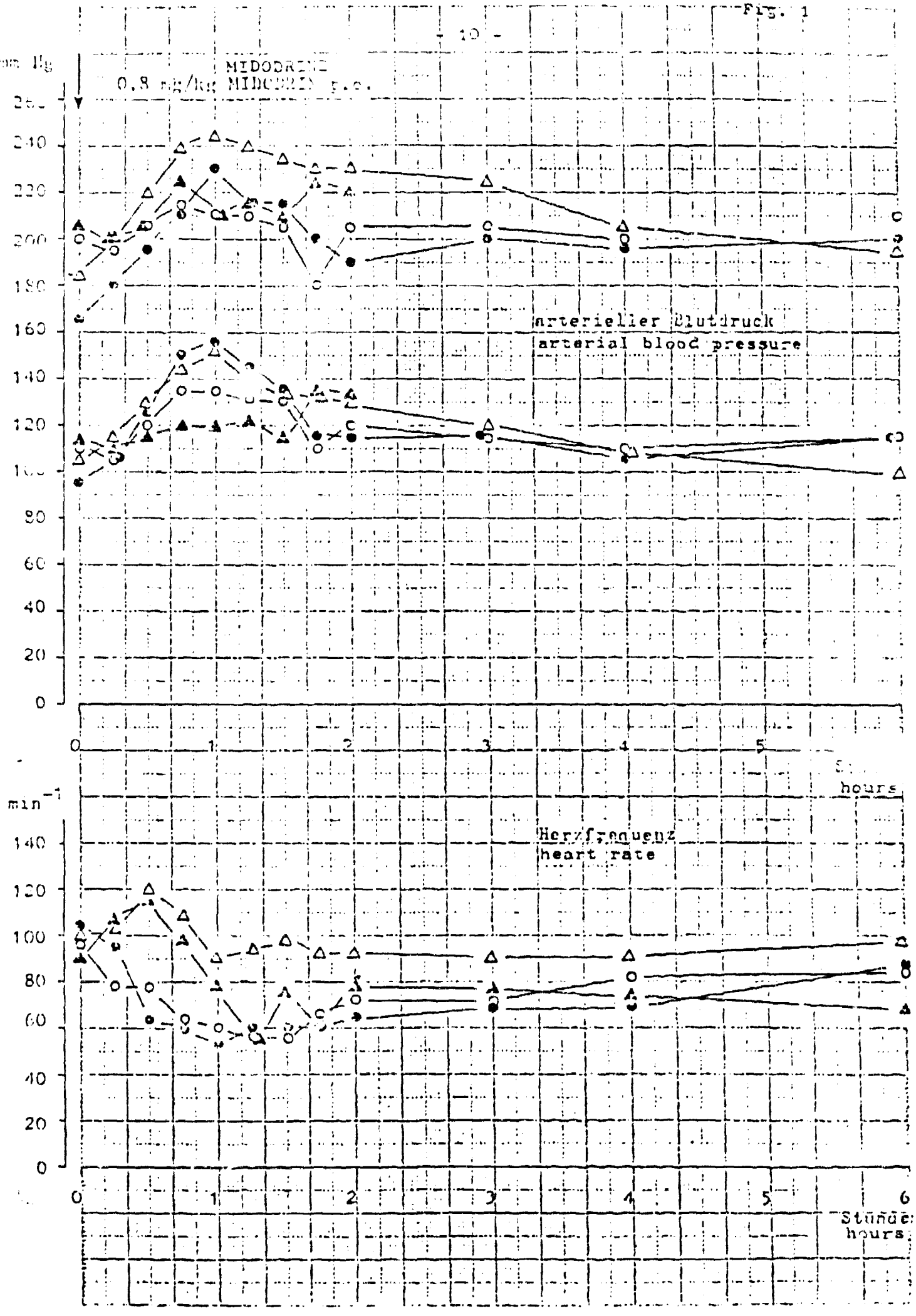
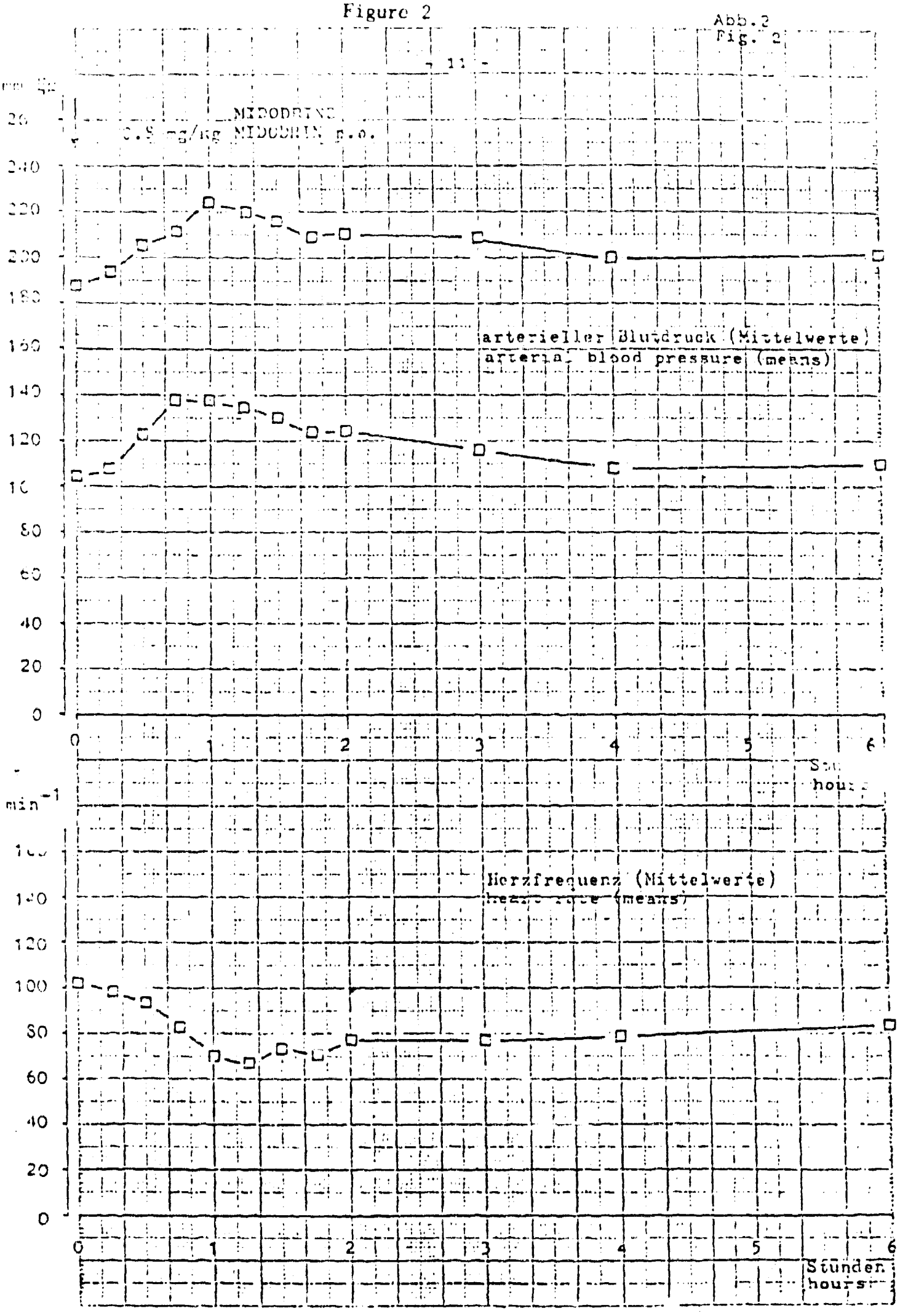


Figure 2



sensitivity. The sponsor suggests that the mechanism of action for midodrine is via its ability to exert an effect to cause a redistribution of blood within the vasculature so that venous pooling in the lower extremities, which occurs upon standing, is substantially reduced. The sponsor notes that it appears that cerebral and renal perfusion are both enhanced even without an increase in the systolic blood pressure.

Midodrine is said to differ from other pharmacologic agents used to treat idiopathic orthostatic hypotension in that it maintains a relatively long pharmacodynamic effect. Thus, in dogs 0.9 mg/kg, iv produced a pressor effect of 31.4 ± 16.6 mmHg within 5 min. Pressure was maintained at this level for 30 min. At minutes 40, 50 and 60, it was 25.9 ± 14.3, 21.4 ± 16.6, and 19.3 ± 18.8 mmHg respectively. Another advantage claimed by the sponsor for midodrine is that it, unlike other alpha sympathomimetic agents, continues to produce a therapeutic effect over time even when administered for a period of years. However, it should be noted that the human data upon which this statement is based differ from the animal data which indicate that tachyphylaxis did develop in the rat.

The sponsor claims that since "midodrine is metabolized to, and exerts its pressor effects through an active metabolite (desglymidodrine), the onset of action is more gradual than other sympathomimetic agents and peak blood levels associated with characteristic alpha receptor agonism (piloerection, urinary hesitancy, "goose-flesh") are minimized" 2:178. Thus, the sponsor states that the use of midodrine avoids the high peak blood levels occurring with phenylephrine or ephedrine and thus its administration is associated with fewer and less severe side effects of the typical alpha agonist, such as piloerection and supine hypertension (2:17). In vol. 2, sec. 2, page 140, it is reported that midodrine is superior to norfenefrine in terms of the percentage of complaints improved. Thus, for midodrine and norfenefrine, respectively, the percentage of complaints improved for the following symptoms were: tendency to collapse 88% vs 47%, dizziness 71% vs 0%, fatigue 38% vs 0%, headache 29% vs 0%, and sleep disturbance 87% vs 73%. Another important way in which midodrine differs from other drugs used to treat orthostatic hypotension is the fact that the clinical use of other sympathomimetic agents such as hydroxyamphetamine and monoamine oxidase inhibitors (MAOI; tranylcypramine) is not completely effective in the treatment of orthostatic hypotension and is associated with side effects reflecting an action in the central nervous system. The active metabolite of midodrine, des-gly-midodrine (ST-1059), is poorly diffusable across the blood brain barrier and thus has fewer side effects attributable to CNS action than hydroxyamphetamine and MAOI agents.

Midodrine also differs from some of the agents used to treat orthostatic hypotension, such as the long acting adrenocortical analogues like DOCA, in that midodrine does not retain salt. Thus, midodrine does not produce side effects, such as the development of congestive heart failure, associated with the increased intravascular volume induced by the use of 9-alpha fluorohydrocortisone (fludrocortisone). The sponsor notes that midodrine used alone improves symptoms as well as or better than fludrocortisone used alone (0.3-1.0 mg daily). The risk of hypokalemia, pulmonary congestion and left ventricular failure is less with the use of midodrine than with high doses of fludrocortisone. Thus, midodrine is of value for patients unable to tolerate the salt and water retaining properties of fludrocortisone.

The sponsor notes that another advantage of the use of midodrine is that clinical studies of idiopathic orthostatic hypotension in patients refractory to multimodal therapy suggest that midodrine may be beneficial in many cases. Also, the sponsor notes that midodrine is useful when administered as one of the pressor components of multimodal therapy. Indeed, midodrine enhances the therapeutic effect of fludrocortisone; the combined effect of both drugs is frequently greater than when either is used alone. The combination of both allows a single AM dose of 0.1 mg fludrocortisone to be used; this minimizes the risk of excessive fluid accumulation and the development of congestive heart failure.

The chore of donning a Jobst garment without assistance may not be possible for patients with advanced orthostatic hypotension disease; the use of midodrine seems to circumvent this problem.

The sponsor states that the indication for the drug is severe idiopathic orthostatic hypotension due to autonomic failure in those individuals who are refractory to other treatments or those who cannot receive optimal antihypotensive treatment with pressor agents or with expanders of the intravascular volume. The sponsor notes that midodrine improves the quality of life of many patients with orthostatic hypotension in as much as patients bed-ridden or those who could not walk unassisted often become ambulatory after therapy and have less need for supportive care (2:2:152).

The recommended starting dose of midodrine is 2.5 mg three times/day (7.5 mg/day). Maximal benefit is noted in most patients with doses at or below 30 mg daily in three or four divided doses (2:2:150). Sponsor recommends the lowest dose which is clinically effective be used. After several days of administration, the dose may be increased above 2.5 mg three times/day (t.i.d.) to determine the effectiveness of this dose. If the clinical response is inadequate and if limiting side effects such as supine hypertension do not occur, the sponsor recommends a gradual escalation, in increments of 2.5 mg t.i.d. (7.5 mg daily), at approximately weekly intervals until the optimal desired clinical response is achieved. The maximum recommended dose is 40 mg/day. Some patients have been treated with larger doses. Sponsor recommends that this be done only with careful clinical monitoring. The sponsor states that discontinuation of midodrine has not been associated with any clinical problems. While chronic dosing is ongoing in a patient, the blood pressure should be monitored at regular intervals while the patient is receiving midodrine, especially if the dose is greater than 30 mg/day since the drug elevates blood pressure.

The pressor profile of midodrine has been characterized in the following nonclinical models: anesthetized rats, dogs and cats; strips of rabbit aorta; isolated perfused rabbit ear preparation; and isolated rat hind limb preparation. Its cardiac actions were studied using: spontaneously beating guinea pig atria; right ventricle strips of rat; isolated electrically stimulated left and right guinea pig atria; guinea pig heart lung preparation; rabbit Langendorff heart preparation; and contractile force and electrocardiographic changes in anesthetized dogs and electrocardiographic changes in unanesthetized standing dogs. The action of midodrine on the

pulmonary circulation was studied in anesthetized dogs while its action on intestinal motility was studied in conscious mice using the charcoal suspension method, in anesthetized cats, and in isolated ileum taken from guinea pigs. The effect of midodrine on liver function was examined in anesthetized rats. Its action on water and electrolyte balance was examined in conscious rats while its effect on urine volume and clearance of p-aminohippuric acid and inulin was studied in anesthetized rats. Anesthetized guinea pigs were used to examine its effect on urinary bladder capacity. Midodrine action on the central and peripheral nervous systems were studied in the mouse using the following tests: chemically and electrically-induced convulsions; pentobarbital sleeping times; spontaneous motor activity after intracerebral injections; hot plate test and phenylquinone writhing test; and interaction with morphine analgesia by using a heated floor model. Five models were used to test the effect of midodrine on the eye: conjunctival hyperemia induced by nicotinic acid and penetration of sulfamethizole in the rabbit eye; the action on the smooth dilator muscle of the mouse pupil; the effect on the intraocular pressures in anesthetized rabbits; and contraction of the nictitating membrane in the anesthetized cat. Midodrine action was examined in in vitro and in vivo rat uteri preparations while its action on the respiratory tract was tested in anesthetized, vagotomized guinea pigs and in anesthetized dogs. Its antiinflammatory action was tested in rats by injecting 1% formalin or 2% carrageenin to induce edema and by the injection of acetic acid into mice to modify the transfer of Evans blue dye from blood into the peritoneal fluid. Metabolic effects were determined by measuring changes in: oxygen consumption in the rat; blood glucose levels in mice, rats, and dogs; free fatty acid levels in the blood of rats and dogs; and free fatty acid production in epididymal adipose tissue obtained from rats. Midodrine action on histamine release from mast cells was studied in vitro and in vivo in rats while its action on monoamine oxidase was examined in liver homogenates prepared from guinea pigs.

As stated by the sponsor in 3:5:27, 28, "the primary alpha-sympathomimetic action of midodrine is manifested as a prolonged pressor action resulting from vasoconstriction. The pressor effect of midodrine (0.075, 0.3, 1.25, 5, and 10 mg/kg, iv) in urethane anesthetized rats was similar to that induced by methoxamine (0.1 mg/kg, iv), norphenylephrine (0.025 and 0.05 mg/kg, iv), etilefrine (0.10, 0.20 mg/kg, iv) and norepinephrine (0.002 mg/kg, iv). Data used to conclude that midodrine exerts its pressor effect via alpha adrenergic stimulation showed that the alpha blocking agent phentolamine decreased the pressor effect of midodrine given intravenously to rats (Report #058-01). The pressor action of midodrine forms the basis of its clinical application for the treatment of orthostatic hypotension. Other cardiovascular actions include a slow fall in heart rate and prolongation of the PQ and QT intervals in the electrocardiograms of dogs, and evidence of reduced cardiac output and force of contraction in isolated rat and guinea pig heart preparations.

Among other pharmacological findings, midriasis was demonstrated in both mice and dogs; this effect was strong in the latter species. Another finding, not unexpected for a sympathomimetic agent, was piloerection; this is a phenomenon which was also prominent in early clinical studies. There was evidence both in rabbit eyes and in mouse peritoneal membranes of an effect of midodrine on capillary permeability, leading to reduced passage of fluids. This was considered also to be part of an antiinflammatory action that was demonstrated in the rat hind paw system.

Midodrine does not appear to exert significant effect on the central nervous system at normal dosages. However, the metabolite ST 1059 did exhibit analgesic action in hot-plate and phenylquinone-writhing tests, and potentiated morphine analgesia, perhaps through effects on morphine metabolism. Among the functions tested on which midodrine did not have major or significant action were intestinal mobility, only inhibited at very high unphysiological levels, pulmonary circulation and respiration, liver function, kidney and urinary bladder function and uterine contraction. In the metabolic area, midodrine only elevated blood glucose levels at high intraperitoneal doses, otherwise acting by the oral route, and as ST 1059, to reduce blood glucose in a manner similar to that of methoxamine. High doses (8 mg/kg) also reduced oxygen consumption. Other changes in the area of lipid metabolism were somewhat inconsistent between species and dosage regimens.

The preclinical toxicologic data suggest that midodrine is well-tolerated at the dosage range which exerts pharmacologic action. The doses producing death in both rodents and dogs are at least 10 to 100 times greater than the doses needed to produce the pressor effect. Fatty infiltration of the liver occurred in female rodents treated subacutely but was not observed with chronic (6-month) administration. This suggests that it resolved during continued treatment. No additional gross or histopathological findings were found in rodents or dogs, beyond scattered foci of myocardial fiber degeneration, known from other sympathomimetics (Simons and Downing: Coronary vasoconstriction and catecholamine cardiomyopathy. Am Heart J 109:297-303, 1985; Gangaly et al. Catecholamine cardiotoxicity in pheochromocytoma. Am Heart J 117:1399-1400, 1989; Haas et al. Pheochromocytoma: catecholamine-mediated electrocardiographic changes mimicking ischemia. Am Heart J 116:1363-1365, 1988).

Indeed, the acute infusion of norepinephrine and isoproterenolol to anesthetized, open-chested dogs has been shown to produce readily identifiable lesions which can be detected within five minutes after initiating catecholamine administration (Eliot, et. al., Pathophysiology of catecholamine-mediated myocardial damage. J. S. Carolina Med. Assoc. 513-518, Nov. 1979). The lesions are related to the dose administered, the redistribution in coronary blood flow, and possibly to the hyperfunctional overdrive. Two different types of lesions induced by norepinephrine or isoproterenol have been noted. The first consists of massive lesions characterized by a "total" myocardial cell disruption of contiguous sarcomeres thought to be due to irreversible hypercontraction. The second lesions are smaller and incorporate myofibrils of only a few sarcomeres adjacent to the intercalated disc. These lesions have been designated "paradiscal" lesions and are generally more numerous than the large lesions. Both lesions induced by norepinephrine and isoproterenol are distributed as individual cells or in small clusters of cells surrounded by "normal" tissue. Although both lesions appear to be randomly distributed throughout the left ventricle, both types are more numerous in the subendocardial layer. Ultrastructural evaluation of the lesions reveal that myofibrillar disruption produce an electron dense region which, for the paradiscal lesions, is evident as a single band adjacent to and parallel to the intercalated disc. Myofilaments in the remainder of the cells return to a normal striation pattern within the space of a few sarcomeres. The total cell lesions exhibit clumping of myofilaments throughout the entire cell, forming a large number of individual transverse "contraction bands". In both types of lesions the mitochondria are swollen and displaced from their normal position. Concomitant with the myocardial

lesions is a decrease in the normal metabolic states, evidenced by a reduction in high-energy phosphates ATP and creatinine phosphate. The disruption of the normal metabolic states, like the lesions, appears to be predominantly located in the subendocardial third of the myocardium.

Death in midodrine treated rodents was commonly associated with convulsions, exophthalmus and dyspnea. LD_{50} studies revealed that the rat was much more sensitive than the mouse (3:89). Chronic studies (6-months) in dogs showed no notable changes in liver function tests or in serum and urine chemistry. The piloerection and midriasis, initially prominent and dose-dependent, gradually disappeared over the course of several weeks of continued treatment. Vomiting was mild, occurring only in the first and second week for a total of 1 to 5 days. The sponsor concludes that the "self-limiting nature of these adverse effects indicates that they are unlikely to be a source of problems in the clinic".

The maximum exposures to midodrine in terms of magnitude and duration for rat and dog were 20 mg/kg/day, po for six months and 27 mg/kg/day, po for six months, respectively.

The maximum doses tolerated in rats and dogs were 5 mg/kg/day (6 months) and 27 mg/kg/day (6 months), respectively.

Three systems were used to evaluate potential mutagenicity of midodrine. These included back-mutation in Salmonella typhimurium, the micronucleus test in mice and rats, and the dominant lethal assay in mice. All three tests gave negative results. A maximum concentration of 1000 ug/dish midodrine was used in the Salmonella back-mutation test. In the micronucleus test, a maximum of 2 doses of 25 mg/kg iv (24 hr dosing interval) was administered to mice while a maximum of 2 doses of 25 mg/kg po (24 hr dosing interval) was given to rats. In the dominant lethal assay, doses of 9, 27, and 81 mg/kg/day, po were given to mice for 14 days.

The effect of midodrine on pregnant rat and fetus after oral doses of 0.1, 1.5, and 20 mg/kg/day by stomach tube from the 6th to 15th day of pregnancy was studied. The effect of these same doses was also studied in pregnant rabbit and fetus by administering midodrine from the 6th to 18th day of pregnancy. After dosing with 20 mg/kg/day, po the maternal rats exhibited mild ataxia 20-30 min after administration of the drug for 1/2 to 1 1/2 hours from the first day of treatment on. Food consumption was reduced during the whole treatment period with the weight curve beginning to flatten from the second day of treatment. Body weight was significantly reduced at the end of the experiments. Dosing with 20 mg/kg/day, po was also associated with a relatively lower number of fetuses, an increased resorption rate, a significant reduction in the body weight of the fetuses, and a decreased weight of the placenta. In the rabbit study, a dose of 20 mg/kg/day, po was associated with ataxia in the maternal rabbits and a significant reduction in food intake. The body weight of the fetuses was significantly reduced and a post-implantation loss rate of 88.2% occurred (vs 12.3% for control animals).

Numerous typos, misspellings or incorrect collation of pages within a given section occur throughout the NDA application. In some cases the typos add humor to the text, but in other cases they alter the findings of the preclinical studies! In all cases the combination of these problems in the writing of the NDA application slowed down the process of the review while

valuable time was spent clarifying the particular section in question. One critical typing error is a deletion in the text (3:4:8 line 10) describing the results of the preclinical studies. Values of the magnitude of midodrine 10 mg induced reduction in heart rate in a guinea pig heart-lung preparation are not included.

When tables 1.1.27 through 1.1.30 (3:40:61-68) were printed out, the top headings of some tables were positioned on the bottom of the previous page, making it harder to read each table. This approach did not save space and merely made the presentation of the results less clear.

Table 1.1.31 (3:4:69) has a double heading of ml/min. This table is confusing to read since the word "before" appears between the numbers 2 and 3 in the first column, 3 and 4 in the second column and over 3 in the third column. The text (3:4:11) fails to indicate whether the 1 and 2 or the 1, 2, and 3rd 30 min collection periods represent values obtained pretest. These typos make it hard to ascertain the effect of midodrine on urine volume and the clearance of para-aminohippuric acid and inulin.

Text 3:4:16 indicates that the data of midodrine action on blood glucose level in rats is found in Table 1.1.44. This is in error since data are found in Table 1.1.46 (3:4:84).

The writing style at some points in this NDA submission could be clearer. For instance, the organization of the text in vol 8:4:pages 172, 173 and 174 is confusing. This section is titled "Study on the Effect of ST 1085/HCl on Pregnant Rat and Fetus with Oral Application". Page 172 contains a table summarizing the teratogenic effects of ST 1085 in rats. Page 173 suddenly describes rabbit results with no previous description of a rabbit study! Page 174 describes the variations noted and one assumes that this is for the rat data, although this is not clear. To add to the confusion, page 198 is a duplicate of 174, and 198 follows a page describing rabbit data. Furthermore, the variations cited on page 174 are not noted in the summary of the results. It is not stated whether these findings were significantly different from the occurrence in the control animals. Data on pages 176 through 186 describe rat data while page 189, 191, 193, 195, etc, are rabbit data. Thus, although report 058-128 (8:4:155) is titled studies on pregnant rats, the report contains rabbit data but the text in the report never describes the findings of the report. A very brief description of the results obtained in the rabbit is included elsewhere in the application 2:2:10 but this does not help the reader when attempting to decipher the findings included in 8:4:173.

Another example where the writing style in this NDA application could be clearer is volume 3, section 4, p. 21, where it is stated that "No gross pathological findings were made in any of the animals." One concludes that a gross pathology study was not done on these animals and hopes that this is not a question of translation from another language stating that the drug induced no pathological changes. This study design should have included a pathology examination since more cardiac and respiratory toxicity data would have been obtained for little additional cost/effort.

The writing style is very confusing on p. 23 in the last line of volume 3 section 4 since the sentence is not completed. It appears to have been placed on the top of page 25. However, the last line of p. 25 is continued on p. 26. Pages 23, 24, and 25 are confusing because of this omission. If the sponsor had proofread this section of the NDA application it would have saved valuable time for the reviewers.

The writing style in vol. 2, sec. 2, p. 136 is vague. It is stated that "... a summary of the between group comparisons of midodrine vs controls on blood pressures, heart rate ...". It would have been better if the sponsor had defined what the word "control" means in this context.

The text on 3:4:11 notes that midodrine had a statistically significant effect on clearance values of inulin and para-aminohippuric acid when compared to predrug values. However, the text does not indicate whether the change was an increase or a decrease. One must spend time searching through numerous numbers found in Table 1.1.31 (3:4:69) to obtain the answer.

Some of the important details of the preclinical studies are not included in the pertinent section of the NDA application. For instance, in the micronucleus test (3:4:25) the treatment used in the mouse control group was not defined. One does not know whether this was the vehicle for midodrine or "the water controls" used in the rat micronucleus test.

A second example of the lack of details in a given section of the application for the preclinical studies is found in the text in 3:4:12. The text never states what route of administration and what doses of midodrine or reserpine were used in the experiments which photographed the spontaneous activity of mice. When reading this section one may speculate that the drugs were given via the intracerebral and intraperitoneal routes, respectively. It is only when one reviews the actual study report contained in another volume of the application that one finds the answer to this question.

A third example of the lack of detail for the preclinical studies is found in Table 1.1.42 (3:4:80). The table does not show the times after the administration of midodrine or ST 1059 when the experimental values were collected. The corresponding text on page 3:4:14 indicates that the minimal bronchoconstrictive action was of short duration but one does not know how "short" the duration actually was and one does not know the "gradual" time required for the onset of the effect. The text on page 15 (3:4) states that higher doses were required perorally to reduce edema formation in rat paws, but it is unclear whether the sentence refers to an action of midodrine, ST 1059, or both. No data for an oral route are given in the corresponding table (3:4:81).

Preclinical details are deleted from page 75 (3:4). Table 1.1.37 does not include the results of the iv and po midodrine groups.

The combination of a typo and a lack of preclinical detail is found four lines from the bottom of page 13 (3:4). Intraocular pressure should be in mmHg, not "nm". This paragraph also fails to state the route of administration for midodrine.

One discrepancy in the details found in the preclinical section of the application deals with the data in Table 1.1.48 (3:4:86). The data indicate that in the pharmacokinetic studies, the urinary recovery (% dose) values of 97.6-99.9 were reported for a 24 h period. This disagrees with the same data given on page 18 of 3:4 which indicate values were reported for a 56 h period.

Another lack of detail provided in this NDA application is apparent when one reads the reference list included in Vol. 2, section 2, p. 18. The list stops with articles published in 1981. One must raise the question of whether any newer references exist? Since midodrine is currently being used in numerous foreign markets, the sponsor should have surveyed the literature published between 1981 and early 1988 (year of submission of NDA) to ascertain whether the continued use of this drug in the foreign clinical setting or in studies conducted within the U.S. has revealed any additional side effects or altered the occurrence and/or the known severity of the side effects.

The preclinical details of the data in Tables 1.1.9 and 1.1.10, volume 3:4:38, 39, could have been more clearly presented. The title of Table 1.1.9 indicates that isoproterenol was administered to anesthetized cats before and after midodrine 1 mg/kg, iv. Data are shown for experimental times 5, 15, and 30 min but it is unclear which values represent the control and post midodrine periods. The heading for table 1.1.10 indicates that isoproterenol was tested before, during and after the infusion of ST 1059. From this title for Table 1.1.10, one could interpret that the values for experimental times 5, 15, and 30 cited in Table 1.1.9 represent the before, during and after periods. However, each table should be labeled clearly enough to allow it to "stand alone" when one is reviewing it. Furthermore, a graph of the parameters included in these tables, with arrows along the x-axis (time) to indicate dosing with isoproterenol and midodrine or ST 1059, would have allowed the reader to quickly ascertain the magnitude and duration of changes in each parameter and to establish that the effect was obtained in these experiments.

The lack of presentation of control blood pressure values in Tables 1.1.9 and 1.1.10 prevents one from ascertaining whether the depth of anesthesia or surgical preparation compromised the animals prior to the start of the experiment. Furthermore, the sponsor does not state criteria used to delete an animal from the study if the blood pressure prior to the start of the experiment was compromised. Although this is important for each experiment done in anesthetized animals, it becomes of the utmost importance for the despinalization experiments (Report #058-01, Table 1.1.6). This technique is surgically difficult and the surgeon must be thorough to induce total denervation while also being fast to prevent excessive blood loss and thereby circumventing the induction of shock in the animal (Lathers and Smith, J Pharmacol Exp Therap. 197:126-134, 1976; Lathers et al, J Clin Pharmacol. 26:515-523, 1986).

The graphs in report #058-31 (Vol 8) justifiably deserve criticism since they correlate the pharmacodynamic effects (pressor and heart rate actions) with the plasma levels of midodrine and its metabolite ST 1059. These data are very important to understand the correlation of these parameters, and yet one cannot read the key (due to poor xerox copies of the graphs) and these data become meaningless. Consequently, the data included in my Table 3-1 only cite values stated in the text of the NDA application.

The evaluation of some of the data in the preclinical pharmacology studies of this NDA application could have been improved. For instance, the data in Table 1.1.2 (Vol. 3, section 4, p. 32) contain no statistical analyses of the blood pressure responses obtained in urethane anesthetized rats. Doses of midodrine 1.25 and 5 mg produced an increase in blood pressure that was probably not statistically significant. However, it is not clear whether doses of 20 and 62 mg produced effects that were significantly different from each other or from the effects of the lower doses.

The statistical analyses in Vol. 2, section 2, p. 55 are not correct. Data obtained in three experimental groups, i.e., tyramine, ST 1059, and midodrine, are compared. This requires a multiple analysis of variance and not a t-test. Furthermore, data with unequal n's necessitate the use of an unpaired t-test.

The sponsor's statistics indicate that the activity time (sec) for animals to leave a designated circle was 7 $\pm$ 1.79 baseline and increased to 42.83 $\pm$ 69.46 and 78.67 $\pm$ 81.64 and 93.67 $\pm$ 94.67 sec at 15, 30 and 60 min, respectively, and that only the last two values are sig different (Table 1.1.35; 3:4:73). It is hard to understand why the 15 min value is not also significant since all three experimental values have large standard errors. The application does not offer an explanation.

Volume 3, section 3, p. 34 indicates that the doses of midodrine (5-50 mg/kg) given via different routes (im, sc, ip, id) produced increases in the blood pressure of the magnitude between 6-40 mmHg. These data were obtained in anesthetized rats. One must question whether the magnitude would have been greater for each dose of drug given if administered to unanesthetized animals. The latter situation is more analagous to the intended clinical use in man.

Another example of sections in the application where evaluation of the preclinical data could have been improved is 6:4:35. It is incorrectly stated in the first line describing pathological changes induced in the hearts of rats after 6 mon of midodrine 1 mg/kg, po, that 4 of 20 animals had changes. In the subsequent sentences pathological changes are described for a total of 5 rats. The same error appears in the summary of data from this group on page 36. The method section for the oral dose 6 month study states that 10 M, 10 F were used for each dose. In some groups (5, 20 mg/kg), data are reported for fewer animals but in the summary section of myocardial alterations the change in N's is not noted and thus at first glance the myocardial effects seem to be of a lower incidence than they actually were. Page 42 states that inconsiderable changes were found in the hearts of other animals. The wording does not indicate how many animals "other" includes. If the final N in this group was 20, as indicated in the methods section, then "other" would be 2.

In parts of the application, the sponsor cites a scientific finding in the animal experiments but fails to fully develop the interpretation of the finding. For instance, the data in Table 1.1.9 (3:4:38) show that midodrine 1 mg/kg, iv given to anesthetized cats did not significantly alter the effect of isoproterenol on femoral blood flow while ST 1059 did (Table 1.1.9, p. 39). The text on page 5 of vol. 3, section 4 fails to mention this finding.

A second example of where the sponsor failed to fully develop the interpretations of the results reported is in the section of the application indicating that animal studies reported a negative interaction with the concomitant use of midodrine and cardiac glycosides. One must question "which glycoside" since not all glycosides exhibit exactly the same effect and since they differ in their pharmacokinetic properties (J. Clinical Pharmacology 25:501-506, 1985). One would hope that digoxin was the pharmacologic agent studied since this is the glycoside most commonly used in the United States.

A third example of where the sponsor failed to fully develop the interpretation of preclinical results is in the study demonstrating that propranolol increased the pressor action of midodrine. No scientific "mechanistic" interpretation of this finding is offered.

A fourth example of where the sponsor fails to fully develop the interpretation of the preclinical results is in the text on 3:4:13. They conclude that the analgesic actions of midodrine in the mouse may be due to an alteration of morphine metabolism rather than to an action on the central nervous system. Absolutely no scientific rationale or data are presented to support this proposed mechanism of action to alter morphine metabolism.

A fifth example of the sponsor citing a preclinical finding but failing to fully develop the interpretation of the finding is revealed in the preclinical data cited for rodents. Four days of dosing with midodrine diminished the effect of an acute injection of midodrine. One might question whether this type of tachyphylaxis would occur in humans requiring prolonged dosing with midodrine. However, the application notes that humans dosed with midodrine maintain a therapeutic effect even when it is administered over a period of years.

A sixth example of where the sponsor failed to fully develop the interpretation of the preclinical results is in 3:4:70, 71. Tables 1.1.32 and 1.1.33 are titled "Effect of Midodrine and ST 1059 on Chemical and Electroshock-Induced Spasms". The text indicates that the criteria for protection against the chemical-induced spasms was whether or not the mice were still alive at 30 min. The sponsor would have gained additional valuable information if they had quantified the time to the onset of the seizure activity, duration of seizure activity, the amount and duration of interictal activity, and the actual times to death. These changes are often evaluated in studies utilizing chemically-induced seizures (Epilepsia 23:633-648, 1982; Ann Emergency Med 16:156-159, 1987; Journal Clinical Pharmacology 28:1106-1111, 1988). These measurements would have indicated whether the amount of time required for formation of the active metabolite was allowed by the experimental design and whether the metabolite ST 1059 exhibits any action on the central nervous system. An alternate experimental design would have been to pretreat the mice with midodrine and to allow sufficient time for the active metabolite to be formed before inducing convulsions with chemicals or with electroshock.

In parts of the application the sponsor interprets data from animal studies in a fairly rigid manner and either draws an incorrect conclusion or fails to acknowledge that there may be alternate explanations for the finding. Volume 3:4:2 states that midodrine administered via the im or sc routes exhibited "little activity" but the data in Table 1:1:5 on page 34 show that 25 mg/kg, im in 6 rats caused a mean rise of 22 mmHg in the blood pressure while 50 mg/kg, sc increased the mean pressure by 31 mmHg. This is not "little activity." However, the standard errors for both means are very large, i.e., 22 $\pm$ 14 and 31 $\pm$ 22 mmHg. The sponsor does not offer an explanation for why this type of variability occurred. The text in volume 3:4:2 also states that although the im and sc routes of administration exhibited little effect, there was a dose-related increase in the blood pressure when midodrine was given via intraduodenal administration. The magnitude of the increase associated with this route was similar to that noted after 25 mg/kg, im or 50 mg/kg, sc although less midodrine was required, i.e., id doses of 2.5, 5, 10, and 20 mg/kg induced mean increases in the blood pressure of 6 $\pm$ 5, 13 $\pm$ 10, 23 $\pm$ 13 and 26 $\pm$ 14 mmHg, respectively. The investigators only examined two doses for the im (10 and 25 mg/kg) and sc (25 and 50 mg/kg); this does not constitute a dose-response curve.

Quantitative data are not given for the effects of reserpine pretreatment (0.1 mg/kg, ip) in the experiments designed to evaluate the intracerebroventricular action of midodrine, ST 1059, or dopamine. Only qualititative results are given on page 12 (3:4) and no scientific interpretation is offered for the effect of reserpine in these experiments. This is of importance since reserpine does exert an action in the central nervous system. This section does not indicate how long the investigator waited after dosing with reserpine.

The text of the application 3:4:2 states that the pressor effect of midodrine is similar in extent to that produced by agonists such as methoxamine, etilefrine, norepinephrine, and norphenylephrine. The text states that midodrine differs from other agonists in that it produces an elevated blood pressure which is notably prolonged. The reader is referred to Table 1.1.2 on page 31 but the data in this table are for midodrine only and do not include the comparison data necessary to support the sponsor's statement. The sponsor must have the data since the studies cited in Table 1.1.1 on page 30 would have provided the duration information. One wonders why the duration data were not included in this section of the report. Norepinephrine 5 ug/kg, iv has been shown in the cat anesthetized with alpha chloralose to produce a pressor effect of approximately 20-40 mmHg. This response has a duration of approximately 1-2 minutes and is definitely completed by three minutes (Kelliher and Roberts, Europ J Pharm 20:243-247, 1972). Midodrine 1.25 mg/kg iv produced a pressor effect of 20 $\pm$ 6 mmHg with the time to the maximum value being 8.35 $\pm$ 3.5 min. Midodrine 5 mg/kg exhibited a pressor effect of 48 $\pm$ 14 mmHg with the time required to reach this value determined to be 16.8 $\pm$ 10.9 min. Thus, a comparison of the data published in Europ J Pharm and the midodrine data suggests that the magnitude of the pressor effect induced by midodrine is similar to that of norepinephrine and that its duration is longer than that of norepinephrine.

The experimental methods were not always appropriate. In particular, animal caging for dogs involved in the 6 month dosing study of 0.5, 2.5 and 12.5 mg/kg/d, po, midodrine was not appropriate since one male control dog was killed during a fight at night (6:4:181; Report #058-22).

The results of the animal experimental designs done to determine the mechanism of action of midodrine are at times confusing and at best fail to provide evidence to support the details of a definitive mechanism of action. The sponsor concludes that midodrine is a prodrug for the active metabolite ST 1059 produced by a proeolytic process, that the metabolite is a peripherally, direct acting alpha-sympathomimetic agonist, and that ST 1059 does not act by releasing catecholamines. The sponsor concludes from the animal studies that midodrine acts "exclusively" on peripheral alpha sympathetic receptors (3:4:32) via a direct action since the pressor action of norepinephrine and tyramine were unaltered by midodrine. Cocaine was used in the rat studies to prevent the reuptake of catecholamines into presynaptic neurons. Treatment with cocaine has no effect on a direct acting sympathomimetic agent. The sponsor concluded that midodrine is direct acting even though cocaine pretreatment significantly increased the pressor effect of ST 1059 (2:2:24). The sponsor does not resolve these conflicting data with scientific evidence or by "verbal reasoning." One could interpret these findings to indicate that the active metabolite ST 1059 is not a "pure" direct acting sympathomimetic agent.

Sympathomimetic amines such as tyramine will displace norepinephrine from storage vesicles after gaining access to the nerve terminal by active uptake. The displaced norepinephrine diffuses out of the nerve terminal to interact with NE receptors to produce a pressor effect; this action has been designated the "indirect" action of tyramine. Cocaine inhibits the plasma membrane uptake mechanism for norepinephrine and thus will block the action of an indirect acting amine. Cocaine will potentiate the action of norepinephrine, epinephrine and dopamine. It is generally concluded that it will not affect a direct acting amine such as phenylephrine [Weiner and Taylor. Chapt 4, p. 83. Drugs Acting at Synaptic and Neuroeffector Junctional Sites. In Goodman and Gilman's The Pharmacological Basis of Therapeutics. Ed. A.G. Gilman, L.S. Goodman, T.W. Rall, and F. Murad. Macmillan Publ. Co., New York, 1985] although one study has suggested that cocaine will potentiate the action of phenylephrine (Bri J Pharmacol 35:428, 1969). Thus, if midodrine was exhibiting an action like that of the indirect amine and was taken up into the adrenergic nerve terminal, pretreatment with cocaine would prevent midodrine from being taken up into the storage vesicle and would prevent the pressor effect exerted by midodrine since the midodrine molecules would no longer be taken up into the storage vesicles to release the displaced norepinephrine. Cocaine 5 mg/kg, iv significantly reduced the pressor effect of tyramine from 31.8 $\pm$ 9.6 to 22 $\pm$ 9.4 mmHg, significantly increased the pressor effect of ST 1059 from 41.2 $\pm$ 7.8 to 50.2 $\pm$ 8.8 mmHg but did not alter the pressor effect of midodrine (45.4 $\pm$ 10.6 vs 39.2 $\pm$ 14.3 mmHg). One must question whether this magnitude of a pressor effect is biologically significant even if the numerical values are statistically significant (3:4:2, 33). One also wonders if the most appropriate dose of cocaine and experimental design was selected in this study included in the NDA application. The mean increase reported in this NDA application when ST 1059 was administered after cocaine pretreatment is only 9 mmHg. In the anesthetized cat, cocaine produces a large

potentiation of the pressor effect exhibited by exogenously infused NE. Indeed, as presented by Jain et al Fed Proc 46:402, 1987, a study in cats anesthetized with alpha-chloralose showed that a dose of 0.25 mg/kg, iv cocaine increased systolic and diastolic blood pressures by 33 $\pm$ 11 and 31 $\pm$ 7 mmHg, respectively. Doses of 0.5 and 1 mg/kg, iv also increased the blood pressure and enhanced the blood pressure response to iv norepinephrine. All effects were greater after a 4 mg/kg iv dose of cocaine but respiratory arrest and ventricular arrhythmias were observed in some animals. Higher doses did not alter the blood pressure and attenuated the blood pressure responses to norepinephrine. The experimental design in this application should have included two additional experimental groups of animals. Both should have been pretreated with cocaine and then given exogenous norepinephrine. One of the two groups should have also been given ST 1059 to determine whether it modified the cocaine-induced potentiation of the pressor effect exhibited after exogenously infused norepinephrine. In addition to the above comments about the design of the experiments using cocaine, the statistical analyses of the study in the NDA application are not appropriate since a multiple analysis of variance should have been done to compare the effect of three drugs. One must also question what kind of an increase in blood pressure would the vehicle for ST 1059 have produced? The study design for all data obtained in the experiments cited in Tables 1.15 and 1.1.1, 1.1.2, 1.13 and 1.14 should have included animal groups receiving only the vehicle administered via the im, sc, ip and id routes.

Although the sponsor concludes that midodrine is a peripherally, direct acting agonist of the alpha sympathetic receptors, the sponsor does not indicate which subtype of alpha receptor(s) they think is (are) being stimulated by midodrine. Indeed, the entire application does not mention the existence of subclassifications of alpha receptors.

In addition to the data suggesting that midodrine acts exclusively to stimulate peripheral alpha receptors, there are data contained in the report suggesting that midodrine may also have additional mechanisms of action. One additional mechanism may involve an action on beta receptors, but when one reviews all of the preclinical data in the application, it is unclear whether midodrine acts to 1. block the beta receptors or 2. stimulate the beta receptors or 3. whether it possesses the capability of doing both or 4. whether it exhibits no effect on beta receptors. Both midodrine and ST 1059 displaced to the right the concentration response curve for isoproterenol when it was tested in a spontaneously beating guinea pig atria preparation (3:4:5). Midodrine exhibited only a slight beta receptor blocking action (lower pA_2) and antagonism for isoproterenol. The sponsor states that depending on the residence time on the receptor, an agonist may also exhibit blocking properties. However, in addition to the data contained in the report suggesting that midodrine may possess beta blocking action, there are studies using the anesthetized cat which indicate that it lacks this action. The data showed that midodrine did not attenuate the isoproterenol-induced increases in heart rate and femoral blood flow. The sponsor merely acknowledges this discrepancy by stating that one experimental design utilized an <u>in vitro</u> preparation while the other used an <u>in vivo</u> preparation.

In addition to the above evidence suggesting that midodrine may block beta receptors only in an in vitro preparation, supporting results for this concept were also obtained in the in vivo rat preparation. Blockade of beta receptors with propranolol 5 mg/kg, iv, in rats increased the pressor effect of midodrine. The authors never explore what these data suggest. One interpretation could be that midodrine exhibits an action to both block beta receptors and to stimulate alpha receptors and that blockade of the beta receptors by propranolol prior to the administration of midodrine would make available more molecules of midodrine to stimulate the alpha receptors.

As if the data on beta receptor interaction were not confusing enough, the NDA application also contains data to support the fact that midodrine does not block beta receptors. Isoproterenol (0.4 ug/kg, iv) was used in rats to demonstrate a mean systolic and diastolic depressor effect of 36.83 ± 21.75 and 49.25 ± 21.42 mmHg. Because midodrine 1 mg/kg, iv, or ST 1059 25 ug/kg/min, iv for 10 min, failed to alter the effect of isoproterenolol, it was concluded that these entities do not block beta receptors. One could argue that the use of this dose of isoproterenolol produced a maximum depressor effect and that if the experimental design had used lower threshold doses of isoproterenolol, midodrine or ST 1059 would have been able to exert an action on beta receptors. It may be that different doses of midodrine are capable of both stimulating and blocking beta receptors, depending on the dose used.

Reserpine depletes catecholamine stores and thus if a drug normally acts on beta receptors by releasing catecholamines, its action will not occur in a reserpinized animal. The sponsor presents evidence that reserpine pretreatment did not enhance the pressor effects of midodrine and again concludes that midodrine is not acting on beta receptors. If midodrine acts on beta receptors and if removal of the neurotransmitter norepinephrine was accomplished by pretreatment with reserpine, a supersensitive response due to upregulation of the beta receptors would have resulted in an increased pressor response induced by midodrine. In the anesthetized rat studies, reserpine 5 mg/kg was administered ip 16 hr before the administration of midodrine. Because no enhancement of the pressor effect occurred, it was concluded that these data support an alpha pressor effect of midodrine. Several comments are pertinent. First, the investigators did not do plasma and tissue catecholamine assays to verify that the reserpine did indeed deplete the catecholamines. Without this supporting evidence, one must question their conclusion about the action of midodrine. Secondly, studies have shown that the action of reserpine at a dose of 5 mg/kg, ip route requires 24 hours or longer to deplete catecholamines in anesthetized dogs and cats. Indeed, the following doses and treatment times have been utilized in studies using reserpine pretreatment in anesthetized animals: cat at 5 mg/kg, ip 24-30 hr prior (Ciofalo et al, Bri J. Pharmacol Chemotherapy 30:143-154, 1967); cat 5 mg/kg, ip, 20-36 hr prior (Levitt and Roberts Clin Res 19:622-631, 1966; J. Pharmacol Exp Therap. 156:159-165, 1966); cat 5 mg/kg, ip 24 hr prior (Lathers et al, Europ J. Pharmacol. 76:371-379, 1981); dog 10 ug/kg, im daily for 6 days prior, or 2.5 mg/kg, im 24 hr prior (Takagi et al, Am J Cardiol. 15:203-205, 1965); and dog 0.01, 0.1, or 1 mg/kg, iv 24 hr prior (Boyajy and Nash, J Pharmacol Exp Therap, 148:193-201, 1965). The study included in this NDA application only waited 16 hr after reserpine 5 mg/kg, ip to administer midodrine; this may have been an insufficient time period for reserpinazation. Inadequate time to allow reserpine to deplete catecholamine stores would negate the sponsor's conclusion that reserpine did not enhance the pressor effect of midodrine.

The sponsor concludes that midodrine is not acting on beta receptors because reserpine pretreatment did not enhance its pressor effects. In making this conclusion, the sponsor fails to discuss data suggesting that reserpine, in addition to its action to deplete catecholamines, has other actions. These include modifications of the ionic milieu by reducing potassium, calcium, and magnesium levels of arterial tissue (Romatsu et al, Can J Physiol Pharmacol. 55:206-211, 1977) and altering the utilization of calcium (Meisher, et al. Life Sciences, 24:473-480, 1979).

In all of the discussions of whether midodrine does or does not act on beta receptors, the sponsor does not acknowledge that more than one type of beta receptor exists.

Doses of imipramine of 0.3 and 3 mg/kg, iv were used in rats to potentiate the effect of biogenic amines by preventing the reuptake of catecholamines into presynaptic neurons. Imipramine was given 15 min prior to iv midodrine or ST 1059. In these experiments, the combination of imipramine and midodrine decreased the pressor effect of midodrine; the sponsor does not offer any explanation for the decreased pressor effect. They could have mentioned that imipramine has been shown to reduce catecholamine secretion from adrenal glands obtained from rats (Gascon and Lelurier: Can J Physiol Pharmacol 53:1198-1199, 1975). They did conclude that since no potentiation occurred, the action of midodrine is not mediated through the release of endogenous neuronal catecholamines. The doses of imipramine and the pretreatment time intervals used were appropriate (Lathers and Lipka: J Clin Pharmacol. 27:1-14, 1987).

The sponsor noted that "despinalization" increased the pressor effect of midodrine and concluded that this drug has a "pure" peripheral site of action. This explanation overlooks the possibility that midodrine may be stimulating inhibitory sites within the central nervous system while simultaneously acting in the periphery. The elimination of neural control between the central and peripheral nervous systems would eliminate any action of midodrine to stimulate a central inhibitory site and this might allow an increased peripheral pressor response.

Although the sponsor concludes that because despinalization increased the effect of midodrine this is evidence of a purely peripheral site of action, alternate explanations could be offered. There are areas in the central nervous system, such as the area postrema, that are outside the blood brain barrier yet still constitute a central site for drug action (Somberg and Smith: Science 204:321-323, 1979). In addition, spinal transection at the C_1 level eliminates the central brain sympathetic nervous system but sympathetic spinal afferent activity, also considered to be central, would have still been functional and thus could have constituted a site of action for midodrine and/or its metabolite (Weaver et al. Am J. Physiol. 245:R345-R352, 1983; Carp and Anderson, J. Pharmacol. Exp. Therap. 216:270-274, 1980).

Definitive experiments to prove whether midodrine is or is not acting within the central nervous system would involve stereotaxic placement of electrodes into discrete brain areas such as the autonomic areas of the hypothalamus (Weaver et al. J. Pharmacol. Exp. Therap. 197:1-9, 1976; Pace and Gillis: J Pharmacol Exp Therap 99:583-600, 1976) or the hippocampus (Tumer et al. Epilepsia 26:250, 1985) or in the brainstem (DiMicco et al. Science, 204:1106-1109, 1979; Gillis et al. Brain Res Bull (Supple 2) 5:303-315, 1980) done in conjunction with experiments using intracerebroventricular injections (Lathers et al. Life Sciences, 43:2287-2298, 1988). The sponsor did do experiments in which midodrine or ST 1059 were injected into the vertebral artery and compared with iv injections in urethane/chloralose anesthetized cats. No enhancement of the pressor effect occurred and it was concluded that these data support the observation that despinalization in cats had no effect on the pressor action of midodrine and thus the drug acts solely in the periphery. The data given do not include the magnitude of the increase in systolic and diastolic blood pressure associated with the intravertebral injection of the vehicle. Furthermore, the data for the intravertebral injection of ST 1059 (Table 1.1.12, 3:4:41) are incorrect in that the difference in the systolic pressure of the carotid artery in one cat was 25 mmHg (192-167); the table states the difference is 5 mmHg. This would change the mean difference. It is hard to understand why the sponsor concludes there is no central effect of ST 1059 when the intravertebral administration produced a systolic pressor effect of 25, 16, 8, 46, 58, 19, 30, 39, and 19 mmHg in eight animals. One additional animal exhibited a negative effect but this was also true of the intravenous action of the drug. It is true that the magnitude of the systolic pressor effect following the intravenous administration was greater than after the intravertebral route, i.e., 69, 93, 62, 52, 56, 71, 105, and 52 mmHg. Midodrine also exhibited a pressor effect when given via the intravertebral route, again suggestive of a central site of action.

Chronic dosing studies in dogs were associated with microscopic necrotic foci in the myocardium. This was thought to be due to the increased myocardial work required to maintain cardiac output in the face of a greater cardiac afterload. An increased oxygen demand may produce myocardial hypoxia which may result in localized cell death. The sponsors indicate that this reaction is believed to be a nonspecific reaction in the canine myocardium to agents which substantially increase cardiac afterload, such as other alpha sympathomimetic agents (2:2:153). However, the clinical adverse effects reported for midodrine included reports of chest pain, "cardiac awareness", and the occurrence of arrhythmias. These symptoms observed in humans cause one to question whether the pathologic cardiac changes observed in dogs are a nonspecific reaction occurring only in the canine myocardium. Other data in the application indicate that similar changes do occur in rat. If they had repeated this preclinical experiment using species other than the dog or rat (see below), they would have answered this question. Additional animal studies could also be done to further explore the adverse cardiac effects of midodrine. For instance, an acute permanent occlusion of the left anterior descending coronary artery of anesthetized cats or dogs (J Pharmacol Exp Therap. 203:467-479, 1977; Circulation 57:1058-1065, 1978; J Clinical Pharmacol 27:582-592, 1987) could be done to determine whether midodrine alone, as a pretreatment before occlusion, or as a treatment after occlusion, modifies serum creatinine levels, alters infarct size, or modifies the occurrence of premature ventricular beats and/or the mean times to arrhythmia or death.

Although the sponsor states that the myocardial changes were a nonspecific reaction in the canine myocardium, the data in the application suggest that nonspecific myocardial changes were also noted in rats dosed for 10 or 20 days. Changes in the heart were characteristic of those produced by sympathomimetic agents, i.e., increased heart weight and focal degeneration of myocardial fibers. Changes noted after midodrine were foci of degeneration in myocardial fibers with connective tissue and accumulation of increased numbers of round cells. These changes were not dose dependent and were not particularly pronounced. Thus, the data indicate myocardial changes attributed to the drug occurring in two different species. The sponsor does not make this comparison and thus deemphasizes the cardiotoxic action of the drug.

To predict what might occur in humans, it would have been of interest to know the agonal death events when acute toxicity doses of midodrine were administered to dogs or cats. One wonders whether the animals would have died primarily as a consequence of cardiac arrhythmias or respiratory arrest. One could question whether the dose range examined in the acute toxicity studies done in dogs was wide enough since only 1 of 8 female dogs died after 126 and 159 mg/kg, po and only 1 of 8 male dogs died after 159 mg/kg, po. It would also have been of interest to know the agonal death events and time of occurrence of these events if larger oral doses had been used in the subchronic toxicity dog studies conducted for one or six months.

Although one of the clinical adverse effects reported for midodrine included chest pain, the sponsor does not comment on the origin of this pain nor do they measure changes in serum creatinine levels. Some individuals reported a "cardiac awareness" (2:2:149); this descriptive symptom is vague and the sponsor makes no attempt to explain its cause. It would be of interest to note whether a search of the recent literature (1981 on) revealed reports of any serious cardiac problems associated with the use of midodrine. This would be important since the sponsor notes that in one patient with preexisting atrial arrhythmias, midodrine increased ectopy and the ventricular response rate; the effect was transient and remitted when the drug was discontinued (2:2:146). In the report of side effects in a study by Dr. Schirger (2:2:146), arrhythmias were reported in 5 patients but the sponsor does not indicate what type(s) of arrhythmia(s) were detected.

The sponsor indicates that midodrine appears to enhance cerebral perfusion even without an increase in systolic blood pressure in clinical studies. This action could be verified using a transcranial doppler flow probe (Frey et al. Aviat. Space Environ. Med 60:A23, 1989). They do not offer an explanation of how this "selective" perfusion could occur. This reviewer suggests one possibility may be that perhaps there is a greater regional concentration of receptors stimulated by midodrine in the cerebral circulation when compared with the peripheral vasculature. One might question whether these data suggest a central site of action for midodrine and/or for its metabolite.

The data in volume 2, section 2, page 167 could have been deciphered faster if it had been presented in a graph form [See Figures 3 and 4 this report (Table XII 2:2:167)].

The design of the clinical studies could have been modified to provide additional data. In the human plasma bioavailability study in which a single oral dose was given and urine samples were collected, urine collections were done between 0-2, 2-4, 4-8, and 8-12 hr post dosing. A range of 2 to 4 hours to collect urines is very wide; it would have been better if urine samples had been collected within a narrower time unit for each sample collected from all subjects. This would have allowed them to ascertain whether any variability detected was due to a variation in the capability of individuals to pharmacokinetically handle the drug rather than to confuse the answer with the possibility that the difference was due to ongoing metabolism/excretion during the window of 2 to 4 hours.

One must question whether unwanted drug interactions may occur when midodrine is prescribed simultaneously with other drugs excreted via the kidneys in an ionized form in an alkaline pH. After dosing with three oral doses of 5.0 mg every 4 hours the mean urinary pH values for control, 0-4, 4-8, 8-12, and 12-24 hr were 5.5, 5.7, 5.8, 6.1, and 5.6, respectively. However, the magnitude of the change in some individuals was much greater. For the six subjects, the following values indicate the control pH, the maximum increase in pH, and the time at which this pH was detected, respectively: 5.4, 6.4, 8-12 h; 5.2, 5.8, 8-12 h; 5.5, 7, 0-4 h; 6.2, 7, 8-12 h; 5.2, 5.5, 8-12 h; and 5.2, 5.8, 8-12 h. One must question whether an increase in the pH of the urine of 1 or 1.5 pH (log) units in 2 of 6 subjects is significant enough to raise concerns in the clinical arena. In any event, all subjects exhibited some degree of alkalinization of the urine. This may change the renal excretion of other drugs given concomitantly with midodrine by altering the amount of drug in the ionized form. This, of course, raises the potential for unwanted drug interactions. A survey of the current midodrine literature and/or studies designed to answer this question would determine whether this potential drug interaction has clinical significance.

In a single iv dose study to evaluate midodrine metabolites in humans (Report 058-39), 2 grams of a solution of d,l-^{3}H-ST 1085/HCl in 0.2% aqueous NaCl were administered. The appropriate control for pressor studies would mandate the administration of just the vehicle. This is most important since Bungo et al (Aviat. Space Environ. Med 56:985-990, 1985) have demonstrated that administration of salt and water equivalent to isotonic saline is an appropriate countermeasure to orthostatic hypotension. This type of control is essential to determine whether the drug produces a pressor effect greater than the isotonic saline used as a vehicle.

Another example of where the clinical experimental design could have been improved is found in this same study (058-39). The test person was treated as an outpatient, so the urine could be frozen immediately after the collection only within the period 0-8 h. If the subject had been institutionalized they could have done a 24 or a 48 h study and would have gained additional pharmacokinetic data.

Figure 3: Effect of Midodrine on Supine and Standing Mean Blood Pressure Values

Figure 4: Effect of Midodrine on Supine and Standing Mean Heart Rate Values

Just as the statistical analyses were not always appropriate in the preclinical studies, a similar statement may be made for some of the clinical studies. Volume 9, section 5, page 158 states that although the experiment was designed as a 3 way crossover study, only two formulations were compared and tested statistically at a time, since only three formulations were being investigated. The mean of the individual bioavailability coefficients based on AUC and the 95% confidence limits based on the related t-test for quotients were calculated. This is not an appropriate statistical design; an analysis of variance should have been used. As this reviewer continued to read, p. 166A suggested that a biostatistician was hired to correct for this error by using a paired t-test. Is this appropriate? The Table 1 in vol. 9, sec. 5, pg. 162 includes plasma concentrations of midodrine HCl after administration of 2.5 mg Gutron via the intravenous dosing form or via the oral solution or oral tablets. The table does not indicate whether any of these values are statistically significantly different from the others. One may guess that the plasma levels after iv dosing for times 5 and 10 min are different from the levels obtained after the administration of the oral solution or tablets; it is not clear whether the iv value at 20 min is different. The table on p. 162 does not indicate at which times the plasma values of ST 1059/HCl are different when given via the iv and oral solution or tablet formulations.

It would have been meaningful if the studies described in vol. 9 had obtained simultaneous blood pressure and heart rate values and correlated these values with the plasma levels of the drug. For instance, it would have been of interest to compare the magnitude of the blood pressure increase when dosing with 5.11 mg, iv midodrine with that produced by a 5 mg oral tablet.

The data obtained in humans and presented in volume 2, sec. 2, p. 169 could have been graphed in a better format to allow the reader to detect with only a glance the action of midodrine on systolic and diastolic pressures and its action on the heart rate. A graph would have allowed the reader to ascertain whether the magnitude of its action was greater than that noted with placebo or ephedrine (see figures 3 and 4 this report). When reviewing figures 1 and 6 on page 169 and 170, it is not possible to determine whether midodrine produced an effect statistically significantly different from the placebo, i.e., the changes in the systolic pressure when going from the supine to the standing position were 65 and 60 mmHg and 4 and 5 bpm for placebo and midodrine, respectively. One must question whether this is biologically significant. Vol. 2, section 2, page 137 stated that an improvement in the drug was defined as an increase in standing systolic pressure, an increase in the frequency of standing systolic pressures greater than 80 mmHg, and an increase in the ability of the patient to stand long enough for the systolic blood pressure to be measured. It may be that the "magnitude" of the pressor response per se is not the most important parameter and that perhaps the actual systolic pressure achieved is more important, i.e., at least 80 mmHg upon standing. However, the application does not make this clear at this point. Figure 2 of the application does not indicate how much time had elapsed after dosing with midodrine and ephedrine before the physiologic changes were noted.

The sponsor indicates the population they deem appropriate for use of midodrine but do not mention the possibility that the drug might have use in the geriatric population, even though these individuals often present with orthostatic hypotension associated with an impairment of the baroreflex mechanism. The occurrence of orthostatic hypotension in the geriatric population may be associated with broken hips, limbs, etc., adding to the overall cost of medical/surgical treatment in the U.S.

In humans, assumption of the upright posture results in pooling of blood in the lower extremities, a decrease in venous return and in the cardiac filling pressure, and a decrease in the stroke volume. The arterial pressure is usually maintained by reflex tachycardia and peripheral vasoconstriction. These reflex adjustments to orthostatic stress have been attributed to the sinoaortic baroreflexes and to cardiopulmonary baroreflexes. In general, the abnormality responsible for orthostatic hypotension is a deficiency in the vasoconstrictor tone in the upright position (Imamura, et. al., Circulation 71:11-16, 1985). One experimental noninvasive parameter that could easily have been used to monitor the degree of vasoconstriction in humans would be forearm vascular resistance with and without the administration of midodrine (Imamura et al. Circulation 71:11-16, 1985, Circulation 72:747-753, 1985). Ferguson et al (Circulation 67:802-807, 1983) studied drug effects on the reflex vasoconstrictor response to simulated orthostatic stress by measuring forearm vascular resistance.

In vol. 2, section 2, pg. 134, the sponsor states that the "long term survival of patients with orthostatic hypotension is estimated to be lower than that of many human cancers." There are no data given to support this statement, i.e., incidence of and mortality in patients with orthostatic hypotension vs the incidence and type of cancer, age of patients, etc.

The sponsor states in vol. 2, sec. 2, pg. 144 that the adverse symptoms associated with the use of midodrine included supine hypotension. On pages 145 and 179 they cite supine hypertension as a potential complaint. They never state that both complaints may be unwanted symptoms so one must conclude that the application is in error in vol 2:2:144 and that "supine hypotension" should have been "supine hypertension." This conclusion is also supported by the section of the application in which the sponsor assesses the benefits and risks. They recommend an assessment be done after one or two days of treatment during dose titration, since this is when the highest risk for hypertension occurs (2:2:155). The sponsor states that the drug should be continued only for those patients who show significant improvement in their symptoms of orthostatism without excessive supine hypertension. This caution again suggests that the use of the expression "supine hypotension" on page 144, vol 2, section 2 is incorrect.

One discrepancy in the application in volume 2, section 2, page 121 involves the description of a multiple oral dose urinary excretion study to evaluate midodrine metabolites in humans. This section indicates that a group of 6 normal healthy, male volunteers received a total of 3 doses of 5 mg midodrine (one dose each four hours). Over 24 hrs the total elimination of desglymidodrine was 44.9% of the administered dose. Tables 1-6 in Volume 9, section 5, pages 42-47 also indicate the study used males since MR is used in

front of the initials of each subject. However, volume 9, section 5, page 48, summary Table 7 indicates the study was done in 6 female test persons. The text (9:5:39) states that the 6 healthy male volunteers used in this study were the same as those used in the previous study which employed 6 male subjects. So, either the heading in Table 7 is in error or the sponsor has found a method that changes the sex of the volunteers without using hormones and surgery, i.e., via drug treatment!

Volume 2, section 2, page 160 indicates that the number of patients decreased in the continued efficacy in long-term therapy study. No dropout rate is given nor is a reason given for why they dropped out.

Volume 2, sec. 2, pg 161, Table VI shows very small mean changes in the cardiovascular parameters of systolic and diastolic blood pressures and heart rate; it is hard to believe that increases in pressure of 3-5 mmHg would have a significant clinical effect. The headings in this table indicate that supine and sitting values are being reported. Some of the numbers in the table are footnoted with a single asterisk. The legend to the table contains only a double asterisk indicating that in some cases supine and sitting (instead of standing) values are reported. They have mixed "apples and oranges", i.e., "standing" and "sitting". The dose given is not shown in this table. It is of interest to note that in Table VIII on page 163 or table IX on page 164, a greater increase in the systolic and diastolic pressures occur with oral midodrine when compared with the data in Table VI. Again, doses are not noted on either table; this addition would have made the job of the reviewer easier.

The following discussion provides a comparison of human and animal dose levels, plasma levels, and metabolic profiles. The adequacy of animal exposures in the chronic and reproductive toxicological studies were appropriate. Plasma levels were not determined in the chronic toxicology studies. All dogs survived 6 month dosing with 27 mg/kg/d, po or 47.25 times the maximum recommended human dose of 40 mg/d in a 70 kg patient. The 6 month chronic dosing study in rats did not provide definitive information since kidney infection confounded the interpretation of results. Two rats died in the control group, 7 at 1 mg/kg/d, 4 at 5 mg/kg/d, and 2 at 20 mg/kg/d. These doses are 1.75, 8.75, and 35 times the maximum recommended human dose of 40 mg/day (0.5714 mg/kg/d in a 70 kg patient). In a supplementary test two rats died in the control group, 1 at 0.3 mg/kg, and 3 after 1 mg/kg/d, po. Midodrine produced a significant reduction in resorption rate and body weight of rat and rabbit fetuses at maternally toxic doses of 20 mg/kg/day (reduced food intake and body weight gain). There was no evidence of harm to the fetus at doses up to 1.5 mg/kg/day or 2.63 times the maximum recommended human dose of 40 mg/day (0.5714 mg/kg/d in a 70 kg patient).

In the conscious dog, tritium-labeled midodrine was given via gastric intubation (0.8 mg/kg). ST 1059 was given iv 0.1, 0.4, or 1.6 mg/kg. There was a close correlation of an increased blood pressure and a decreased heart rate with the plasma concentration of the midodrine metabolite ST 1059 over a six hour period. Maximum pharmacodynamic action and plasma levels of ST 1059 (0.3-1.0 nmole/ml) in the dogs were obtained 0.75-2.0 h after administration. Plasma values at 6 h were like those obtained at minute 15 but neither of the

pharmacodynamic parameters had returned to baseline. Plasma levels of 0.2 nmole/ml ST 1059 were needed for pharmacodynamic activity; above this level there was a linear relationship between the plasma concentration and the decrease in the heart rate after oral and intravenous dosing.

There was a correlation between the increase in perfusion pressure and the amount of ST 1059 formed during hind quarter perfusion of rats, with changes in the pressure mmHg and mg of ST 1059 being 66, 373; 97, 1035; and 128 and 1840 at 15, 30, 60 min, respectively.

The metabolic pathway in the rat followed an initial hydrolysis with splitting of the glycyl residue to give ST 1059, demethylation to ST 1062, followed by deamination or glucuronidation. Biliary excretion is a minor process.

The plasma t1/2 for the rat was 1.0 h and 1.75 h for midodrine and for ST 1059 after iv and po dosing, respectively; in the dog it was 2 h and 2.5 h for midodrine and for ST 1059 after iv and po dosing, respectively. After an oral dose of 2.5 mg in humans, the plasma t1/2 was 0.5 h for oral midodrine and 3 h for ST 1059; Cmax values of 10 and 5 ng/ml at tmax of 20-30 min and 1 hour were found for midodrine and ST 1059, respectively. In humans, after 5 mg iv midodrine or 5.3 mg po, the plasma t1/2's were 3.87 h and 3.58 h, respectively; a Cmax value of 53.9 ng/ml followed the oral dosing with a tmax of 0.66 h. Conclusions from the human studies were that midodrine was rapidly metabolized to desglymidodrine (ST 1059) and the metabolites did not appear to accumulate. The metabolite has a longer plasma t1/2 than midodrine, is amply present in the urine, and is responsible for the pharmacodynamic actions of midodrine.

The species employed in the chronic (dog and rat) and reproductive toxicology studies appear to be reasonable surrogates for the evaluation of human safety.

Adverse preclinical findings in dogs that are clearly related to the action of midodrine include piloerection, mydriasis, and vomiting. These changes, initially prominent and dose-dependent, gradually disappeared over the course of several weeks of therapy. Both rodents and dogs exhibited scattered foci of myocardial fiber degeneration.

The clinical adverse effects associated with the use of midodrine have been reported in clinical studies conducted within the United States and in foreign countries. J.F. Colquhoun (21:7:2; 4/21/88) summarized the midodrine clinical published and unpublished international literature by reviewing the results of 56 clinical studies which addressed the safety and efficacy of midodrine. Of the 3996 patients receiving midodrine, 87% had hypotensive disorders generally accompanied by orthostatic circulatory dysregulation. Some patients had secondary hypotension due to disease or drug therapy or were diagnosed with urinary incontinence or ejaculatory disorders. Midodrine was used from less than one day up to 15 months. Most (56%) of the patients received midodrine for 3 to 6 weeks. Thirty-nine percent of the patients were administered a total daily dose of 5 mg or less; this was most often prescribed as a single dose. Forty percent of the patients received between 5 and 10 mg as one to three doses. Colquhoun noted that of 3265 patients evaluated for the incidence of adverse drug reactions, 307 (9.4%) reported one or more adverse reactions. Fifty-two (1.6%) discontinued the drug due to an adverse

reaction. A mild or clinically insignificant pilomotor reaction was the adverse reaction most often noted (55%). An improvement of the hypotensive condition was reported for all patient categories. The change in the blood pressure was variable among the studies but 70-100% of the patients reported that the subjective complaints were significantly improved or eliminated. In 1874 patients with orthostatic hypotension enrolled in two large multicenter studies, 91-98% exhibited a positive therapeutic response.

Studies conducted in the U.S. indicated that of 87 patients, 17 (19.5%) treated with midodrine noted one or more adverse reactions. In five short term controlled clinical studies of 53 patients, 7 (13.2%) reported one or more adverse reactions. In a long term compassionate use study of 34 patients, 10 (29.4%) reported one or more adverse experiences. Treatment duration varied from 1 to 6 months (18 patients) to 7 to 12 months (3 patients), 13 to 24 months (8 patients) and 25 to 58 months (15 patients).

In these trials, the most frequent adverse reactions were: pruritis of the scalp (9.2%), supine hypotension (3.4%; this is an error and should be supine hypertension); and nausea and vomiting (3.4%). An incidence of 2.3% was reported for symptoms of chest pain, flushing, and urinary frequency. Most patients concomitantly received fludrocortisone and dietary salt supplements. Adverse reactions noted in patients with a frequency greater than 2% in controlled clinical trials included: dizzy, lightheaded, dysequilibrium, pruritis, tingling of scalp; cardiac awareness, photosensitivity, pounding in ears, fever, neuropathy, limb pain; fatigue; nausea, vomiting; hypokalemia; breathing difficulty; supine hypertension; headache; gastroparesis; syncope; chest pain; and depression (See upper Table 4.4 this report). Adverse reactions occurring in 0.5 to 2.0% of patients in controlled and uncontrolled trials included: cardiac palpitations; tingling of the scalp and piloerection (goose-pimpled skin); abdominal discomfort; dysuria, fullness of the bladder, urinary retention, and incontinence; and chills. One patient with preexisting atrial arrhythmias exhibited an increase in ectopy and an increase in the ventricular response rate after midodrine treatment. The effect was transient and remitted when the drug was discontinued. In a study by Dr. Schirger, 146 patients received midodrine for the treatment of orthostatic hypotension for up to 57 months. The most frequently reported side effects noted were pruritis or itching of the scalp and supine hypertension, followed by piloerection and headache. Adverse reactions to midodrine noted, for which no causal relationship was found, are included in the lower half of Table 4.4 this report.

In the short term studies, there were few abnormal laboratory test values. In a long term safety study, 34 patients were treated for periods ranging from one week to 58 months (avg. 23.7). The sponsor states that there were no patterns of drug-related changes in the laboratory tests (see Table 11 this report). Eleven hematologic values, i.e., hemoglobin, hematocrit, and red cell counts, changed in seven patients from normal to abnormal. This reflected the development of a moderate anemia. Eight chemistry values changed in seven patients from normal to abnormal. Four were moderate increases in cholesterol, three were moderate increases in glucose, one a moderate drop in glucose, and one a moderate increase in total protein.

The sponsor concludes that the most commonly reported adverse drug reactions on a worldwide basis include pilomotor changes, pruritis, paresthesiae, and tingling in the scalp. These reactions rarely required the drug to be discontinued, are not of a major concern, and "usually" disappear with continuing treatment. Supine hypertension was noted to occur in 29% of 146 patients (Dr. Schirger) before and after treatment with midodrine. Twenty-five percent developed supine hypertension during treatment. This problem may occur abruptly or insidiously. Dr. Schirger noted an incidence of morning supine systolic hypertension (greater than 180 mmHg) of approximately 6.8%, and supine diastolic hypertension (greater than 110 mmHg) of approximately 5.4%. Approximately fifteen percent of the patients on long term treatment exhibited supine systolic pressures greater than 180 mmHg about 20% of the time. The incidence of supine diastolic hypertension was stated to be significantly less [illegible] the incidence was not given.

The sponsor concludes that studies of midodrine in more than 2800 patients showed short term and long term benefits and that an excellent safety profile has been established in many long term patients when treatment has continued for up to five years.

The sponsor notes that the dose-related occurrence of supine hypertension which may lead to excessive systemic blood pressure has been controlled by elevating the head of the patient's bed. In some cases it has been controlled by the administration of cardioselective beta receptor blocking agents. Phentolamine and other alpha receptor antagonists have been used to produce a prompt reversal of the pressor effect.

The sponsor notes that the pressor response induced by midodrine may be associated with a reflex inhibition of heart rate. This is manageable but the possibility of bradycardia should be considered when using the drug in patients with cardiac conduction defects or for those in decompensation.

Transient urinary retention may occur due to midodrine-induced sphincter contraction. The effect is transient but the prescribing physician should consider "the chronic use of midodrine against the disadvantages of such an effect" (sponsor 2:2:15). The sponsor concludes that benefit/risk assessment should be ongoing, given the different time aspects. The ratio should be assessed after one or two days of treatment during dose titration, when the highest risk for hypertension occurs. At this time the therapeutic effect should be obvious. Thus, midodrine use should be continued only for patients who exhibit significant improvement in subjective symptoms of orthostatism without excessive (supine) hypertension when compared to the effects of prior therapy. If a clinical therapeutic response is not obvious within four to seven days, the patient should be changed to a different drug.

The labelling section 2:2:9 lacks a statement that a WHO brochure was used to indirectly evaluate the carcinogenicity of midodrine. Report 058-05, written in April of 1976 by), used the brochure "assessment of the carcinogenicity and mutagenicity of chemicals" (WHO Technical report series 546, 1974) to examine the question of an eventual carcinogenicity with the use of midodrine. The literature was reviewed for: 1. Known carcinogenic structures and groups of substances; 2. A special search for suggested

carcinogenicity in the group of biogenic amines and their derivatives; 3. Special search for a suggested carcinogenicity of glycine; 4. Special search for a suggested carcinogenicity of methoxamine; 5. Assessment of eventual carcinogenic properties on basis of its solubility; and 6. Possibility of an eventual cocarcinogenicity. This evaluation was supplemented by a literature search in an international documentation (RINGDC DERWENT) which covered the time from 1960 to 1976. It was concluded that based on analysis of the structure of the prodrug and the metabolite, the poor lipid solubility, and negative findings in the literature for reports of carcinogenicity with midodrine, catecholamines, glycine, and methoxamine, there is no evidence available to indicate carcinogenicity. No evidence of tumors was found upon autopsy of organs after chronic dosing studies in rat (0.3, 1, 1.5, 20 mg/kg/d, po for 6 mon) and dogs (0.5, 2.5, 12.5 mg/kg/d, po or 3, 9, 27 mg/kg/d, po for 6 mon).

On 2/6/85, Dr. Raymond Lipicky of the FDA had a telephone conversation with Dr. Robert J. Gaughran, Vice President of Roberts Laboratories, Inc., in which the need for two year animal carcinogenicity studies for midodrine were discussed. Dr. Gaughran (as noted in memo 2/11/85 to himself) explained that if an animal carcinogenicity study was a precondition to obtaining an approved NDA, seeking approval for midodrine for other indications such as the treatment of female urinary stress incontinence, retrograde ejaculation, and certain types of secondary hypotension, would be an economic disaster. Dr. Gaughran indicated that the company would seek a waiver and if unable to get one, they would request the ability to perform the studies during the first few years of commercial introduction after having obtained an approved NDA.

It should be noted that the sponsor states in the NDA application #19-815 that since the FDA had declared midodrine an "orphan drug", carcinogenicity studies were not required.

CONCLUSIONS:

Sections of the NDA should be rewritten to clarify the material being presented. One clarification that could be requested of the sponsor stems from a statement in Vol. 2 section 2 page 144. This section states that one of the most frequent adverse reactions to the use of midodrine was "supine hypotension." This is an error and should be "supine hypertension." The sponsor should correct the name of the adverse symptom noted.

Parts of the labeling section of the application, discussed on pages 45-46 of this report, should be rewritten to meet the requirements of the FDA.

In general, the summary of the preclinical studies is not as well written as one would like. Portions of the summaries of the preclinical studies are too brief, omitting details required to evaluate the significance of the results being discussed. To make matters worse, the reviewer is forced to spend much time finding necessary details buried in volumes not clearly referenced. In particular, Report #058-01 contains many different preclinical studies but the reviewer is left to search through 344 pages of volume 4 to detect the practically invisible pink pages which separate the many different reports contained in this volume. If the sponsor had tabulated the individual reports contained within this one volume, the job of the reviewer would have been much easier.

In addition to a poorly written preclinical summary section, portions of the entire NDA application are also not well written. This problem may have stemmed from the fact that the application is a compilation of studies done in numerous laboratories in different countries over a period of time that spans 19 years. (The earliest report is #058-20 dated 1/70.) The studies were done under the direction of different sponsors since the IND has been held by various sponsors over the years. Numerous typos, misspellings, and incorrect collation of pages within a given section slow down the process of the review. The scientific and statistical evaluation of some of the data in the preclinical pharmacology studies could have been improved by developing the conclusions further or by utilizing the appropriate statistics. The latter problem may again reflect the fact that some of the statistical evaluations were done in the early to mid 1970's. Since this time statistical evaluation of biological data has continued to evolve at a very rapid rate. Some of the results of the animal experimental designs done to determine the mechanism of action of midodrine are at times confusing and at best fail to provide evidence to support the details of a definitive mechanism of action. Improvements in the designs of the animals studies conducted and/or conduction of additional experiments would have strengthened the preclinical studies. Some of the conclusions drawn about the mechanism of action suggested for midodrine by the results of the preclinical studies could have alternate explanations but the sponsor fails to mention them. The sponsor states that midodrine is a potent agonist of peripheral alpha sympathetic receptors but never alludes to which subtype of the alpha receptor is involved.

The sponsor never discusses in the application the possibility that another potential clinical use for midodrine might be in the treatment of orthostatic hypotension occurring in the geriatric population.

The sponsor is proposing to use midodrine tablets to treat idiopathic orthostatic hypotension. The data obtained in the preclinical studies designed to examine its pharmacodynamic actions clearly indicate that midodrine induces a pressor effect when given orally. The pressor effect is followed by a slow fall in the heart rate. The preclinical animal studies found no evidence that midodrine exhibited a significant action on the central nervous system (although there was a suggestion of an analgesic action), intestinal motility, pulmonary circulation and respiration, liver function, kidney and urinary bladder function, and uterine contraction. Midodrine significantly prolonged PQ and QT intervals in the electrocardiograms of conscious standing dogs. Dyspnea was also noted. The margin between the dose required to produce a desired pharmacodynamic effect and unwanted side effects is very good. Indeed, the dose producing death in rodents and dogs is 10 to 100 times greater than the doses needed to produce pharmacodynamic effects. No major gross or histo- pathological findings were noted in rodents or dogs, other than fatty infiltration of the liver after subacute but not chronic dosing and scattered foci of myocardial fiber degeneration also observed with other sympathomimetics.

Although the sponsor indicates that the microscopic necrotic foci in the myocardium is believed to be a nonspecific reaction in the canine myocardium, the sponsor fails to acknowledge in this portion of the NDA that myocardial changes were also noted in 10 or 20 day dosing study done in rats. Additional experiments utilizing long term midodrine administration in other species would determine whether this unwanted effect occurs in species other than dogs or rats. Support for doing experiments in other animals is provided by clinical adverse reports of chest pain, "cardiac awareness", and the occurrence of arrhythmia noted in studies conducted in humans.

All of the above report was written after reading only the original NDA #19-815 application. I have just read a September 8, 1988 amendment - midodrine safety update report submitted as a four month, post-NDA evaluation. Data include those obtained from 19 patients in the U.S. who were treated with midodrine at the time of the NDA submission and from an additional 4 patients who received midodrine after the submission. The adverse cardiovascular reactions and total number of patients exhibiting these symptoms include: chest pain (2), flushing (1), palpitations (2), supine hypertension (8), atrial fibrillation (2), cardiac failure (1), and ventricular arrhythmia (2). Adverse reactions related to the central and peripheral nervous system were: headache (1), cerebrovascular disorder (2), hemiparesis (1), tremor (1), and seizure (1). Gastrointestinal abdominal discomfort occurred in one patient while 2 exhibited nausea. Pruritis of the scalp was reported in 5 and piloerection in 1 patient. One patient noted night cramps while 4 reported increased urinary frequency, 1 dysuria, 1 incontenance, and 1 fullness of the bladder. One patient reported chills. A total of 23 patients (60.5%) reported one or more adverse reactions (with multiple reports of the same adverse reaction for a single patient being counted once). Fifteen patients reported no adverse reactions.

Supine hypertension occurred in 8 patients; the drug was discontinued in 2 of these 8. Altogether, the drug was discontinued in a total of seven patients. In two the reason for discontinuing the drug was systemic hypertension in the supine position and in two because the physician deemed that the clinical response was only fair or that the regimen was complex.

Of the two patients (#1202 and 1203) exhibiting ventricular arrhythmias, both died. Patient #1203 had received 30 mg/day of midodrine for 4 years. The patient had supine hypertension for 2 years and died in sudden cardiac death, presumably due to ventricular fibrillation. Three patients died in respiratory arrest (#0120, 0301 and 1102). These cardiac symptoms and/or deaths occurring in humans emphasize the multispecies occurrence of adverse cardiac effects reported in the preclinical studies conducted in dogs and rats.

This reviewer would like the sponsor to clearly define the incidence of arrhythmias, sudden cardiac death, or respiratory arrest in the patient population with the clinical problem of orthostatic hypotension when no drug treatment is used vs the incidence when drugs currently approved in the U.S. are prescribed for the treatment vs the incidence when midodrine is used alone and in combination with other agents to treat this problem. Specifically, the sponsor should address the question of whether the clinical use of midodrine alone or in combination makes the incidence of arrhythmias, sudden cardiac death, or respiratory arrest worse than in cases when no drug or drugs other than midodrine are used.

An updating of the references, in the worldwide published literature, in particular those referring to clinical studies published since 1981, should be done in some sections of the application (such as 2:2:18) to allow the reviewers to ascertain whether the incidences of unwanted side effects associated with the use of midodrine have changed or whether any additional side effects have been noted. For instance, a recent article published in the June 1988 issue of Neurology (38:951-956) could be added to the literature cited in the application. The sponsor should review the articles included in Volumes 2:21 through 2:25 to ascertain whether sudden cardiac death and respiratory arrest occurred in those patients taking midodrine and, if it did occur, they should note its incidence. The sponsor should ascertain whether only long term dosing with high doses of midodrine results in sudden cardiac death or in respiratory arrest. This information becomes more important when one considers the information included in the September 8, 1988 amendment which notes that patients on midodrine died of these events.

One experimental design that could still be done by the sponsor to clarify its arrhythmogenic potential is one in which a permanent occlusion of the coronary artery is performed in anesthetized cats or dogs. However, one argument against doing additional preclinical studies is that midodrine has been used clinically in foreign markets since 1974. Since 1. the most commonly reported adverse drug reactions on a worldwide basis are pilomotor changes, pruritis, paresthesiae, and tingling in the scalp; 2. these reactions have rarely necessitated that the drug be discontinued; and 3. the side effects generally disappear with continuing treatment, it would seem that the use of midodrine in most humans is safe. Nevertheless, the most recent data obtained from clinical studies conducted in the U.S. indicate that some individuals taking midodrine have died from ventricular arrhythmias and/or respiratory arrest. These data support the suggestion that additional animal studies should be done. The deaths of humans in the U.S. study emphasizes that the selection of midodrine for use in any given patient must be done carefully, with monitoring for unwanted symptoms of supine hypertension and/or changes in the electrocardiogram.

RECOMMENDATIONS:

The NDA should be approved only if the sponsor can establish that the number of patients dying in the U.S. study summarized in Sept. 8, 1988 amendment is not signifcantly different than the predicted numbers of patients dying with no drug treatment or when approved drugs are used to treat orthostatic hypotension. That the sponsor has an estimate of long term survival in these patients is suggested by statement in the application (2:2:134). See below. The sponsor should define the incidence of arrhythmias, sudden cardiac death, or respiratory arrest in the patient population with orthostatic hypotension when no drug treatment is used vs the incidence when midodrine and/or other approved drugs are used to treat this problem.

An updating of references should be done to look for all suggestions of toxicity associated with the clinical use of midodrine. This search should screen for evidence of sudden death, respiratory arrest, an increased incidence of carcinogenicity, or altered fertility. Carcinogenicity studies should be required for this NDA (orphan drug) only if the projected lifespan of patients with orthostatic hypotension while on midodrine treatment is significantly increased. If the use of midodrine does nothing more than improve the quality of life before the patient dies at a time equivalent to that with no treatment, then carcinogenicity studies should not be required. The sponsor states that "the long term survival of patients with orthostatic hypotension is estimated to be lower than that of many human cancers" (2:2:134) but no data are given to support this statement. Animal carcinogenicity studies should be required if the sponsor seeks approval for indications other than orthostatic hypotension treatment which would require treatment with midodrine for many years. Such indications would include the treatment of female urinary stress incontinence, retrograde ejaculation, and certain types of secondary hypotension due to disease or drug therapy.

It is suggested that the sponsor do additional animal experimants to determine the extent of myocardial necrotic foci after long term dosing with midodrine in a species other than dog or rat, such as monkeys or baboons. Experiments should also be done to evaluate the arrhythmogenic potential of midodrine in an animal model of permanent occlusion of a coronary artery.

If the above questions are answered satisfactorily, the use of midodrine should be approved with recommended changes in labeling (see page 45 and 46 of this report) since the data suggest that in some patients midodrine may offer a clinical advantage if they are presently bedridden or unable to walk without assistance. Its use is said to differ from other drugs employed in the treatment of idiopathic orthostatic hypotension and thus midodrine offers something not available from drugs presently on the U.S. market in as much as the sponsor states that it maintains a therapeutic effect even when administered over a period of years and since fewer side effects have been reported with its use. The clinical use of midodrine in the U.S. should be safe if cautions are observed in patient selection, if patients are monitored for supine hypertension and/or changes in the electrocardiogram, and if, as

recommended by the sponsor, the drug is used to treat severe idiopathic orthostatic hypotension due to autonomic failure in those individuals who are refractory to other treatments or in those who do not respond optimally to antihypotensive treatment with pressor agents or with expanders of the intravascular volume.

Claire M. Lathers

Claire M. Lathers, Ph.D.

cc:
Orig NDA
HFD-110
HFD-110/CSO
HFD-110/CLathers
clb/6/19/89;7/5/89;7/21/89;
8/3/89;10/27/89;11/3/89;
11/15/89;12/8/89;1/22/90/1550C

cm 1/22/90

Statistical Review

MR. Buehler

Statistical Review and Evaluation

MAR 28 1996

Review of study 20, 762-201 of NDA 19-815 (In Association With IND

DATE:

NDA 19-815 (In Association With IND 20-762):

DATE OF IND RECEIVED BY CDER: March 16, 1995.

DATE DATA RECEIVED BY CDER FOR STATISTICAL REVIEW: March 07, 1996.

DRUG NAME: Amatine (Midodrine Hydrochloride) Tablets (2.5 and 5 mg tablets): Given once a day in a 4-Period 4-Sequence 4-Treatment crossover design. Treatment arms were placebo and midodrine 2.5 mg, 10 mg, and 20 mg doses.

Sponsor: Roberts Pharmaceutical Corporation.

INDICATION: Management of Orthostatic Hypotension (Low Standing Blood Pressure).

VOLUMES REVIEWED: Vol 1 of 2 the NDA.

This review has been discussed with Dr. Maryann Gordon, the medical reviewer from Division of Cardio-Renal Drug Products (**HFD-110**) of the FDA, and she agrees with these findings.

NOTE:

This review might be regarded as an addendum review to the Statistical Review of studies 20,762-320C and 20,762-318C, dated January 16, 1996. As requested by Dr. Raymond Lipicky, the Director of Division of Cardio Renal Drug Products (HFD-110) of the FDA, the review should aim to investigate the effectiveness of 2.5 mg, 10 mg and 20 mg midodrine doses as compared to placebo with respect to maximum (peak) and minimum (trough) effect. Thus, to fulfil this interest the metrics (variables) to be considered are the maximum (peak) and minimum (trough) values of the standing systolic blood pressures. Thus, our analyses compares the baseline adjusted means of post treatment MIN and MAX values of the standing systolic blood pressures of the patients in the midodrine dose groups with the corresponding means of those patients in the placebo group.

[redacted]

STUDY 201 DESCRIPTION

Design

This was a 6-day, single dose, placebo-controlled, double-blind, 4-period 4-sequence 4-treatment crossover trial on the subjects with neurogenic orthostatic hypertension (OH).

The 6 days of the trial consist of:

Day 1: Pretreatment
Day 2 to Day 5: Double-Blind treatment phase
Day 6: Withdrawal from the medications and the post treatment evaluation.

The primary efficacy variable was the **elevation from baseline** in standing systolic blood pressure (**StSBP**) .

The primary objectives was to study the dose response to a single dose of placebo/midodrine doses with respect to **StSBP**.

Additional primary objective was to assess the **duration of action** with respect to StSBP.

There were secondary objectives, as well as the safety assessment. In this review we focus on the primary efficacy objectives.

The doses used and their codes were:

A: Placebo
B: 2.5 mg of midodrine
C: 10 mg of midodrine
D: 20 mg of midodrine.

Three patients received 5 mg of midodrine instead of 20 mg. These three patients were excluded from our analyses.

Patients Population

The study randomized 25 patients from whom 23 completed the study. Of the 25 randomized patients 11 were males and 14 were females with the average age of 62 years and the range of 38 to 78 years.

The following table gives the etiology by treatment distribution of the patients.

TABLE I

Distribution of Patients With Respect to Etiology by Treatment

ETIOLOGY	TREATMENT				TOTAL
	Placebo	Mido 2.5 mg	Mido 10 mg	Mido 20 mg	
BRADBURY-EGGLESTON	3	4	2	5	14
SHY-DRAGER	1	1	3	2	7
PARKINSON	0	1	0	0	1
DIABETES	2	0	0	0	2
OTHERS	0	1	0	0	1
TOTAL	6	7	5	7	25

As Table I shows that the Bradbury-Eggleston patients have the highest frequency of 14 patients. The next highest frequency was 7 and belongs to the Shy-Drager patients.

We will consider the data of the 22 Intent-to-Treat patients who took at least one dose of the placebo or a midodrine treatment. We also fucose on the primary efficacy variable StSBP.

Data Structure

The StSBP measurements were obtained on **Days** 1 to **6** and for each day at **Hours** 0 (pre-dose) and **hours 1 - 6** (post dose). For each day and at each hour the StSBP were measured at **Minutes 1 - 6** for **Hours 0, 2, 3, 4, 5, 6** and at **Minutes 1 - 15** for **Hour 1**. The following notations and discussions help to understand the data structure.

$StSBP_{d,h,m}$ = The standing systolic blood pressure at **Day d**, **Hour h**, and **Minute m**;
d = 1, 2, 3, 4, 5, and 6
h = 0, 1, 2, 3, 4, 5, and 6
m = 1, 2, 3, ..., 13, 14, and 15.

So, under ideal situation a total of 306 StSBP (6x6x6 + 15x6 = 306) measurements could be obtained from a given subject. However, due to various technical difficulties, such as undetectable blood pressure value, failing to measure, and patient unable to stay standing up for 15 minute, there are lots of **missing observations** in the data set.

Statistical Methods

The sponsor's efficacy analysis consist of regression analysis to evaluate the dose response for the differences in StSBP for the first hour post-treatment. In particular, the sponsor considers the analysis on StSBP for the Minute 1 of the Hours 0 to 6 as the main analysis.

In a discussion between this reviewer and Dr. Raymond Lipicky, the Division Director of HFD-110, he suggested to investigate the effectiveness of 2.5 mg, 10 mg and 20 mg midodrine doses as compared to placebo with respect to MIN (trough) and MAX (peak) drug effect. Thus, the metrics (variables) of interest will be the MIN and MAX values of the standing systolic blood pressures. Our analyses compares the means of baseline adjusted post treatment MIN/MAX values of StSBP of midodrine patients with the corresponding means of those patients in placebo group.

To fulfil our goal we consider **FIVE PROCEDURES**. These procedures are different with respect to calculation of baseline and post treatment MIN and MAX of the StSBP. Considering our notation $StSBP_{dhm}$, the description for calculation of post treatment MIN and MAX of the StSBP and the determination of the baseline for the five procedures are as follows.

PROCEDURE 1:

For each day of double blind treatment period d = 2 - 5;

Post-Treatment MIN_d = MIN($StSBP_{d,1,1}$, $StSBP_{d,2,1}$, $StSBP_{d,3,1}$, $StSBP_{d,4,1}$, $StSBP_{d,5,1}$, $StSBP_{d,6,1}$)
Post-Treatment MAX_d = MAX($StSBP_{d,1,1}$, $StSBP_{d,2,1}$, $StSBP_{d,3,1}$, $StSBP_{d,4,1}$, $StSBP_{d,5,1}$, $StSBP_{d,6,1}$).

Namely, the two post treatment MIN_d/MAX_d metrics are defined as the minimum/maximum of the 6 $StSBP_{d,h,m}$ measurements obtained at **Minute m=1** of the **Hours d=1-6.** This process is to be repeated for each **Day d=2-5** to generate the MIN_d/MAX_d for that day.

Baseline MIN_d = $StSBP_{2,0,1}$
Baseline MAX_d = $StSBP_{2,0,1}$.

Namely, the baseline is the $StSBP_{d,h,m}$ measurement at **Minute m=1** of **Hour h=0** of **Day d=2** which is the first day of double-blind treatment period and is the same for both post treatment MIN_d and MAX_d of $StSBP_{d,h,m}$ measurements. This baseline will be used for the baseline adjustment of **Days d=2-5** post treatment MIN_d/MAX_d of $StSBP_{d,h,m}$ measurements.

PROCEDURE 2:

For each day of double blind treatment period d = 2 - 5;

Post-Treatment MIN_d = Same as the MIN in Procedure 1
Post-Treatment MAX_d = Same as the MAX in Procedure 1.

Baseline MIN_d = $StSBP_{d,0,1}$
Baseline MAX_d = $StSBP_{d,0,1}$.

Namely, the baseline here is the $StSBP_{d,h,m}$ measurement at **Minute m=1** of **Hour h=0** of the same **Day d** as the post treatment measurement day for both minimum and maximum. This baseline will be used for the baseline adjustment of **Day d** post treatment MIN_d/MAX_d of $StSBP_{d,h,m}$ measurements.

PROCEDURE 3:

For each day of double blind treatment period d = 2 - 5;

Post-Treatment MIN_d = Same as the MIN in Procedure 1
Post-Treatment MAX_d = Same as the MAX in Procedure 1.

Baseline MIN_d = $MIN=MIN(StSBP_{1,1,1}, StSBP_{1,2,1}, StSBP_{1,3,1}, StSBP_{1,4,1}, StSBP_{1,5,1}, StSBP_{1,6,1})$
Baseline MAX_d = $MAX=MAX(StSBP_{1,1,1}, StSBP_{1,2,1}, StSBP_{1,3,1}, StSBP_{1,4,1}, StSBP_{1,5,1}, StSBP_{1,6,1})$.

Namely, the baselines are the minimum/maximum of the 6 $StSBP_{d,h,m}$ measurements obtained at **Minute m=1** of each of the 6 **Hours h=1-6** of **Day d=1**. These baselines will be used to adjust the **Day d=2-5** post treatment MIN_d/MAX_d of $StSBP_{d,h,m}$ measurements.

PROCEDURE 4:

For each day of double blind treatment period d = 2 - 5;

Post-Treatment MIN_d = $MIN(StSBP_{d,1,1} - StSBP_{d,1,15}, StSBP_{d,2,1} - StSBP_{d,2,6}, ..., SBP_{d,6,1} - StSBP_{d,6,6})$
Post-Treatment MAX_d = $MAX(StSBP_{d,1,1} - StSBP_{d,1,15}, StSBP_{d,2,1} - StSBP_{d,2,6}, ..., SBP_{d,6,1} - StSBP_{d,6,6})$.

Namely, the two post treatment MIN_d/MAX_d metrics are defined as the minimum/maximum of the 45 $StSBP_{d,h,m}$ measurements obtained at **Minutes m=1-15** for **Hour h=1** and at **Minutes m=1-6** for **Hours h=2-6**. This process is to be repeated for each **Day d=2-5** to generate the MIN_d/MAX_d for that day.

Baseline MIN_d = $MIN(StSBP_{d,0,1}, StSBP_{d,0,2}, StSBP_{d,0,3}, ..., StSBP_{d,0,5}, StSBP_{d,0,6})$
Baseline MAX_d = $MAX(StSBP_{d,0,1}, StSBP_{d,0,2}, StSBP_{d,0,3}, ..., StSBP_{d,0,5}, StSBP_{d,0,6})$.

Namely, the two baseline metrics are defined as the minimum/maximum of the 6 $StSBP_{d,h,m}$ measurements obtained at **Minutes m=1 - 6** of **Hour h=0** of **Day d**. This process is to be repeated for each **Day d=2-5** to generate the baseline for **Day d** which will be used for the baseline adjustment of the post treatment MIN_d/MAX_d of $StSBP_{d,h,m}$ measurements.

PROCEDURE 5:

For each day of double blind treatment period d = 2 - 5;

Post-Treatment MIN_d = Same as the MIN in Procedure 4
Post-Treatment MAX_d = Same as the MAX in Procedure 4.

Baseline MIN_d = MIN($StSBP_{2,0,1}$, $StSBP_{2,0,2}$, $StSBP_{2,0,3}$, ..., $StSBP_{2,0,5}$, $StSBP_{2,0,6}$)
Baseline MAX_d = MAX($StSBP_{2,0,1}$, $StSBP_{2,0,2}$, $StSBP_{2,0,3}$, ..., $StSBP_{2,0,5}$, $StSBP_{2,0,6}$).

Namely, the baselines are the minimum/maximum of the 6 $StSBP_{d,h,m}$ measurements obtained at Minutes m=1 - 6 of Hour h=0 of Day d= 2. This process is to be repeated for each Day d=2-5 to generate the baseline for Day d which will be used for the baseline adjustment of the post treatment MIN_d/MAX_d of $StSBP_{d,h,m}$ measurements of Day d.

Overall, Procedures 1, 2, and 3 use the same definition of post treatment MIN_d/MAX_d values but different baselines. Also, procedures 4 and 5 use the same definition of post treatment MIN_d/MAX_d but different baselines.

Rationale

The rationale for considering the above metrics could be explained as follows:

- The sponsor's primary analysis consists of analysis of Minutes 1 at each Hour 1,..., 6 separately. For Procedures 1, 2, and 3 our analysis uses the MIN and MAX of Minute 1 StSBP over the Hours 1 to 6 rather than the hour-by-hour analysis. Consequently, our analysis, in a sense, aims at the evaluation of the trough and peak effect at Minutes 1 over the range of post treatment StSBP measurements over Hour 1 to 6.

- We considered Procedures 4 and 5 because these procedures use more information (in terms of more detailed observations over the range of Hour 1 to 6) for the determination of trough and peak. Therefore, one will be able to more precisely determine the trough and peak values of the StSBP over the range of Hours 1 to 6.

Efficacy Analysis

The analysis of variance (ANOVA) was used to analyze the data for carry over effect and the ANOVA for a crossover designs was used to evaluate the efficacy the treatments.

Carryover effect: The Hour 0 values were the pre-medication values and at this point of time there was supposed to be no drug effect left. Thus, Hour 0 is the point of time that the patients' StSBP should have been returned to the baseline values. In the light of this view, there should be no significant differences between the means of the treatment groups with respect to at Hour 0 of every day.

For each Days 2-5, separately, we performed the ANOVA on baseline adjusted metrics:

(1) $StSBP_{d,0,1}$ = StSBP at Minute 1 of Hour 0 of Day d,

(2) MIN-VAL = MIN ($StSBP_{d,0,1}$, $StSBP_{d,0,2}$, ..., $StSBP_{d,0,6}$),
Namely, MIN of Minutes 1-6 of StSBP at Hour 0 of Day d,

and

(2) MAX-VAL = MAX ($StSBP_{d,0,1}$, $StSBP_{d,0,2}$, ..., $StSBP_{d,0,6}$),
Namely, MAX of Minutes 1-6 of StSBP at Hour 0 of Day d,

The results of these analyses are summarized in Table II.

TABLE II

ANOVA on Hour 0 of Day 2 to 5 of Standing Systolic Blood Pressures
For determination of Carryover Effect Using Various Metrics

Metric (Variable)	Day	Least Square Adjusted Means (mmHg) On Systolic Standing Blood Pressure				P-Value ANOVA
		Placebo	Mido 2.5 mg	Mido 10 mg	Mido 20 mg	
MINUTE 1 of Hour 0 of Day 2 to 5 $StSBP_{d,0,1}$	2	83.33	81.42	84.50	102.5	0.5354
	3	97.75	92.75	85.80	93.29	0.1500
	4	89.40	111.33	74.80	99.25	0.5077
	5	97.60	90.00	93.25	77.50	0.7468
minimum Value Over MINUTE 1 to MINUTE 15 of Hour 0 $MIN(StSBP_{d,0,1}, ..., StSBP_{d,0,15})$	2	83.33	73.57	71.50	85.33	0.7083
	3	86.50	80.75	73.20	73.20	0.8879
	4	76.20	80.50	62.80	79.25	0.7258
	5	81.20	71.00	74.75	69.00	0.8746
maximum Value Over MINUTE 1 to MINUTE 15 of Hour 0 $MAX(StSBP_{d,0,1}, ..., StSBP_{d,0,15})$	2	89.33	83.29	86.25	104.67	0.5614
	3	103.25	92.75	85.80	97.14	0.7957
	4	94.80	98.50	77.80	102.25	0.7324
	5	100.80	90.00	97.00	77.50	0.6721

As Table II shows for all metrics and for all days the P-Values are greater than 0.150. Therefore, the results suggest no statistically significant difference between the treatments at any day and with respect to any metric. This in turn suggest no indication of carryover effect from any period to the subsequent periods.

Figures I to III provide visual illustration of the entries of Table II

FIGURE I

Standing Systolic Blood Pressure at Minute 1 of Hour 0 (in mmHg)

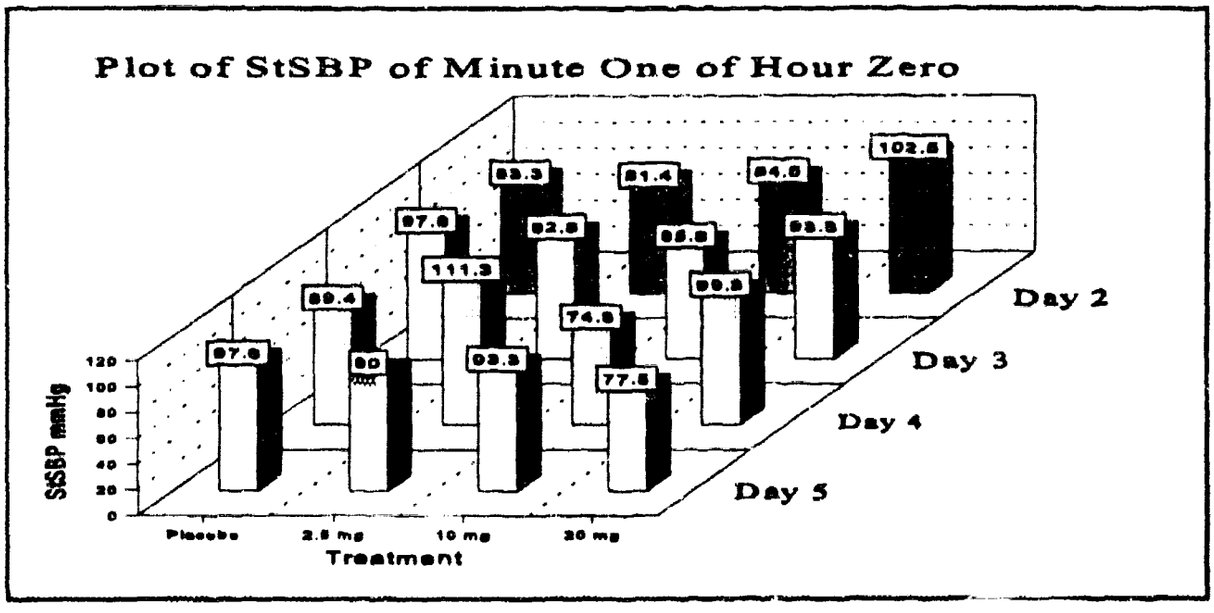


FIGURE II

Minimum Over Minute 1 to 6 of Hour 0 of Standing Systolic Blood Pressure (in mmHg)

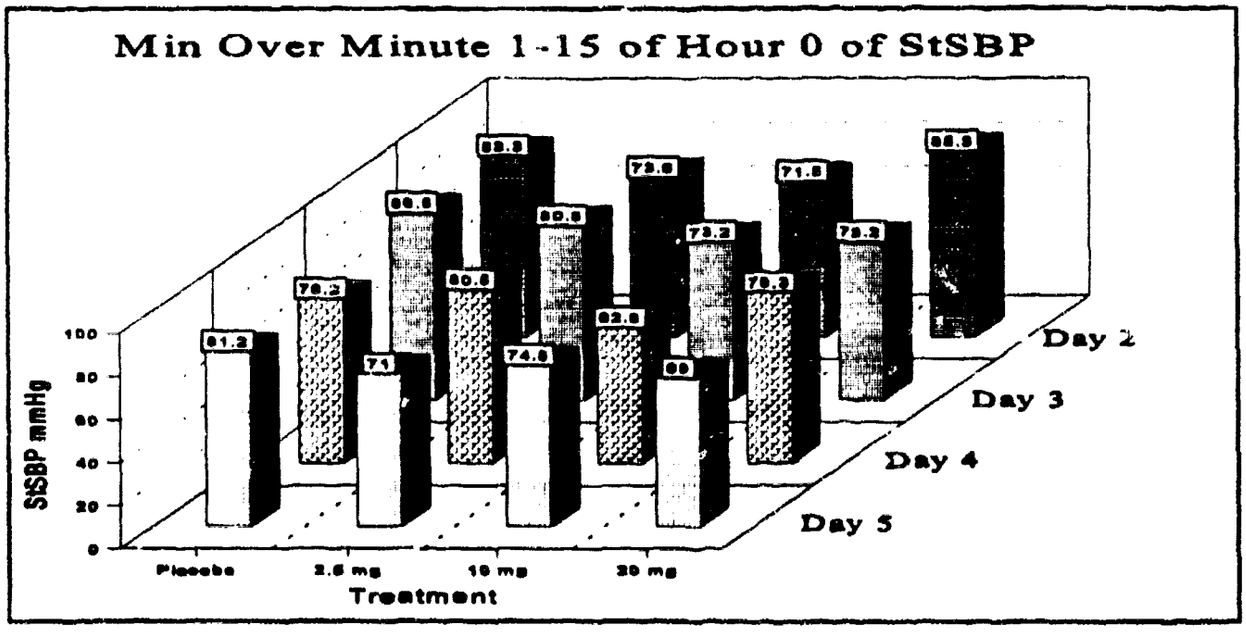
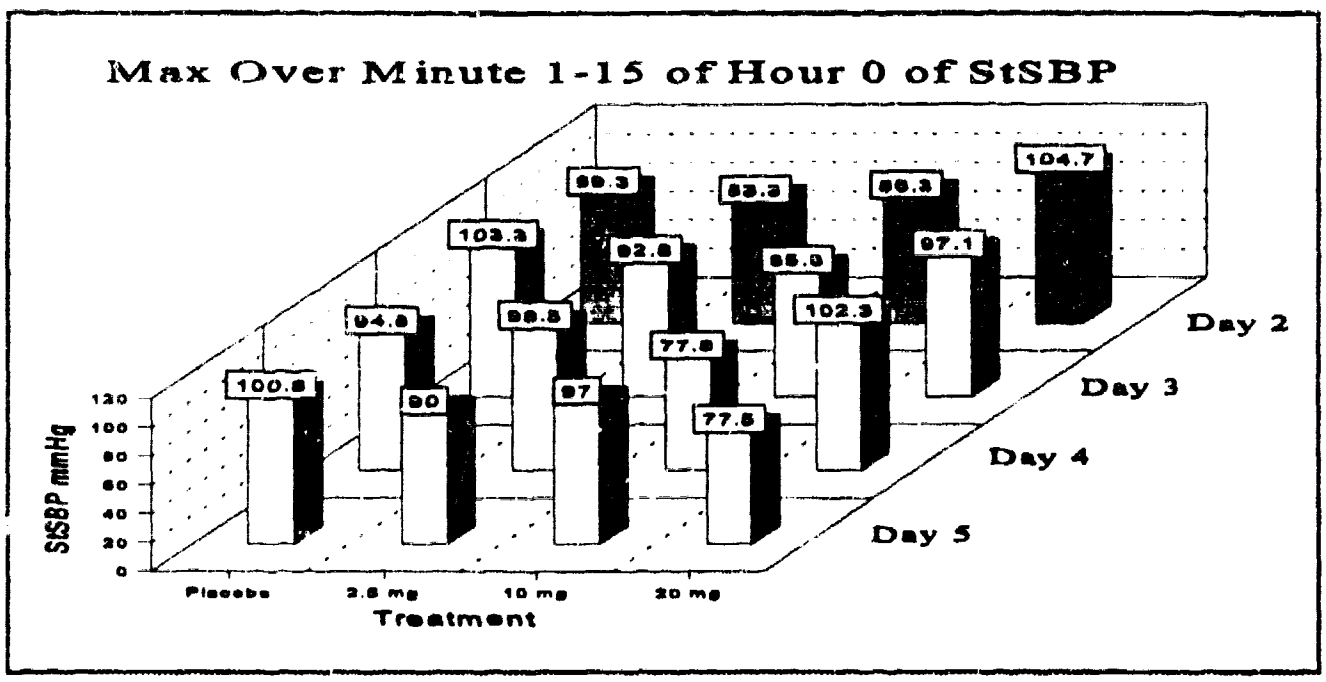


FIGURE III

Maximum Over Minute 1 to 6 of Hour 0 of Standing Systolic Blood Pressure (in mmHg)



Efficacy: The results of ANOVA on the StSBP for the crossover design with respect to the five procedures discussed above are summarized in Tables III -VII.

Procedure 1: This procedures uses MIN/MAX of Minute 1 of Hour 1-6 StSBP measurements, for each day d=2-5, as the post treatment and uses the StSBP at Minute 1 of Hour 0 of the Day 2 for the baseline (see Page 4 for the detail). The results are summarized in Table III which shows that:

At the MIN (trough effect) there was an overall statistically significant difference among the treatments with P = 0.0272; the Dunnett multiple comparison shows that the 20 mg midodrine was significantly superior to placebo.

At the MAX (peak effect) there was an overall statistically significant difference among the treatments with P = 0.0001; the Dunnett multiple comparison shows that the 10 mg and 20 mg midodrine were significantly superior to placebo.

The table below summarizes the relationship between drug content, delivery rate, and patch size.

Transdermal Fentanyl-In Vitro

Nominal Delivery Rate	Drug Content	Area (size)	Designed Delivery @24hr
25 mcg/hr	2.5 mg	10 cm^2	0.6 mg
50 mcg/hr	5.0 mg	20 cm^2	1.2 mg
75 mcg/hr	7.5 mg	30 cm^2	1.8 mg
100 mcg/hr	10.0 mg	40 cm^2	2.4 mg

As shown in the table above there is a 4 to 1 ratio between patch size and drug content while there is is a 100 to 1 ratio between drug content and the programmed delivery rate. The patch formulation tested in these studies is identical to that of the proposed to be marketed formulation.

Analytical Methodology

Laboratory:

Procedures

For the studies in this submission the sponsor chose to use Radioimmuno assay techniques (RIA) to detect and quantify the presence of fentanyl in plasma. This method involves the use of tritiated fentanyl and goat anti-serum to detect fentanyl.

Specificity

According to the journal articles submitted, this assay technique can be validated down to [redacted] pg/ml of fentanyl in plasma. The articles also concede that the assay cross-reacts with three fentanyl metabolites to some degree. The metabolites are:

1. Hydroxyfentanyl
2. 1-(2-phenethyl)-4-N-anilino piperidine
3. 4-N-(N-propionyl-anilino)-piperidine.

The sponsor in the body of the analytical report states that this interaction is not significant but fails to substantiate the claim of non-interference by the metabolites. No measures of specificity are reported that are related to the studies being reviewed.

Precision

The issue of assay precision is addressed by the sponsor by comparing the results of five sample assays on five different drug levels on one day to a similar series of concentrations prepared nine months later. The results from this comparison are contained in the attached Tables I and II. According

TABLE III

PROCEDURE 1: Analysis on Minute 1 Standing Systolic Blood Pressure
Post Treatment = MIN/MAX of the StSBP Values at Minute 1 of Hours 2-6
Baseline = StSBP at Minute 1 of Hour 0 of Day 2

Variable		Means in (mmHg)				P-Value ANOVA	Dunnett Comparisons*		
		Placebo A	Mido 2.5 mg B	Mido 10 mg C	Mido 20 mg D		B	C	D
MIN	Baseline	84.8 (18)	84.6 (19)	84.8 (18)	88.7 (20)	---	---	---	---
	Post Treatment	76.7 (20)	77.7 (21)	80.3 (20)	96.6 (22)	---	---	---	---
	LS Adj Diff	-6.2	-6.1	-2.6	10.2	0.0272	NS	NS	SIG
MAX	Baseline	84.8 (18)	77.7 (21)	80.3 (20)	96.6 (22)	---	---	---	---
	Post Treatment	104.6 (20)	115.6 (21)	129.7 (20)	149.7 (22)	---	---	---	---
	LS Adj Diff	25.9	29.9	50.3	63.1	0.0001	NS	SIG	SIG

* Dunnett Multiple Comparison compares the active treatments with the placebo and protects experimentwise Type I error of $\alpha = 0.05$.
Numbers inside ( ) are the sample sizes.

Procedure 2: This procedures uses the same MIN/MAX post treatment values as in procedure 1 and the uses the StSBP at Minute 1 of Hour 0 of Day d (the same day as the post treatment) as the baseline (see page 4 for the detail) to adjust the same day post treatment values. The results are summarized in Table IV:

TABLE IV

PROCEDURE 2: Analysis on Minute 1 Standing Systolic Blood Pressure
Post Treatment = MIN/MAX of StSBP Values at Minute 1 of Hours 2-6
Baseline = StSBP at Minute 1 of Hour 0 of the Day d

Variable		Means in (mmHg)				P-Value ANOVA	Dunnett Comparisons*		
		Placebo A	Mido 2.5 mg B	Mido 10 mg C	Mido 20 mg D		B	C	D
MIN	Baseline	92.7 (17)	90.8 (18)	84.1(18)	94.1 (21)	---	---	---	---
	Post Treatment	76.7 (20)	77.7 (21)	80.3 (20)	96.6 (22)	---	---	---	---
	LS Adj Diff	-11.8	-9.7	-1.0	6.3	0.0572	NS	NS	NS
MAX	Baseline	92.7 (17)	90.8 (18)	92.7 (17)	94.1 (21)	---	---	---	---
	Post Treatment	104.6 (20)	115.6 (21)	129.7 (20)	149.7 (22)	---	---	---	---
	LS Adj Diff	20.8	25.8	48.8	59.0	0.0001	NS	SIG	SIG

* Dunnett Multiple Comparison compares the active treatments with the placebo and protects experimentwise Type I error of $\alpha = 0.05$.
Numbers inside ( ) are the sample sizes.

Table IV shows that at the MIN there was no statistically significant difference among the treatments. At the MAX (peak effect) there was an overall statistically significant difference among the treatments with P = 0.0001; the Dunnett multiple comparison shows that the 10 mg and 20 mg midodrine were significantly superior to placebo.

- Procedure 3: This procedures uses MIN/MAX of StSBP measurements as those in Procedure 1. The baseline is the MIN/MAX of Minute 1 of Hours 2-6 StSBP measurements of Day 1. These baseline values will be used for the adjustment of every MIN/MAX post treatment values (see Page 5 for the detail). The results are summarized in Table V which shows that:

TABLE V

PROCEDURE 3: Analysis on Minute 1 Standing Systolic Blood Pressure
Post Treatment = MIN/MAX of StSBP Values at Minute 1 of Hours 2-6
Baseline = MIN/MAX of the StSBP Values of Minute 1 of Hours 2-6 of Day 1.

Variable		Means in (mmHg)				P-Value ANOVA	Dunnett Comparisons*		
		Placebo A	Mido 2.5 mg B	Mido 10 mg C	Mido 20 mg D		B	C	D
MIN	Baseline	78.4 (20)	78.7 (21)	78.4 (20)	80.5 (22)	---	---	---	---
	Post Treatment	76.7 (20)	77.7 (21)	80.3 (20)	96.6 (22)	---	---	---	---
	LS Adj Diff	0.36	-0.4	3.6	16.1	0.0075	NS	NS	SIG
MAX	Baseline	110.9 (20)	115.1 (21)	110.9 (20)	116.5 (22)	---	---	---	---
	Post Treatment	104.6 (20)	115.6 (21)	129.7 (20)	149.7 (22)	---	---	---	---
	LS Adj Diff	-5.9	0.3	19.0	33.0	0.0001	NS	SIG	SIG

* Dunnett Multiple Comparison compares the active treatments with the placebo and protects experimentwise Type I error of $\alpha = 0.05$.
Numbers inside ( ) are the sample sizes.

At the MIN there was an overall statistically significant difference among the treatments with P = 0.0075; the Dunnett multiple comparison shows that the 20 mg midodrine was significantly superior to placebo.

At the MAX there was an overall statistically significant difference among the treatments with P = 0.0001; the Dunnett multiple comparison shows that the 10 mg and 20 mg midodrine were significantly superior to placebo.

- Procedure 4: This procedures uses MIN/MAX value over all observation from Hour 1 to Hour 6 for each day (Day 2 - 5). Baseline is the MIN/MAX and was taken over the values of Minute 1 - 6 of Hour 0 of the same day as the post treatment values. These baselines used for the adjustment of every day MIN/MAX post treatment values (see Page 5 for the detail).

The results are summarized in Table VI which shows:

TABLE VI

PROCEDURE 4: Analysis on MIN and MAX Standing Systolic Blood Pressure
Post Treatment = MIN/MAX of all StSBP Measurements at Hours 2-6
Baseline =MIN/MAX of the StSBP Values of Minute 1 - 6 of Hour 0 for Each Day d

Variable		Means in (mmHg)				P-Value ANOVA	Dunnett Comparisons*		
		Placebo A	Mido 2.5 mg B	Mido 10 mg C	Mido 20 mg D		B	C	D
MIN	Baseline	81.4 (17)	76.0 (19)	70.3 (18)	78.7 (21)	---	---	---	---
	Post Treatment	69.1 (20)	71.1 (21)	72.4 (20)	77.1 (22)	---	---	---	---
	LS Adj Diff	-10.5	-3.6	3.1	1.2	0.0287	NS	NS	SIG
MAX	Variable	97.6 (17)	89 9 (19)	86.2)18)	96.5 (21)	---	---	---	---
	Post Treatment	108.0 (20)	118.5 (21)	133.8 (20)	152.1 (22)	---	---	---	---
	Post Treatment	19.4	30.1	50.7	58.9	0.0001	NS	SIG	SIG

* Dunnett Multiple Comparison compares the active treatments with the placebo and protects experimentwise Type I error of $\alpha = 0.05$.
Numbers inside ( ) are the sample sizes.

At the MIN there was an overall statistically significant difference among the treatments with P = 0.0287; the Dunnett multiple comparison shows that the 20 mg midodrine was significantly superior to placebo.

At the MAX there was an overall statistically significant difference among the treatments with P = 0.0001; the Dunnett multiple comparison shows that the 10 mg and 20 mg midodrine were significantly superior to placebo.

PROCEDURE 5: This procedures uses the same MIN/MAX value over all observation from Hour 1 to Hour 6 for each day (Day 2 - 5). Baseline is the MIN/MAX taken over the values of Minute 1 - 6 of Hour 0 of the Day 2. These baselines used for the adjustment of every day MIN/MAX post treatment values (see Page 5 for the detail). The results are summarized in Table VII which shows:

At the MIN there was no statistically significant difference among the treatments. At the MAX there was an overall statistically significant difference among the treatments with P = 0.0001; the Dunnett multiple comparison shows that the 10 mg and 20 mg midodrine were significantly superior to placebo.

TABLE VII

PROCEDURE 5 Analysis on MIN and MAX Standing Systolic Blood Pressure
Post Treatment = MIN/MAX of all StSBP Measurements at Hour 2-6
Baseline =MIN/MAX of StSBP of Minute 1 - 6 of Hour 0 of Day 2

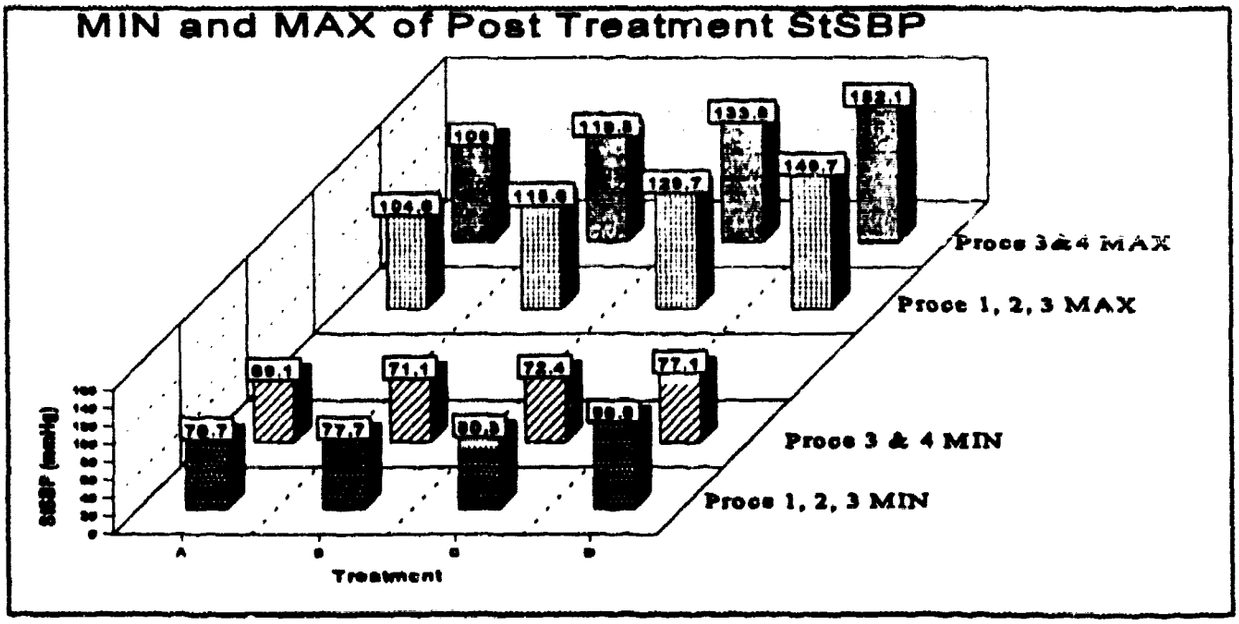
Variable		Means in (mmHg)				P-Value ANOVA	Dunnett Comparisons*		
		Placebo A	Mido 2.5 mg B	Mido 10 mg C	Mido 20 mg D		B	C	D
MIN	Baselin	83.3 (20)	73.6 (20)	71.5 (20)	85.3 (20)	---	---	---	---
	Post Treatmnt	69.1 (20)	71.1 (21)	72.4 (20)	77.1 (22)	---	---	---	---
	LS Adj Diff	-7 5	-6.5	-4.4	-1.3	0.3576	NS	NS	NS
MAX	Baseline	89.3 (20)	83.3 (20)	86.3 (20)	104.7 (20)	---	---	---	---
	Post Treatmnt	108.0 (20)	118.5 (21)	133.8 (20)	152.1 (22)	---	---	---	---
	LS Adj Diff	26.8	30.6	51.9	62.2	0.0001	NS	SIG	SIG

* Dunnett Multiple Comparison compares the active treatments with the placebo and protects experimentwise Type I error at $\alpha = 0.05$.
Numbers inside ( ) are the sample sizes.

Figure IV demonstrates the contrast between the MIN and MAX post treatment values. Again, we need to mention that procedures 1, 2, and 3 use the same post treatment MIN/MAX and procedures 4 and 5 use the same MIN/MAX values.

FIGURE IV

Plot of MIN and MAX Values of the Standing Systolic Blood Pressures



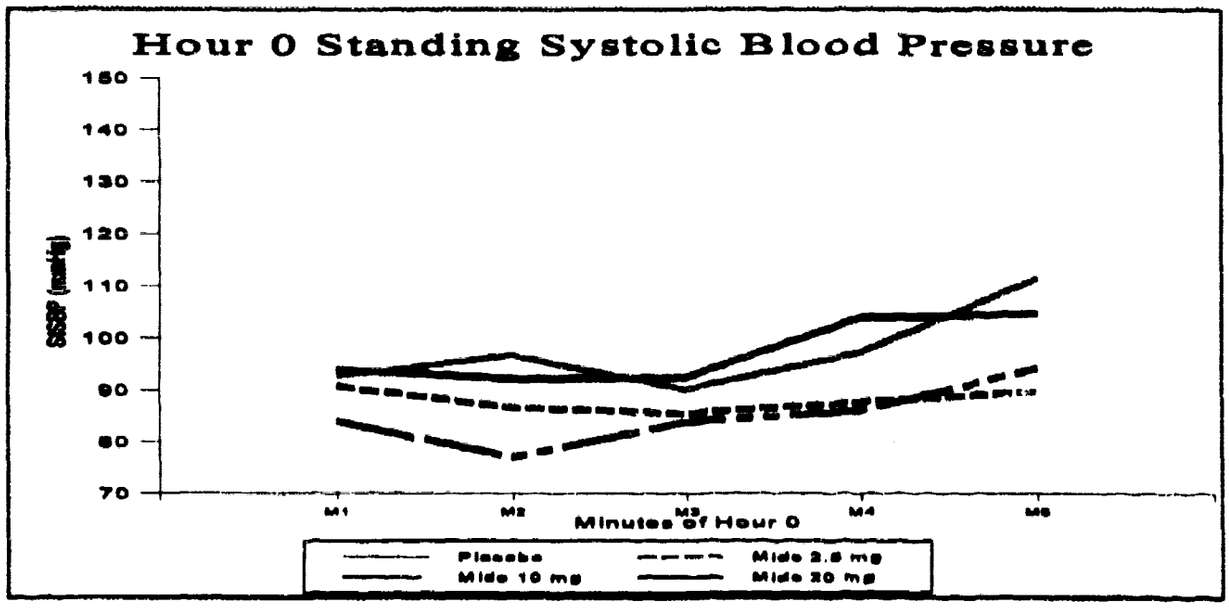
Duration of Action

Perhaps a practical way to study the duration of action is by the descriptive statistics. Figures V-VII present the profiles of the StSBP at Hours 0 to 6. The profiles show the variations in StSBP from minute to minute for placebo and midodrine 2.5 mg, 10 mg and 20 mg doses. As mentioned before, the data provides StSBP measurements for minutes 1 to 6 for Hours 0, 2, 3, 4, 5, and 6 and the measurements for Minutes 1 to 15 for Hour 1. There was only the measurements for one patient for Minute 6 of Hours 0, 2, 3, 4, 5, and 6 and hence we excluded Minute 6 for Hours 0, 2, 3, 4, 5, and 6.

- ***Hour o Of Day 2 to 5:*** Figure V shows the StSBP profiles at Hour 0. The profiles show a similarity between the treatment groups with no indication of the superiority of on treatment over the others.

FIGURE IV

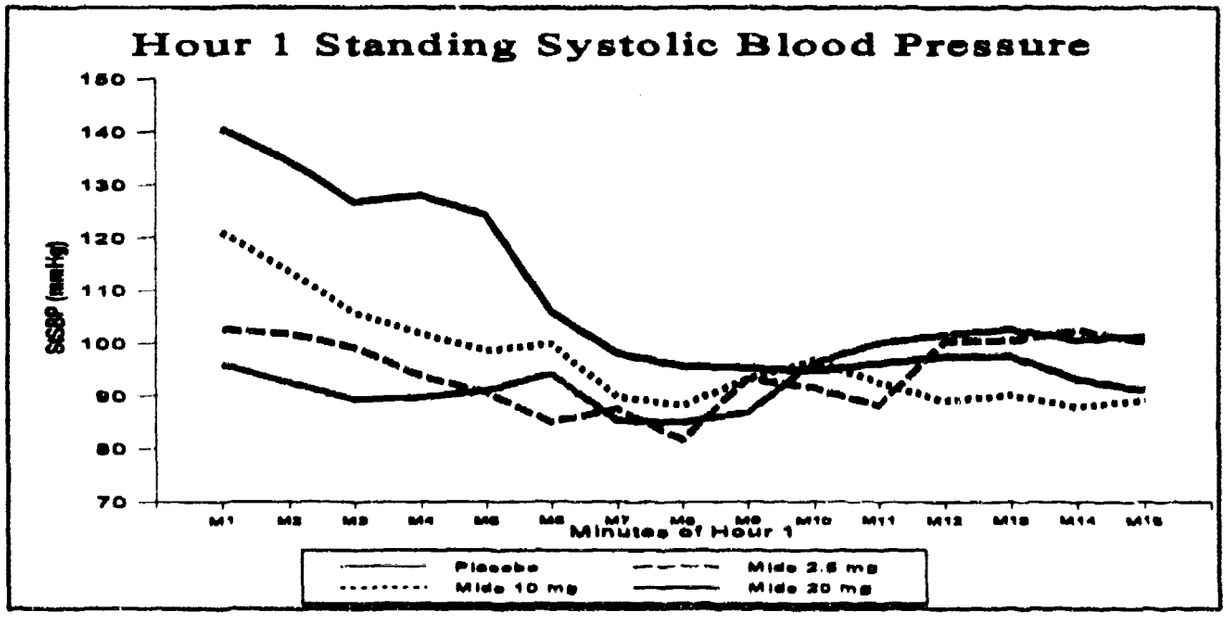
Profiles of Minute 1 to 5 of Hour 0 of Standing systolic Blood Pressures
Averaged Across Patients and Day 2 to 5



Hour 1 of Day 2 to 5: Figure VI shows the StSBP profiles at Hour 1. As Figure VI shows, overall, the profiles for midodrine 10 mg and 20 mg show high values for StSBP at Minute 1 (about 140 mmHg for midodrine 20 mg and about 120 mmHg for midodrine 10 mg) which are distinctively higher than those of placebo (about 95 mmHg) and midodrine 2.5 mg (about 102 mmHg). The high values gradually taper down from Minute 1 to Minute 9 then within the interval of Minute 10 to 15 they are flat. The profiles for placebo and midodrine 2.5 mg are virtually flat from Minute 1 to 15. Also, from Minute 1 to 15 there is no distinction between the treatments with respect to StSBP. These observations suggest that midodrine 2.5 mg is not effective at all and for the patients who are able to stay standing up for 15 Minutes or longer the midodrine doses of 10 mg and 20 mg will be effective for only about 10 Minutes.

FIGURE VI

Profiles of Minute 1 to 15 of Hour 1 of Standing systolic Blood Pressures
Averaged Across Patients and Day 2 to 5



Hour 2 to 6 of Day 2 to 5: Figure VII shows the StSBP profiles at Hour 2 to 6. Figure VII shows, overall, the profiles demonstrate a down ward trend with respect to StSBP from Hour 2 to Hour 6. From Hour 2 to 4 only the midodrine 20 mg has shown to be superior to placebo, as well as to the other two midodrine doses. The profiles for placebo, midodrine 2.5 mg and midodrine 10 mg are virtually flat from Hour 2 to 6 with no preference of one treatment over the other relative to elevation is StSBP.

FIGURE VII

Profiles of Minute 1 to 5 of Hours 2 - 6 of Standing systolic Blood Pressures
Averaged Across Patients and Day 2 to 5

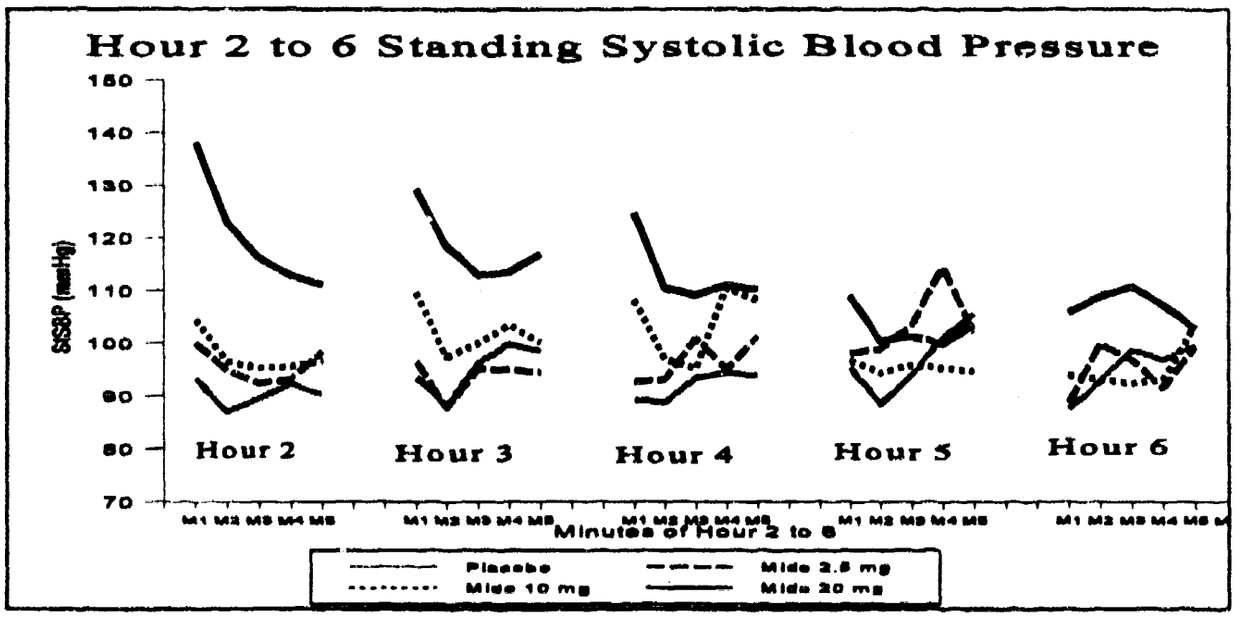


Figure VII shows, overall, the profiles demonstrate a down ward trend with respect to StSBP from Hour 2 to Hour 6. From Hour 2 to 4 only the midodrine 20 mg has shown to be superior to placebo, as well as to the other two midodrine doses. The profiles for placebo, midodrine 2.5 mg and midodrine 10 mg are virtually flat from Hour 2 to 6 with no preference of one treatment over the other relative to elevation is StSBP.

OVER ALL CONCLUSION

Overall, from all analysis on MIN/MAX and the profiles of StSBP (Figures V-VII) we conclude that:

- From all analysis procedures discussed in pages 4 and 5 the MAXIMUM elevations (MAX = peak values) have consistently suggest a statistically significant difference among the treatments with an overall F-Test P-value of 0.0001. For the MAX values the Dunnett multiple comparisons indicate that the 10 mg and 20 mg midodrine doses are statistically significantly superior to the placebo.

- With respect to the MINIMUM elevations (MIN = trough; see pages 4 and 5) the results show that for the procedures 1, 3, and 4 the 20 mg midodrine dose is significantly superior to placebo. No statistically significant difference among the treatments is demonstrated by procedures 2 and 5.

- With respect to **Duration of Action**, the profiles of StSBP (see Figures V-VII) suggest that: (1) No significant difference among the treatments during the Minutes 1 to 5 at Hour 0 (Figure V); (2) At Hour 1 the midodrine doses of 10 mg and 20 mg have demonstrated to be distinctively more effective than placebo and the midodrine 2.5 mg, however with a down ward trend from Minute 1 to Minute 9 (Figure VI). The midodrine 2.5 mg has not shown to be effective at all (Figure VI); and (3) From Hour 2 to 6 only the midodrine dose of 20 mg has shown some effectiveness with respect to elevation in StSBP. The profiles for placebo and the midodrine 2.5 mg and 10 mg are flat (stationary) from hour 2 to 6 (Figure VII). The profiles for the midodrine 20 mg show an overall downward trend from hour 2 to 4 and then becomes stationary for the duration of Hour 4 to 6.

Given the objective of midodrine treatment is to elevate the standing diastolic blood pressure, from the ANOVA results on MIN/MAX of StSBP and the profiles of StSBP one may conclude that for the patients who were able to stay standing up for 15 Minutes or longer, the single midodrine dose of 10 mg might be effective up to two hours and the single midodrine dose of 20 mg might be effective up to 4 hours.

Kooros Mahjoob, Ph.D.
Mathematical Statistician

Concur: Dr. Chi 3/28/96

CC:

Arch. NDA 19, 815 (in association with IND)
HFD-701/Dr. Anello
HFD-110
HFD-110/Dr. Lipicky
HFD-110/Dr. Fenichel
HFD-110/Dr. Gordon
HFD-110/Mrs. Morgenstern
✓ HFD-110/Mr. Buehler
HFD-344/Dr. Lisook
HFD-710/Dr. Chi
HFD-710/Dr. Hung
HFD-710/Dr. Mahjoob
HFD-710/Chron.

K. Mahjoob: 4-5301: Biometrics 1/Team 1: km.

STATISTICAL REVIEW AND EVALUATION

MAR 13 1996

NDA: NDA #19-815

Applicant: Roberts Pharmaceutical Corporation

Name of Drug: Amatine (midodrine HCl) Tablets

Documents Reviewed: Volumes. 11.1-11.4

1. Introduction

This statistical review focuses on the two carcinogenicity studies submitted by Roberts Pharmaceutical in NDA #19-815. The intention of the two studies was to assess the carcinogenicity potential of midodrine in rats and mice.

2. The Rat Study

2.1 Overview

This study was designed to obtain carcinogenicity information of midodrine in rats. The study had a parallel and randomized design with four treatment groups. During the 104 week study period, Sprague-Dawley rats including both males and females were dosed once daily with midodrine at dose levels of 0 (control), 1 (low dose), 3 (medium dose), or 10 (high dose) mg/kg/day according to assigned treatments. During the dosing period, all animals were checked regularly for mortality, mobility and presence of any palpable masses. After 104 weeks of dosing, all surviving animals were killed and necropsied. All control and high dose animals and all premature decedents underwent a full histopathological examination after death.

2.2 Results

Male

There were a total of 300 male rats (100 for control, 50 for low dose, 50 for medium dose, and 100 for high dose) in this study. One hundred thirty-five of them died before or in Week 104 (42 out of 100 for control, 22 out of 50 for 1mg, 23 out of 50 for 3mg, and 48 out of 100 for 10mg). In the sponsor's analyses, the difference in survival among the treatment groups was assessed graphically using K-M survival curve and tested formally

using Gehan-Wilcoxon test. No statistically significant difference in survival was reported. The sponsor's analysis of the tumor data showed a significantly increase in incidence of testicular interstitial cell tumor for the high dose males as compared to the control males. The incident rates are 19% and 6% for the high dose and the control group respectively ($p<0.05$).

Female

According to the sponsor's original plan, 300 females rats were randomly assigned to the four treatment groups and receive 1 (50 subjects), 3 (50 subjects), 10 (100 subjects)mg/kg/day, or no midodrine (100 subjects). After starting the dosing period, the sponsor decided to add one satellite control group as a consequence of 2 instances of the female control group receiving test material (on 7/8/87 and 1/30/88).

Among the 300 original female rats, there were 139 premature deaths (41 for control, 21 for low, 24 for medium, and 53 for high dose). The difference in survival among the treatment groups was assessed graphically using K-M survival curve and tested formally using Gehan-Wilcoxon test by the sponsor. No statistically significant finding was reported. No statistically significant difference in tumor incidence rate of any type of tumor was reported.

2.3 The Reviewer's Evaluation and Comments

The reviewer analyzed the survival and tumor data. The homogeneity of the survival distributions of rats among different treatment groups was assessed for male and female separately using Cox test (Journal of Royal Statistical Society, B, 34, 187-220. 1972) and Gehan-Wilcoxon test. The K-M estimates of the survival functions were obtained (Figure 1 and Figure 2 in the Appendix). There was a numerically increasing dose trend in mortality in both males and females. However no statistically significant (at 0.05 level) positive linear dose trend in mortality or difference in survival among the treatment groups was found for both male rats and female rates.

Death Rate / Rat Study

sex	number of death (%)			
	control	low	medium	high
male	42 (42)	22 (44)	23 (46)	48 (48)
female	41 (41)	21 (42)	24 (48)	53 (53)

The positive linear dose trend in incidental tumor rate or fatal tumor rate was tested using prevalence method

or death rate method (Peto et al, 1980) respectively. For tumors occurring in both categories (the same tumor was fatal for some animals and non-fatal for some other animals), a combined test was performed. The exact permutation trend test and asymptotic test were used to calculated the p-values of all trend tests. In the reviewer's analyses, the p-value based on the exact test was reported, if a tumor was fatal or non-fatal for all animals. Otherwise, the p-value based on the asymptotic test was used. In the analyses, the time intervals used were 0 to 52 weeks, 53 to 78 weeks, 79 to 104 weeks, and >104 weeks.

For male rats, the analysis indicated a statistically significant positive linear dose trend (at the nominal level 0.005 for a common tumor) in incidence of testes interstitial-cell tumor (p-value based on the exact permutation test was 0.001). The most incidence occurred in the high dose group. The p-value for a positive linear dose trend in tumor incidence rate for adrenals phaeochromocytoma in male rats was 0.0472 (asymptotic test). No rejection of the null hypothesis was made at the nominal level 0.005 (the tumor incidence rate for the control males=14%). This tumor was fatal for some of the animals. The results of the analyses on tumor data are given in Table 1 and Table 2 in the Appendix.

The results of analyses of survival and tumor data for the female rats using only the satellite control were similar to those using the original control as described in §2.2, except that the positive linear dose trend for liver hepatocellular adenoma was statistically significant (p=0.006, exact test) at the nominal level 0.025 (for a rare tumor) or nearly statistically significant at the nominal level 0.005 (for a common tumor). No tumor of this kind was observed in the satellite female control group, but six such incidences were found in the original control group.

Tumor Incidence /Rat Study

sex	tumor	n (%)				p-value (unadjusted)	significance
		control	low	med	high		
M	testes interstitial cell tumor	6 (6)	0 (0)	3 (13)	19(19)	0.001	S
	adrenals phaeochromocytoma	14(14)	2 (9)	1 (4)	21(21)	0.047	NS
F	liver hepatocellular adenoma	6 (6)	1 (5)	0 (0)	10 (10)	0.088	NS
		0 (0)*	1 (5)	0 (0)	10 (10)	0.006	S

* satellite control only

The survival rates of both male and female rats at the end of Week 104 in the four treatment groups were all greater or about 50%. In this study, the relative reduction in overall body weight gain (high dose vs. low dose) was about 16% for males and 9% for females. A slight numerical increase in mortality could be observed in the high dose group as compared to the control.

3. The Mouse Study

3.1 Overview

This study was designed to obtain carcinogenicity information of midodrine in mice. The study had a parallel and randomized design with four treatment groups. During the 78 week study period, 600 CD-1 mice including both males and females were dosed once daily with midodrine at dose levels of 0 (control), 1.7 (low dose), 5 (medium dose), 15 (high dose) mg/kg/day according to assigned treatments. During the dosing period, all animals were checked regularly for mortality, mobility and presence of any palpable masses. After 78 weeks of dosing, all surviving animals were killed and necropsied. All control and high dose animals and all premature decedents underwent a full histopathological examination after death.

3.2 Results

Male

There were a total of 300 male mice (100 for control, 50 for low dose, 50 for medium dose, and 100 for high dose) in this study. Fifty-four of them died before or in Week 78 (14 out of 100 for control, 7 out of 50 for 1.7mg, 13 out of 50 for 5mg, and 20 out of 100 for 15mg). In the sponsor's analysis, the difference in survival among the treatment groups was assessed graphically using estimated survival curves and tested formally using Gehan-Wilcoxon test. No statistically significant finding was reported . The sponsor's analysis of the tumor data did not show an evidence of any carcinogenic effect.

Female

Among 300 female mice (100 for control, 50 for low dose and 50 for medium dose, and 100 for high dose) 65 died (22 for control, 13 for low, 10 for medium, and 20 for high) before or in Week 78. In the sponsor's analysis, the difference in survival among the treatment groups was assessed graphically using K-M survival curve and tested formally using Gehan-Wilcoxon test. No statistically significant finding was reported. No statistically significant difference in tumor incidence rate for any type of tumor was reported.

3.3 The Reviewer's Evaluation and Comments

The reviewer analyzed the survival and tumor data. The homogeneity of the survival distributions of mice among

different treatment groups was assessed for male and female mice separately using Cox test (Journal of Royal Statistical Society, B, 34, 187-220. 1972) and Gehan-Wilcoxon test. The K-M estimates of the survival functions were obtained (Figure 3 and Figure 4). No statistically significant (at 0.05 level) positive linear dose trend in mortality or difference in survival among the treatment groups was found for both male and female mice.

The positive linear dose trend in incidental tumor rate or fatal tumor rate was tested using prevalence method or death rate method (Peto et al, 1980) respectively. For tumors occurring in both categories (the same tumor was fatal for some animals and non-fatal for some other animals), a combined test was performed. The exact permutation trend test and asymptotic test, were used to calculated the p-values of all trend tests. In the analyses, the time intervals used were 0 to 26 weeks, 27 to 52 weeks, 53 to 78 weeks, and >78 weeks.

For both male and female mice, no statistically significant positive dose trend in tumor incidence rate was found for any type of tumor except eye and optic nerve malignant schwannoma for females. The trend test for this type of tumor in female mice yielded p-value=0.0501; no incidence of this tumor was found in female control, low dose, and medium dose group and only one for the high dose group. From statistical point of view, this numerical dose trend is not conclusive based on this p-value compared to the nominal level 0.025 (for a rare tumor). Numerically, the death rate in male mice for medium or high dose was higher than that for control or low dose. However, no statistical evidence of difference in either mortality rate or survival distribution was found.

Death Rate / Mouse Study

sex	number of death (%)			
	control	low	medium	high
male	14 (14)	7 (14)	13 (26)	20 (20)
female	22 (22)	13 (26)	10 (20)	20 (20)

Tumor Incidence /Mouse Study

sex	tumor	n (%)				p-value unadjusted	significance
		control	low	med	high		
F	eye malignant schwannoma	0 (0)	0 (0)	0 (0)	1 (1)	0.050	NS

The survival rates of both male and female mice at the end of Week 78 in the four treatment groups were higher than 74%. A numerical increase in mortality could be seen in the high dose male group as compared to the control males. The relative reduction in overall body weight gain (high dose vs. control) was about 1% for the male mice and -2% for the female mice. These percentages were much less than those for male and females rats,

even though the mice got larger highest dose (15mg/kg/day for mice vs. 10mg/kg/day for rats). The reviewing pharmacologist might need to check if the length of the dosing period or the dose used was long or high enough.

Summary

The sponsor studied the carcinogenic potential of midodrine in rats and mice. The rat study used the doses 0, 1, 3, and 10mg/kg/day for 104 weeks. The mouse study used the doses 0, 1.7, 5, 15mg/kg/day for 78 weeks. A positive linear dose trend with respect to testes interstitial cell tumor was found in male rats ($p=0.001$). A significant linear dose trend with respect to liver hepatocellular adenoma for female rats was found only when the satellite control was used ($p=0.006$). Such a trend was observed using the original control group but not statistically significant ($p=0.088$). No final conclusion was drawn with respect to this tumor by this reviewer. There is no evidence of a survival difference among the treatment groups in male/female rats and male/female mice. In the mouse study, the relative reductions in body weight gain (high dose vs. control) were minimal and much less than those in the rat study. The reviewing pharmacologist might need to check the adequacy of the dosing and the length of the two studies.

Investigator: Richard Hotchkiss, M.D.

Study Site: Emory University Hospital
Atlanta, GA

Objective: This study was conducted to determine the pharmacokinetics and efficacy of the TTS-100 system in the treatment of severe postoperative pain following surgery.

Methods

This study was designed as a double blind, randomized, placebo controlled, parallel group study to assess the efficacy of the TTS-100 system in controlling postoperative pain. In addition, plasma levels were to be obtained to assess the performance of the TTS-100 system. All subjects in the study were healthy males and females in ASA categories I, II, or III (attachment 2) undergoing major thoracic, abdominal and head and neck surgery. Because this is a rather broad description, the demographics and initial diagnosis of these subjects are included in the report as attachment 15. The inclusion/exclusion criteria used in this study are reproduced as attachment 16 and 17 and are appropriate for a study of this type. Of the twenty-three subjects receiving the active patch, seven subjects dropped out of the study for a variety of reasons (attachments 18 and 19) ranging from cancellation of surgery to respiratory depression. This left 17 sets of data available for analysis.

On the study day each subject had one TTS-100 patch applied to the anterior chest two hours prior to entry into the surgical suite. Local preparations could include the trimming of chest hair if necessary. Approximately one hour prior to anesthesia induction each subject received 5-15mg of oral diazepam. Anesthesia was induced with thiopental 2-3mg/kg and fentanyl 300mcg. A single does of i.v. atropine 0.3mg was also given at this time. General anesthesia was maintained with nitrous oxide (60%), oxygen (40%), and enflurane (0.5-1.5%).

To assess the pharmacokinetic performance of the product, venous blood samples were collected at the following times: time zero (application), 4, 8, 12, 16, 20, 24 (patch removed), 32, 40, 48, and 60 hours post-dosing. The blood samples(10ml) were allowed to clot and, after centrifugation, 2ml samples were separated and frozen for shipment to Endocrine Sciences for analysis. The patches, once removed, were shipped to Alza for analysis of residual fentanyl levels.

Results

Attached as Tables XIII-XV are the individual subject results including the analysis of the patch residuals. Reproduced below is a summary table of the information:

	AUC(0-36) (ng*hr/ml)	Cmax (ng/ml)	Tmax (hr)	Residual (mg)	Delivered (mg)
Mean	54.84	2.40	20.3	6.23	3.47
%CV	9.7	8.3	11.8	4.5	8
Min					
Max					

Lu Cui

Lu Cui, Ph.D. (Mathematical Statistician)
3/12/96

Concur: Dr. H. M. James Hung 3/13/96
Dr. George Chi 3/11/96

cc:
NDA #19-815, Amatine (Midodrine HCl)
HFD-701 / Dr. Anello
HFD-110 / Dr. Lipicky
HFD-110 / Dr. Link
HFD-110 / Dr. DeFelice
HFD-110 / Ms. Morgenstern
HFD-110 / Mr. Bulchler
HFD-344 / Dr. Lisook
HFD-710 / Dr. Chi
HFD-710 / Mr. Ortickc
HFD-710 / Dr. Hung
HFD-710 / Dr. Cui
HFD-710 / Chron.
Lcui/19-815/midodrine/precli/rev/rober/5945322

Appendix

Table 1. Tumor Incidence / Male Rat

Organ Name	Tumor Name	Poly-3*	Asymptotic P-Value	Exact P-Value	# of tumor by treatment 0	1	2	3
ABDOMEN	FIBROMA	S	0.5127	0.58820	0	0	1	0
ABDOMEN	LIPOMA	S	1.0000	0.82460	1	0	0	0
ABDOMEN	SARCOMA	S	0.5566	0.76900	0	1	0	0
ADRENALS	CORTICAL ADENOMA	S	1.0000	0.91100	2	0	0	0
ADRENALS	PHAEOCHROMOCYTOMA	M	0.0501	0.06715	14	2	1	21
BRAIN	GLIOMA	M	0.0510	0.04990	0	2	0	2
BRAIN	GRANULAR CELL TUMOR	S	0.7289	0.75690	0	1	0	0
BRAIN	RETICULOSIS	S	0.3182	0.87575	0	0	0	1
DIAPHRAGM	METASTASIS FROM PRIMARY IN	S	0.7289	0.75690	0	1	0	0
EPIDIDYMIS	MESOTHELIOMA	S	1.0000	0.82460	1	0	0	0
ESOPHAGUS	ADENOCARCINOMA	S	0.4111	0.11850	0	0	0	1
LIVER	HEPATOCELLULAR ADENOMA	S	0.2684	0.27205	0	1	1	5
LIVER	HEPATOCELLULAR CARCINOMA	M	0.3403	0.31575	6	0	0	6
LUNGS	ALVEOLAR/BRONCHIOLAR CARCIN	S	1.0000	0.82460	1	0	0	0
LYMPHORETICULAR/HAEMOPOIETI	LYMPHOCYTIC LEUKAEMIA	S	0.4214	0.12366	0	0	0	1
LYMPHORETICULAR/HAEMOPOIETI	LYMPHOMA	M	0.2944	0.30741	0	0	1	1
MAMMARY GLANDS	FIBROADENOMA	S	0.7644	0.79455	1	0	1	0
MAMMARY GLANDS	FIBROMA	S	0.5217	0.58820	0	0	1	0
MESENTERIC LYMPH NODE	HAEMANGIOENDOTHELIOMA	S	0.6868	0.26305	1	0	0	2
PANCREAS	CARCINOSARCOMA	S	0.5680	0.76518	0	1	0	0
PANCREAS	ENDOCRINE ADENOCARCINOMA	S	0.3140	0.87575	0	0	0	1
PANCREAS	ENDOCRINE ADENOMA	S	0.6820	0.67408	1	0	0	1
PANCREAS	ISLET ADENOCARCINOMA	M	0.6719	0.72185	2	0	1	1
PANCREAS	ISLET ADENOMA	S	0.3190	0.32975	2	0	2	3
PARATHYROIDS	ADENOMA	S	0.3709	0.20660	1	0	0	2
PITUITARY	ADENOCARCINOMA	S	0.8056	0.82815	1	1	0	1
PITUITARY	ADENOMA	M	0.7760	0.77320	53	12	11	51
PITUITARY	ADENOMA (INTERMEDIATE LOBE	M	0.7357	0.78650	2	1	1	1
SCIATIC NERVE	NEUROLEMMOMA	S	0.6643	0.14215	0	0	0	1
SKIN/SUBCUTIS	FIBROMA	M	0.0897	0.09005	14	1	2	8
SKIN/SUBCUTIS	FIBROSARCOMA	M	0.5722	0.53398	2	0	2	2
SKIN/SUBCUTIS	KERATOACANTHOMA	S	0.4318	0.40682	0	0	1	4
SKIN/SUBCUTIS	LIPOMA	S	0.4939	0.39975	5	0	0	5
SKIN/SUBCUTIS	PAPILLOMA	S	0.3737	0.42258	1	1	1	2
SKIN/SUBCUTIS	SARCOMA	S	0.9414	0.93908	3	0	2	0
SKIN/SUBCUTIS	SQUAMOUS-CELL CARCINOMA	M	0.2968	0.31438	1	0	1	2
SKIN/SUBCUTIS	TRICHOEPITHELIOMA	S	0.6325	0.41715	1	0	0	1
SPINAL CORD	GLIOMA	S	0.6643	0.14215	0	0	0	1
SPLEEN	HAEMANGIOENDOTHELIOMA	S	1.0000	0.82858	1	0	0	0
SPLEEN	HAEMANGIOMA	S	0.6643	0.14215	0	0	0	1
STOMACH/GLD	OSTEOMA	S	0.6643	0.14215	0	0	0	1
TESTES	INTERSTITIAL-CELL TUMOR	S	0.0018	0.00188	6	0	3	19
TESTES	MESOTHELIOMA	S	0.3140	0.87575	0	0	0	1
TESTES	TUMOR(S) SIMILAR AND INT	S	0.4821	0.63400	0	0	1	0
THYMUS	THYMOMA	S	0.6643	0.14215	0	0	0	1
THYROIDS	C-CELL ADENOMA	S	0.7248	0.72983	6	1	2	6
THYROIDS	C-CELL CARCINOMA	S	0.7249	0.60118	3	0	0	2
THYROIDS	CYSTADENOMA	S	0.5358	0.62230	0	0	1	0
THYROIDS	FOLLICULAR ADENOMA	S	0.6902	0.71770	1	2	1	1
THYROIDS	FOLLICULAR CARCINOMA	S	0.8969	0.80120	3	0	0	1
TONGUE	SQUAMOUS-CELL CARCINOMA	S	1.0000	0.82550	1	0	0	0
URINARY BLADDER	POLYP	S	0.6666	0.81080	0	1	0	0
VASCULAR SYSTEM	HAEMANGIOMA	S	0.6325	0.41715	1	0	0	1

*S either fatal for the all or non-fatal for the all, M fatal for some and non-fatal for others

Table 2. Tumor Incidence / Female Rat (Original Control)

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	# of tumor by treatment C	1	M	F
ABDOMEN	LIPOMA	S	0.6594	0.76560	0	1	0	1
ADRENALS	CORTICAL ADENOMA	S	0.6416	0.41975	1	0	0	1
ADRENALS	PHAEOCHROMOCYTOMA	S	0.1593	0.04420	0	2	0	2
BRAIN	GLIOMA	M	1.0000	0.46705	4	0	0	0
BRAIN	GRANULAR CELL TUMOUR	S	1.0000	0.81425	1	0	0	0
CERVIX	LEIOMYOMA	S	1.0000	0.81425	1	0	0	0
CERVIX	POLYP	S	1.0000	0.82960	1	0	0	0
LIVER	CHOLANGIOMA	S	0.3626	0.09790	0	0	0	1
LIVER	HEPATOCELLULAR ADENOMA	S	0.0081	0.00155	6	0	0	10
LIVER	HEPATOCELLULAR CARCINOMA	S	0.1287	0.16080	0	1	0	2
LYMPHORETICULAR/HAEMOPOIETI	HISTIOCYTIC SARCOMA	S	0.4662	0.14360	0	0	0	1
LYMPHORETICULAR/HAEMOPOIETI	LYMPHOMA	S	0.2771	0.38170	0	1	0	1
MAMMARY GLANDS	ADENOCARCINOMA	M	0.5315	0.52920	3	1	2	8
MAMMARY GLANDS	ADENOMA	S	0.1045	0.09210	3	0	1	6
MAMMARY GLANDS	FIBROADENOCARCINOMA	S	0.8831	0.91345	1	2	0	0
MAMMARY GLANDS	FIBROADENOMA	M	0.3816	0.37665	28	6	4	28
MAMMARY GLANDS	LIPOMA	S	0.5963	0.40310	1	0	0	1
OVARIES	LUTEOMA	S	0.3709	0.20105	1	0	0	2
PANCREAS	CARCINOSARCOMA	S	1.0000	0.81425	1	0	0	0
PANCREAS	ISLET ADENOCARCINOMA	S	0.0566	0.01605	0	0	0	3
PANCREAS	ISLET ADENOMA	S	0.0691	0.02030	0	0	0	3
PITUITARY	ADENOCARCINOMA	M	0.5379	0.47275	3	1	3	4
PITUITARY	ADENOMA	M	0.8655	0.86355	77	14	27	66
SKELETAL MUSCLE	RHABDOMYOSARCOMA	S	0.4824	0.62845	0	0	1	0
SKIN/SUBCUTIS	FIBROMA	S	0.5699	0.58300	4	0	2	3
SKIN/SUBCUTIS	FIBROSARCOMA	M	0.4967	0.54415	2	1	0	2
SKIN/SUBCUTIS	KERATOACANTHOMA	S	0.5164	0.60870	0	0	1	0
SKIN/SUBCUTIS	LIPOMA	S	1.0000	0.81425	1	0	0	0
SKIN/SUBCUTIS	LIPOSARCOMA	S	0.3626	0.09790	0	0	0	1
SKIN/SUBCUTIS	PAPILLOMA	S	0.6426	0.41975	1	0	0	1
SKIN/SUBCUTIS	SARCOMA	M	0.3221	0.37725	0	1	0	1
THYROIDS	C-CELL ADENOMA	S	0.8519	0.85190	5	1	2	2
THYROIDS	C-CELL CARCINOMA	S	0.6594	0.76560	0	1	0	0
THYROIDS	FOLLICULAR CARCINOMA	S	0.6879	0.43390	1	0	0	1
UTERUS	ADENOCARCINOMA	S	0.2930	0.36220	0	1	0	1
UTERUS	LEIOMYOMA	S	0.4393	0.22965	0	0	0	1
UTERUS	POLYP	S	0.7318	0.72475	10	3	4	8
UTERUS	SQUAMOUS-CELL CARCINOMA	S	1.0000	0.81425	1	0	0	0
VAGINA	POLYP	S	0.1018	0.10595	0	0	1	2
VASCULAR SYSTEM	HAEMANGIOSARCOMA	S	1.0000	0.82960	1	0	0	0

*S either fatal for the all or non-fatal for the all, M fatal for some and non-fatal for others

Table 3. Tumor Incedence /Male Mouse

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	# of tumor by treatment C	L	M	H
ADRENAL GLANDS	MALIGNANT PHEOCHROMOCYTOMA	S	0.4681	0.14400	0	0	0	1
CAECUM	ADENOCARCINOMA	S	0.4637	0.14145	0	0	0	1
COLON	ADENOCARCINOMA	S	0.4819	0.14990	0	0	0	1
HARDERIAN GLANDS	HARDERIAN GLAND ADENOMA	S	0.4451	0.33590	6	0	0	7
KIDNEYS	TUBULAR ADENOCARCINOMA	S	0.4819	0.14990	0	0	0	1
KIDNEYS	TUBULAR ADENOMA	S	0.4819	0.14990	0	0	0	1
LIVER	HAEMANGIOMA	S	1.0000	0.83260	1	0	0	0
LIVER	HAEMANGIOSARCOMA	S	1.0000	0.83260	1	0	0	0
LIVER	HEPATOCELLULAR ADENOMA	S	0.6809	0.66460	17	0	1	14
LIVER	HEPATOCELLULAR CARCINOMA	M	0.3305	0.31175	4	0	2	6
LUNGS	PULMONARY ADENOCARCINOMA	S	0.6242	0.46415	3	0	0	3
LUNGS	PULMONARY ADENOMA	S	0.2170	0.21610	21	1	2	25
LYMPHORETICULAR/HAEMOPOIETI	MALIGNANT LYMPHOMA	M	0.9337	0.93960	5	0	1	1
PANCREAS	ISLET CELL ADENOMA	S	0.4819	0.14990	0	0	0	1
PROSTATE	ADENOMA	S	0.4819	0.14990	0	0	0	1
SKIN & MAMMARY AREA	LIPOMA	S	1.0000	0.83260	1	0	0	0
SKIN & MAMMARY AREA	SEBACEOUS ADENOCARCINOMA	S	0.4923	0.63605	0	0	1	0
SKIN & MAMMARY AREA	SQUAMOUS PAPILLOMA	S	0.4819	0.14990	0	0	0	1
SPLEEN	HAEMANGIOSARCOMA	S	1.0000	0.83260	1	0	0	0
STOMACH, KERATINISED	SQUAMOUS PAPILLOMA	S	0.2307	0.07070	0	0	0	2
TESTES	LEYDIG CELL ADENOMA	S	1.0000	0.91435	2	0	0	0
THORAX	FIBROSARCOMA	S	0.4819	0.14990	0	0	0	1
THYROID GLANDS	FOLLICULAR CELL ADENOMA	S	0.3056	0.07335	0	0	0	1

* S either fatal for the all or non-fatal for the all, M fatal for some and non-fatal for others

Table 4. Tumor Incidence / Female Mouse

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	# of tumor by treatment C	L	M	H
ADRENAL GLANDS	BENIGN PHEOCHROMOCYTOMA	S	0.5117	0.58820	1	0	0	0
EYES AND OPTIC NERVE	MALIGNANT SCHWANNOMA	S	0.0501	0.04715	0	0	0	1
HARDERIAN GLANDS	HARDERIAN GLAND ADENOMA	S	0.8897	0.89005	2	1	0	1
LUNGS	OSTEOSARCOMA	S	0.5222	0.53390	0	0	1	0
LUNGS	PULMONARY ADENOCARCINOMA	M	0.4310	0.40680	2	1	0	0
LUNGS	PULMONARY ADENOMA	S	0.4939	0.39975	8	0	0	11
LYMPHORETICULAR/HAEMOPOIETI	MALIGNANT LYMPHOMA	M	0.3737	0.42250	13	3	2	7
OVARIES	CYSTADENOMA	S	0.5966	0.76900	2	0	0	3
OVARIES	LUTEOMA	S	1.0000	0.82460	4	1	0	0
PANCREAS	ISLET CELL ADENOMA	S	1.0000	0.82850	1	0	0	1
PITUITARY GLAND	ADENOCARCINOMA	S	0.4214	0.12360	0	0	1	0
PITUITARY GLAND	ADENOMA	S	0.2944	0.30740	2	0	0	0
SKIN & MAMMARY AREA	MAMMARY ADENOACANTHOMA	S	0.7644	0.79455	0	0	0	1
SKIN & MAMMARY AREA	MAMMARY ADENOCARCINOMA	M	0.5117	0.58820	2	0	0	1
SPINAL CORD	MALIGNANT SCHWANNOMA	S	0.4460	0.24345	0	0	0	1
URINARY BLADDER	TRANSITIONAL CELL PAPILLOMA	S	0.3140	0.07575	0	0	0	1
UTERINE CERVIX	FIBROUS POLYP	S	0.6820	0.47400	1	0	0	0
UTERINE CERVIX	SARCOMA, NOS	S	0.6719	0.72105	1	0	0	0
UTERUS	CHORIOCARCINOMA	S	0.8055	0.82015	0	0	0	1
UTERUS	ENDOMETRIAL STROMAL POLYP	M	0.7760	0.77320	4	1	0	3
UTERUS	ENDOMETRIAL STROMAL SARCOMA	S	0.7357	0.78850	0	1	0	2
UTERUS	FIBROMA	S	0.4643	0.14215	3	0	0	0
UTERUS	FIBROSARCOMA	S	0.3192	0.32875	1	0	0	0
UTERUS	LEIOMYOMA	S	0.5600	0.76510	0	0	0	3
UTERUS	SARCOMA, NOS	S	0.3709	0.20680	1	0	0	2
VAGINA	BASAL CELL ADENOMA	S	1.0000	0.91100	1	0	0	0

* S either fatal for the all or non-fatal for the all, M fatal for some and non-fatal for others

Survival Function / Male Rat

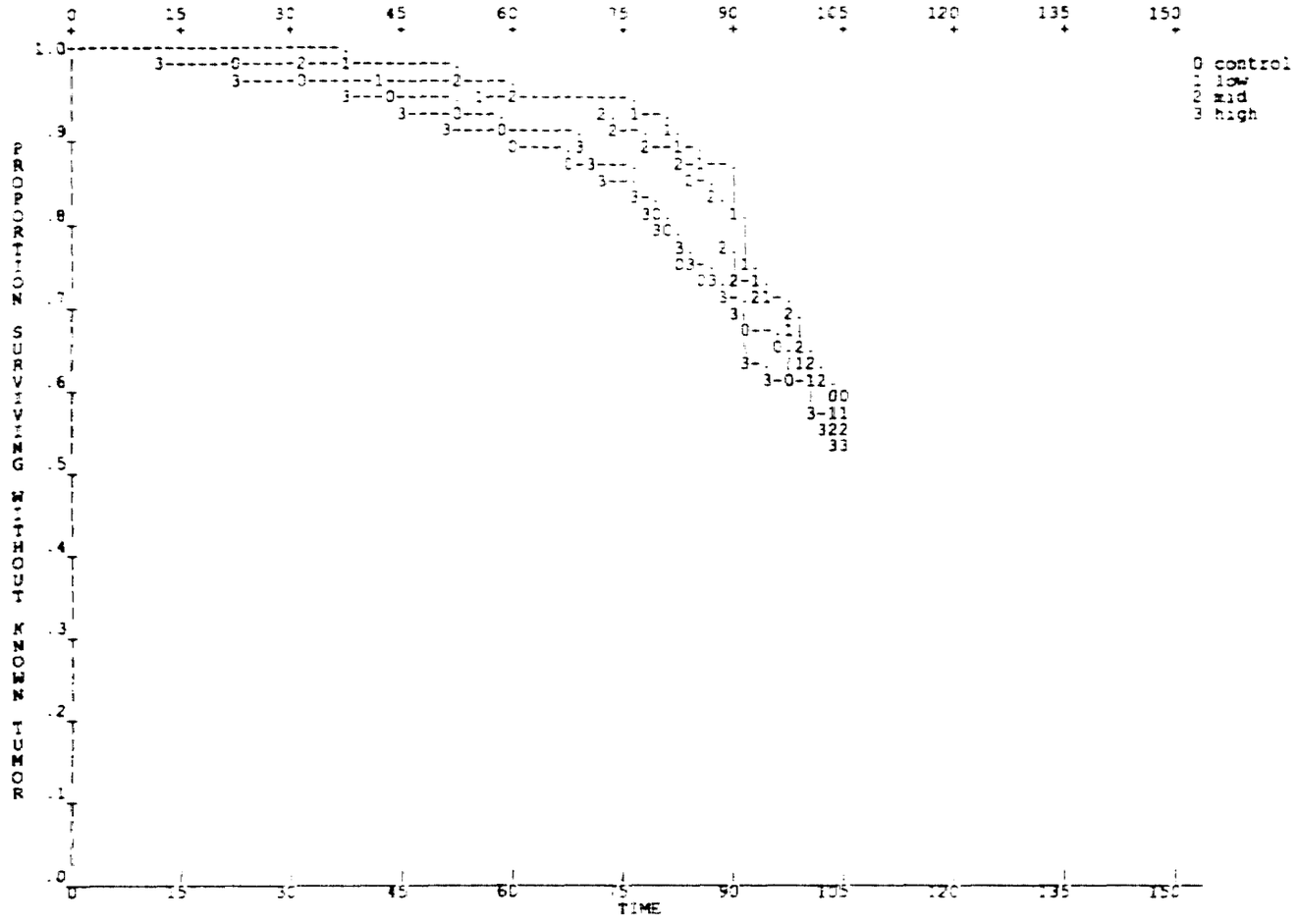


Figure 1

Survival Function / Female Rat (Original Control)

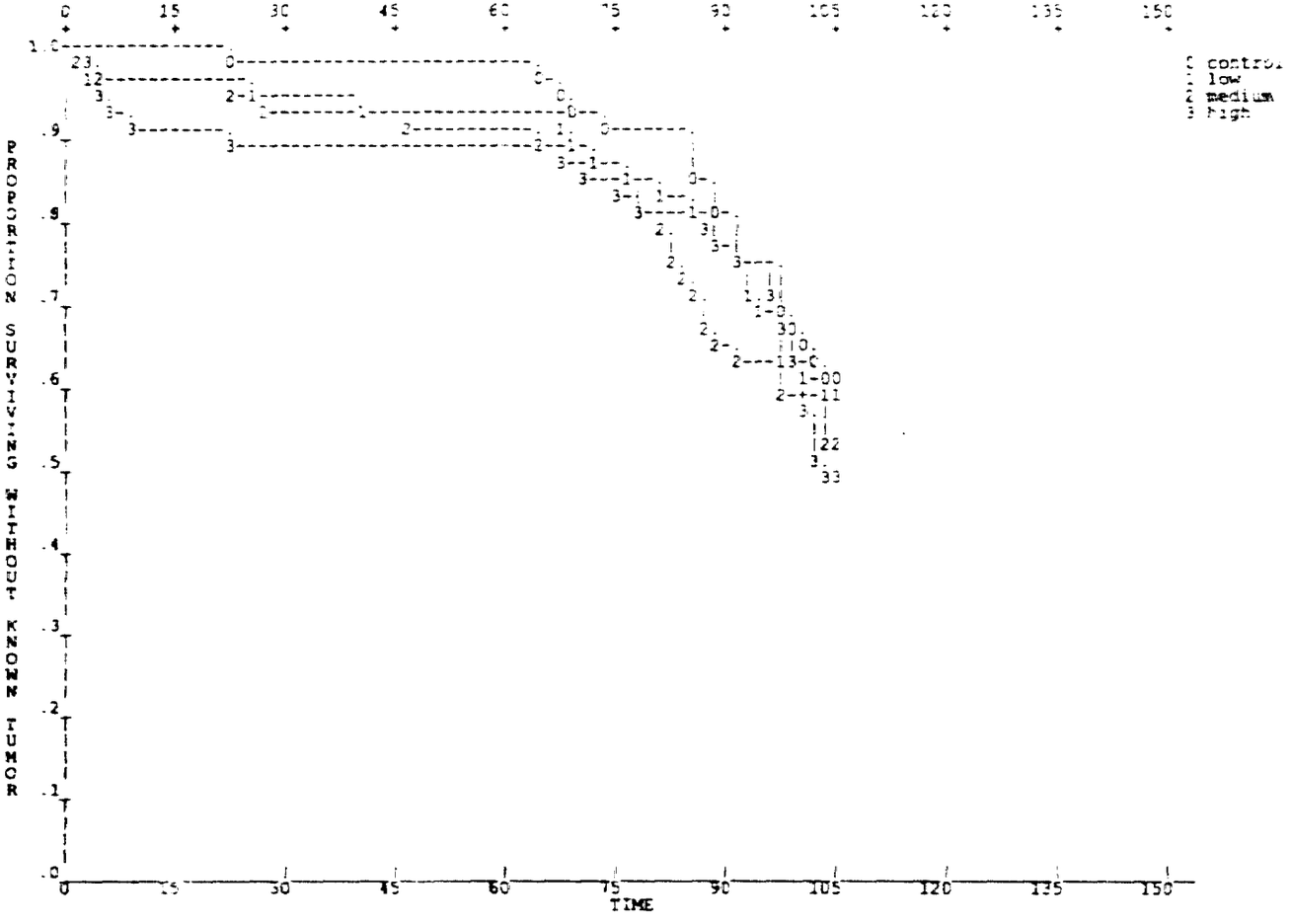


Figure 2

Survival Function / Male Mouse

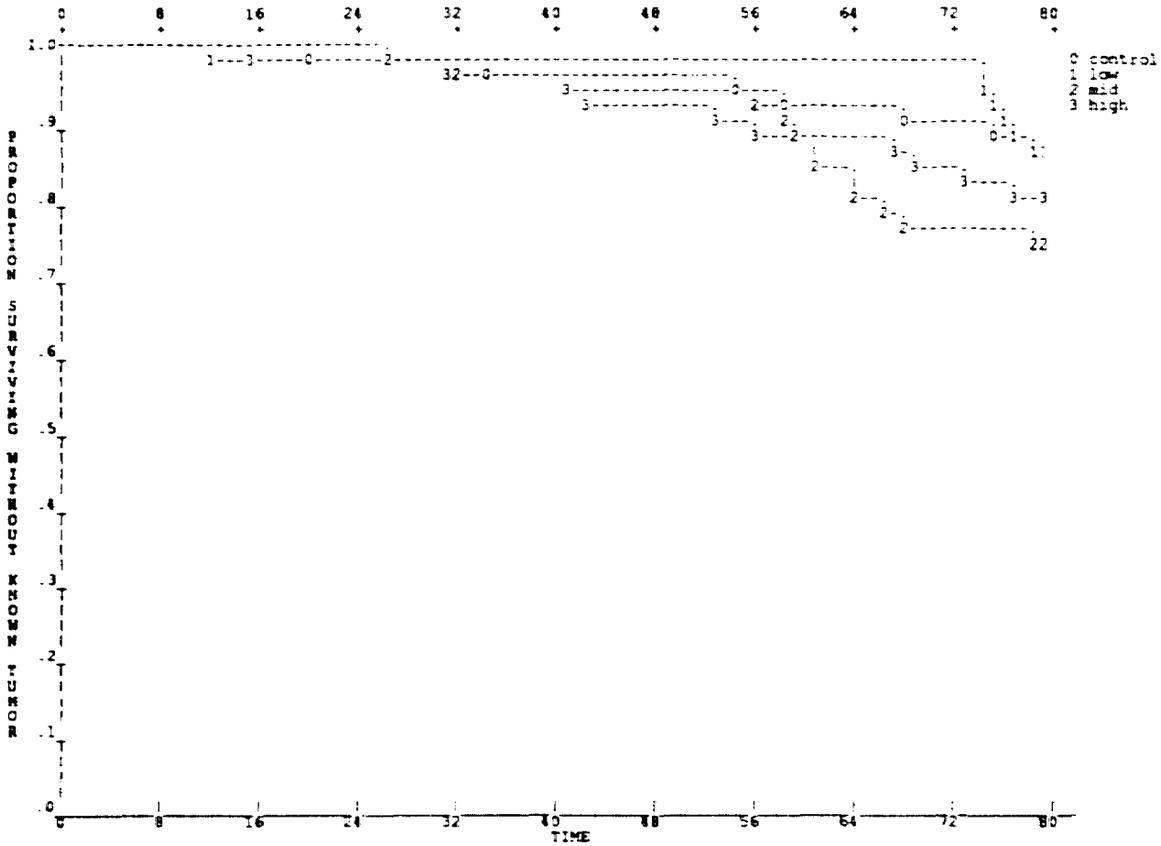


Figure 3

Suvival Function / Female Mouse

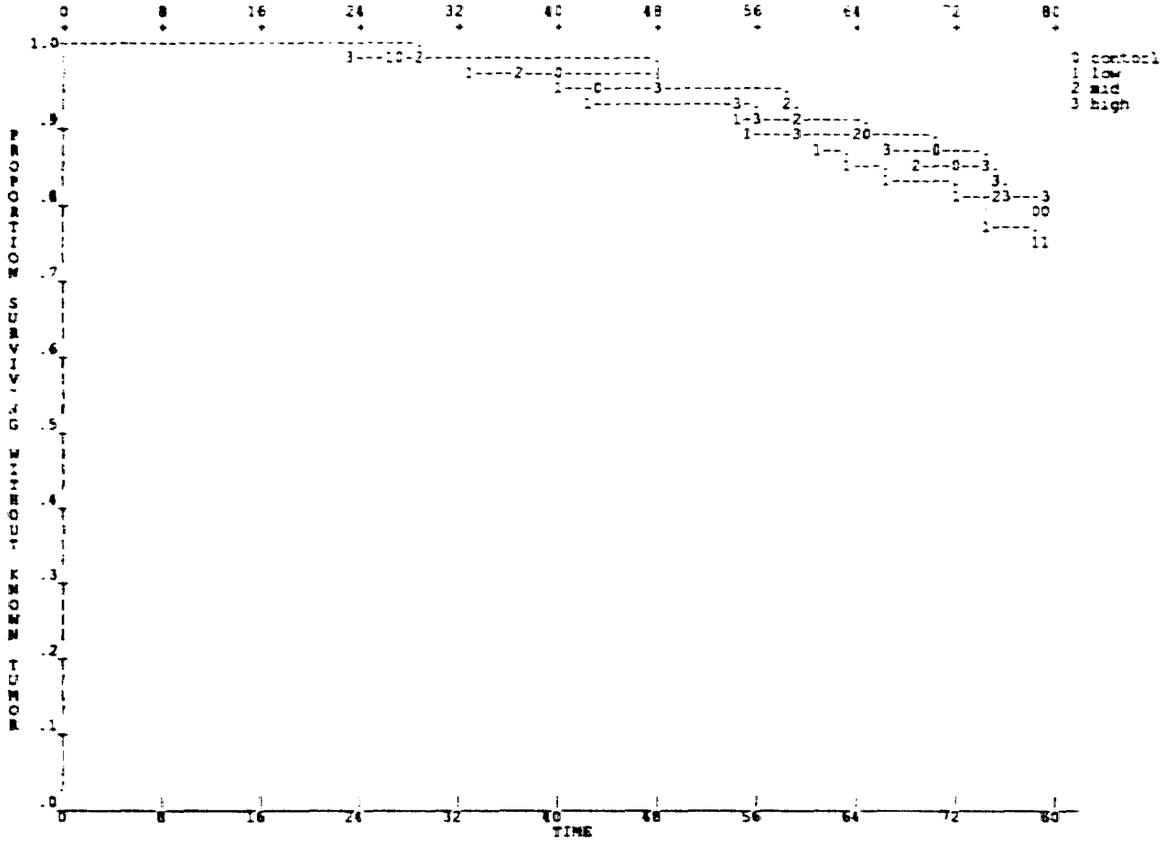


Figure 4

STATISTICAL REVIEW AND EVALUATION

NDA #: 19-815 **Drug Class**: # **Date:** SEP 2 1993

Applicant: Roberts Pharmaceutical Corporation

Name of Drug: Amatine (Midodrine HCl)tablets, 2.5 mg, 5.0 mg, and 10.0 mg, tid.

Indication: Severe Orthostatic Hypotension due to Autonomic Dysfunction.

Documents Reviewed: Volumes 1 and 2 of the sponsor's submission dated November 6, 1992. Also the Statistical Review and Evaluation by Dr. Stan Lin, dated June 2, 1991.

Medical Officer: The medical officer for this review is Dr. Joel Morganroth, an outside consultant.

Relevant Issues discussed in this Review:

1. This study was carried out in an 'enriched' population of midodrine responders.
2. The study lasted a total of three days, while the double-blind portion was only seven hours.
3. Only one dose of midodrine was used, and that dose is the upper end of the dosing range which had been studied.
4. The dosing interval was given as t.i.d., but the drug was actually given every three hours.
5. The potential for unblinding of both patient and investigator is very high.

I. INTRODUCTION

Amatine (Midodrine Hydrochloride) is being proposed for the management of severe orthostatic hypotension due to autonomic dysfunction. It is designated as an orphan drug. The NDA was previously submitted in October, 1990, and a Statistical Review and Evaluation, dated June 25, 1991, was written by Dr. Stan Lin of the Division of Biometrics. Two studies were discussed in that review. Study 20,762-1 was very small (7 analyzable patients). Due to its size and other difficulties with the study, no statistical conclusions could be drawn. Study 20,761-11/11A was a larger study (75 analyzable patients) comparing three doses of midodrine (2.5, 5.0. and 10.0 mg) with placebo. At the final visit the 10 mg group had a statistically significantly greater increase from baseline in standing systolic blood pressure than did the placebo group, but this significance was compromised by a significant baseline imbalance between the groups. There were no significant differences in symptom scores. This current submission consists of one additional study, which will be discussed in this review.

II. STUDY NO. 20,762-318C

II.A. Study Description

Study 20,762-318C was a multi-center (5 centers) randomized, 3-day in-house study designed to compare midodrine HCl with placebo in patients with moderate to severe orthostatic hypotension associated with autonomic dysfunction. It was composed of two phases, a single blind qualifying phase and a double-blind study phase. Each phase was one day in length. Patients were required to have been treated with midodrine for a period of at least 2 weeks prior to entering the study and had to have the ability to stand while under midodrine treatment. Concomitant medication for orthostatic hypotension was not prohibited, and 45% of the patients were taking fludrocortisone, 19% were on a high sodium diet, and 10% were using Jobst garments.

On the first day of hospitalization patients underwent a controlled washout of all prior medications which lasted at least 15 hours. Blood pressure and symptomology responses were recorded upon entry and 6 hours later. On the second day patients were randomized and entered a one day single blind period where their qualifications for the double-blind phase was established. Patients received two doses of midodrine 10 mg which were taken six hours apart, with the time of the first dose called hour 0. Standing and supine blood pressure readings, standing time, and symptomatology scores were taken at hours 0, 1, 3, 4, 6, and 7. At the hour 0 evaluation (pre-dose), patients were required to have a supine to standing systolic blood pressure fall of at least 15 mmHg, a symptom score of at most 5 on a ten point scale (lower number indicating greater severity) for one or both of the two primary symptoms, feelings of dizziness/lightheadedness/unsteadiness or dimming/blurring of vision, and not be able to stand motionless for 15 minutes without significant symptoms. At the evaluation taken one hour post-dose, patients were required to fulfill two criteria, at least a 10 point increase in standing systolic blood pressure and an improvement of at least one point from the qualifying pre-dose symptom score. Patients who did not meet both of these criteria were considered non-responders and were discontinued.

Patients who were responders to the single-blind midodrine treatment on day two proceeded to the double-blind evaluation (day 3). At the hour 0 evaluation (pre-dose), patients were again required to have a supine to standing systolic blood pressure fall of at least 15 mmHg, a symptom score of at most 5 for one or both of the two primary symptoms, and the inability to stand motionless for 15 minutes. Patients meeting these criteria received three doses of their randomized treatments (midodrine or placebo) at three hour intervals. Blood pressure and symptomatology scores were measured at hours 0, 1, 3, 4, 6, and 7. Standing time was also measured for those patients who had been unable to stand for more than five minutes at the pre-dose day 3 measurement, but not for those whose standing time was between 5 and 15 minutes. The primary endpoints were standing systolic blood pressure and symptoms of orthostatic hypotension. Secondary endpoints were standing diastolic blood pressure and supine systolic and diastolic blood pressure. Supportive data included standing time and sitting systolic and diastolic blood pressure.

A total of 70 patients were enrolled in the study, but two dropped out during the washout (day 1). Five patients dropped out on day 2 prior to randomization, three due to symptom scores >5, one from investigator error, and one from supine hypertension pre-dose. The remaining 63 patients were randomized, but four patients dropped out during the single-blind phase (day 2), three from no blood pressure response and one from no symptom response. One additional patient had a symptom score > 5 pre-dose on day three, which left 58 patients in the double-blind phase (day 3). Five patients were considered not evaluable, one because of a symptom score > 5 on day 2, three because of no blood pressure response on day 2, and one from investigator error on day 2. One additional patient was considered evaluable for blood pressure but not for symptoms because their day 2 symptom score, while < 5, was determined to be the result of 'situational confusion'. This left 53 evaluable patients for the blood pressure analyses and 52 for the symptom analyses, although many of these patients were excluded from certain analyses because of missing data.

II.B. Sponsor's Analysis

The evaluable patients included 27 who had been randomized to midodrine 10 mg and 26 who had been randomized to placebo. The groups did not differ significantly in age, sex, or race. While all patients suffered from orthostatic hypotension, the patients had differing primary diagnoses, as can be seen in Table 1:

Table 1
Primary Diagnosis

Diagnostic Group	Midodrine	Placebo	Total
Shy Drager Syndrome	13	9	22
IOH (Bradbury-Eggleston)	5	8	13
Diabetes	7	5	12
Parkinson's Disease	2	1	3
Mitral Valve Prolapse	0	2	2
Orthostatic Hypotension	0	1	1

The primary efficacy variables, according to the sponsor, were standing systolic blood pressure (1 and 3 minutes) and symptoms of orthostatic hypotension. Secondary endpoints were standing diastolic blood pressure and supine diastolic and systolic blood pressure. The sponsor classified standing time and sitting blood pressure as supportive data. A repeated measures analysis of covariance with hour 0 as the covariate was used to compare the blood pressure and symptom responses at one hour post dose (hours 1, 4, and 7). This analysis included only patients with complete data sets (i.e. measurements at hours 0, 1, 4, and 7). The results, as presented by the sponsor, are given in Table 2. The two measures of systolic blood pressure both reach statistical significance, as does Symptom 1, dizzy/lightheaded/unsteady. Only patients with baseline (hour 0) symptom scores of at most five were included in the analyses of symptom 2, dimming/blurring of vision and the two groups do not differ statistically. Standing time is marginally statistically significant.

Table 2 - Sponsor's Results

1 minute standing systolic blood pressure

	Midodrine (N=24)		Placebo (N=24)		
	Mean (s.e.)	Change	Mean (s.e.)	Change	P-value
Baseline	72.6 (3.8)		75.2 (4.6)		
Hour 1	90.6 (5.8)	18.0	86.4 (5.1)	11.2	
Hour 4	96.0 (5.9)	23.4	81.5 (5.0)	6.3	
Hour 7	104.2 (7.0)	31.6	89.2 (6.3)	14.0	.0224

3 minute standing systolic blood pressure

	Midodrine (N=17)		Placebo (N=17)		
	Mean (s.e.)	Change	Mean (s.e.)	Change	P-value
Baseline	69.9 (5.4)		73.5 (6.2)		
Hour 1	86.8 (6.2)	16.9	84.1 (7.0)	10.6	
Hour 4	97.7 (8.5)	27.8	83.8 (7.4)	10.3	
Hour 7	103.3 (8.5)	33.4	90.3 (8.2)	16.8	.0192

Symptom 1 - Dizzy/Lightheaded/Unsteady

	Midodrine (N=24)		Placebo (N=25)		
	Mean (s.e.)	Change	Mean (s.e.)	Change	P-value
Baseline	3.7 (0.3)		3.4 (0.3)		
Hour 1	5.8 (0.5)	2.1	4.8 (0.4)	1.3	
Hour 4	7.0 (0.4)	3.3	5.4 (0.5)	2.0	
Hour 7	7.6 (0.5)	3.9	6.4 (0.5)	2.9	.0314

Symptom 2 - Dimming/Blurring of Vision

	Midodrine (N=12)		Placebo (N=8)		
	Mean (s.e.)	Change	Mean (s.e.)	Change	P-value
Baseline	4.2 (0.3)		3.8 (0.5)		
Hour 1	6.9 (0.8)	2.8	6.6 (1.2)	2.9	
Hour 4	7.8 (0.8)	3.7	5.9 (1.0)	2.1	
Hour 7	8.0 (0.8)	3.8	6.6 (1.1)	2.9	.5475

Standing Time

	Midodrine (N=26)		Placebo (N=24)		
	Mean (s.e.)	Change	Mean (s.e.)	Change	P-value
Baseline	1.4 (0.5)		1.1 (0.2)		
Hour 1	2.9 (0.8)	1.5	1.6 (0.4)	0.5	
Hour 4	3.0 (0.7)	1.6	1.4 (0.4)	0.3	
Hour 7	3.5 (0.9)	2.1	2.0 (0.4)	0.9	.0679

II.C. Reviewer's Comments

This reviewer repeated the sponsor's analyses including all patients for which data is available. The results were similar to the evaluable patient analysis. The study was designed as a multicenter study, but the centers were not balanced in size. The distribution of patients involved in the various analyses are given below. Complete data in each case refers to data at hours 0, 1, 4, and 7. Center 1 enrolled over half of the patients, and dominated all of the analyses except that of symptom 2.

Distribution of Patients from the Five Centers

Center	Enrolled Day 3	Complete 1 min bp	Complete 3 min bp	Complete standing time	Complete symptom 1	Complete symptom 2
1	30	26	24	26	26	7
2	14	13	6	12	13	7
3	4	2	1	4	4	2
4	3	3	1	3	3	1
5	6	4	2	5	5	3
Total	57	48	34	49	50	20

The data for center 1 was analyzed separately. Although the smaller sample sizes resulted in less statistical significance, the results were not substantially different from those of all studies combined.

In many ways this trial resembles a randomized withdrawal, since all patients had received midodrine for at least two weeks prior to randomization and again on day 2. However, all patients were off treatment for approximately 18 hours after their day-2 drug exposure, so the baseline values for the randomized day-3 exposure are evaluated after the treatment effect has washed out. It appears from a comparison of hour 7 of day 2 and hour 0 or day 3 that most, if not all, of the drug effect has disappeared. One-minute systolic blood pressure dropped from 105.1 mmHg to 73.9, three-minute systolic blood pressure dropped from 101.5 mmHg to 71.7, standing time dropped from 3 minutes to 1.25 minutes, and the first symptom score dropped from 6.7 to 3.55 in this period. A randomized withdrawal trial would have had the baseline evaluations for the double-blind study taken while the drug effect was present, and then some patients randomized to be removed from treatment while others remained on treatment.

The study employed what has been referred to as an 'enrichment' design. Patients who were unable to stand while under midodrine treatment were not allowed to enroll in the trial. It was further midodrine-enriched because patients had to demonstrate at least a 10 mmHg increase in systolic blood pressure and an increase in the qualifying symptom score one hour following dosing on day two. The results, therefore, are not applicable to the general orthostatic hypotension population, but only those who respond to midodrine treatment.

b) undergoing colo-rectal surgery at Jefferson University Hospital,

c) expected to require narcotic analgesic for 72 hours postoperatively to control pain.

2.3.2 Exclusion Criteria

Subjects were excluded from the study for any of the following:

a) ASA status above III,

b) major central nervous system deficits, including paraplegia or a history of cerebral vascular accidents,

c) clinically significant hepatic or renal disease, or congestive heart failure.

d) history of respiratory problems and CO_2 retention with a resting pCO^2 of >45 torr,

e) body weight less than 50 or greater than 100 kg,

f) known hypersensitivities to any of the drugs used in the protocol,

g) experiencing pain as a direct result of malignancy,

h) history of drug abuse or addiction.

2.3.3 Sample Size

A total of 9 subjects entered treatment.

2.4 Treatment

2.4.1 Study Medication

Each TTS (fentanyl)-75, 30 cm^2, contained 7.5 mg of drug and released nominally 75 mcg/hour fentanyl. (Code number 04332, Control number 728185)

2.4.2 Treatment Assignment

This study was open-label.

2.4.3 Dose Selection

The TTS (fentanyl) dose used in this study wa

This study was only three days in length, with the double-blind portion lasting a total of seven hours. The results cannot be extrapolated to longer treatment periods, and only give an indication of what happens with very short-term dosing. Treatment over a prolonged periods will need to be evaluated in further trials.

All patients in this trial received midodrine 10 mg dose of midodrine. Earlier studies had examined doses ranging from 2.5 mg to 10 mg. In these studies, reviewed in 1991 by Dr. Stan Lin of the Division of Biometrics, a dose response pattern over this dosing range was suggested for both systolic blood pressure and the symptom score (syncope and dizziness/lightheadedness). There is no discussion in this submission about the feasibility of higher doses, so it appears that only the highest end of the dosing range was used in this study.

The dosing regimen for this trial was listed as 10 mg t.i.d. However, patients actually received the drug at three hour intervals on the third day (the double-blind period). If this pattern were continued, patients would need about six doses each day, even assuming medication was not needed during the night. A clear dosing interval needs to be established in another trial.

This reviewer is concerned about the extent of blinding during this trial. Since all patients had received midodrine prior to randomization, were washed out during day one of the trial, and then again given midodrine on day two, it is entirely possible that both the patient and the investigator were able to tell whether they were receiving midodrine or placebo on day three. If patients and/or investigators were aware of treatment assignment it could lead to bias for the standing time measurements, and would very likely bias the symptom scores.

III. OVERALL SUMMARY AND CONCLUSIONS

In summary, this study demonstrates that midodrine treatment has a significant effect on systolic blood pressure, and appears to effect standing time and dizziness in this highly selective group of patients. This study is unable by design to show that this temporary effect can be sustained over long-term use. The study contributes very little toward establishing that midodrine is an effective treatment for orthostatic hypotension. The study was too short (seven hours), involved only one dose at the upper level of the dosing range and a three-hour dosing interval, was compromised by potential unblinding, and was limited to an enriched population of patients known to respond to midodrine treatment.

The overall summary and conclusions section may be conveyed to the sponsor.

Nancy D Smith

Nancy D. Smith, Ph.D.
Mathematical Statistician

JUN 2 1991

JUN 2 1991

STATISTICAL REVIEW AND EVALUATION

NDA#: 19-815/1c

APPLICANT: Roberts Laboratories

NAME OF DRUG: Midodrine HCl (Amatine) tablets 2.5, 5 mg

INDICATIONS: Idiopathic Orthostatic Hypotension

DOCUMENTS REVIEWED: Vol 1-6 of the NDA submission dated 10/90, Protocol document in Vol 2.12 dated 04/88, Research report for Tarazi's results (04/88), Statistical report for Tarazi's results.

RELEVANT ISSUES DISCUSSED IN THIS REVIEW:

1) Criteria for efficacy.
2) Side effects.
3) Results from a single, small site, of a multi-site trial.

This reviewer has read the medical review for the NDA by Joel Morganroth, M.D.

BACKGROUND:

In this NDA the applicant is seeking the approval of Midodrine for the treatment of idiopathic orthostatic hypotension. Midodrine is designated for the orphan drug class. Two of the studies pivotal to the approval are examined in this review.

PROTOCOL 20,762-1 (Tarazi)

INTRODUCTION: According to the medical review, this study was intended as a multicenter trial, but due to enrollment problems, only the Tarazi site collected data on more than one or two patients. Data from 8 patients at the Tarazi site were collected. Regarding the number of patients planned for the study the protocol stated as follows:

> "A minimum of ten and a maximum of 20 adult patients, for whom complete and acceptable case report forms are submitted, will be studied with each investigator."

Thus it confirms the medical reviewer's comment above. Therefore, not only the data were collected from a small number of patients, but they were also all from a single center. Clearly under such a circumstance, the reliability of the 'study' results would suffer. (Eight patients enrolled, only 7 analysable).

This reviewer would also point out that because this was

designed to be a multicenter study, it is not known whether the results would be similar to the Tarazi's if data from any other sites were also collected. That is, was it because it was believed that the Tarazi site had found something and therefore got analyzed and reported? At least one report of the results from this site was available since April 1, 1988. Was there no additional data since then? Has the study been terminated?

The medical review also indicated that the blood pressure measurements used for efficacy analyses were not pre-defined, and therefore "the 'positive' finding in this study cannot be seriously considered as evidence of efficacy".

This review, in what follows, further discusses the results from the Tarazi site.

The objective of the study was to evaluate the efficacy and safety of midodrine as compared to that of ephedrine as pressor treatment (elevation of systolic blood pressure?) for severe idiopathic orthostatic hypotension[1]. The study design was double-blind, crossover with initial placebo run-in and placebo washout between treatments. The first period for each treatment involved a 3-5 day dose titration until optimal blood pressure control was achieved. After dose titration the optimal dose was maintained for another period of 3-5 days.

REVIEWER COMMENT: Appendix 1 is taken out of the sponsor's protocol document. Even though it states that a double-blind design was used, the reading of item C of the appendix seems to imply that dose-titration was done open-labelled. If this was indeed done, blinding then becomes impossible during the maintenance period, and the results may be seriously biased.

All medication was administered at least 30 minutes before meals. Dose titration involved up to four dose levels for each drug. Midodrine dose levels ranged from 2.5 mg to 10 mg b.i.d. or t.i.d. in 2.5 mg increments. Ephedrine was administered in doses ranging from 6 to 24 mg t.i.d. in 6 mg increments.

---

[1]Systolic blood pressure is transiently and minimally decreased in normal individuals upon assuming the upright posture. Normal physiologic feedback mechanisms work through neurally mediated pathways to maintain the standing blood pressure and thus support adequate cerebral perfusion. These compensatory mechanisms to regulate blood pressure upon standing are deficient in patients with severe orthostatic hypotension due to autonomic nervous system failure leading to inadequate cerebral perfusion with accompanying symptoms of syncope, dizziness/lightheadedness, among others. (NDA)

Eight patients with severe idiopathic orthostatic hypotension were enrolled into the Tarazi site. The average age of the 4 males and 4 females studied was 60.4 ± 13.5 years. The duration of their disease was: 1-2 years in 3 patients, 3-4 years in 3 patients, and 10-14 years in 2 patients.

> REVIEWER COMMENT: The sponsor's preferred analyses of the results totally ignored the crossover nature of the trial. The sponsor's analyses treated the six treatment periods (refer to Figure 1), as six independent treatment groups and conducted ANOVAs accordingly. As a result the error-degrees-of-freedom for the ANOVAs was made ridiculously high and as a consequence significant differences among treatments (with 5 degrees of freedom !) were declared everywhere. Clearly the analyses were incorrect.

An examination of the design for the trial would show that only parallel comparisons between midodrine and ephedrine were possible. Comparisons between the active treatments vs placebo are within treatment comparisons at best. These are not placebo-controlled comparisons (sponsor's terminology).

One of the 8 patients was not dosed ephedrine during the maintenance period, therefore for the change-from-baseline analyses only 7 patients were considered. There were 2 patients in the treatment sequence where midodrine was first, and 5 in the sequence where ephedrine was first.

As mentioned earlier in the introduction, with such a small number of patients, results of the study cannot be considered reliable, especially in a confirmatory study. For example, in terms of the primary blood pressure efficacy endpoint -- the standing systolic blood pressure increased from the placebo period, the table below would have one believe that midodrine was effective compared to ephedrine. However in terms of supine and sitting systolic blood pressure, the results would pose a problem: it appears there was a treatment by sequence interaction in the study. Because of such inconsistencies, usually inherent in such small studies, this reviewer is reluctant to make conclusions based on this study and agrees with the medical reviewer's view of not considering seriously the study results as evidence of efficacy.

Variable	Seq	N	Midodrine Mean	Midodrine SD	Ephedrine Mean	Ephedrine SD
SuSBP	1	2	9.4	2.7	9.9	8.4
	2	5	20.8	12.2	14.7	2.0
SiSBP	1	2	19.1	12.4	4.3	9.3
	2	5	25.2	17.5	8.8	10.2
StSBP	1	2	16.0	4.2	2.0	14.3
	2	5	15.9	9.1	-0.6	9.8

Table 1 contains the sponsor's results on the standing systolic blood pressure (Average and Median). It is interesting to note that the baseline standard deviations were 8.249 and 8.634 respectively for the two tables. However, for the subsequent periods following the baseline, all the standard deviations (on the same patients) had substantially increased. If nothing else can be said, this phenomenon indicates that all the estimates for the means following baseline (i.e. post-treatment) were less reliable. It would also imply that following the baseline period, the treatments made the responses from individuals more diverse, so that some individuals responded favorably, but also some responded very unfavorably. Unless it is a characteristic of the drugs, this must be interpreted as saying that the study was too small to be reliable.

Another related point should also be pointed out. The sponsor stated that ephedrine was chosen as a comparator in this study because it elevates blood pressure and cited a published report in this connection (Appendix 2). The sponsor further stated that the result on the supine blood pressure for the ephedrine patients was to be used as a validity check for the trial (page 68, statistical report). An examination of the data in the above table shows that the average SuSBP increase was about 13.3, SiSBP increase was about 7.5, and the StSBP increase was about 0.12. However all of the blood pressure increases averaged over 30 mmHg for the ephedrine patients in Appendix 2. All 4 patients in Appendix 2 took only 30 mg b.i.d. compared to 5 patients taking the maximum 24 mg T.I.D (the remaining two on 18 mg T.I.D) in the current study. Obviously there appears to be a discrepancy in the responses. For example, the current study suggests no pressor effect of ephedrine on standing blood pressure on average of 70 mg of ephedrine per day, whereas Appendix 2 suggests substantial such effect with only 60 mg per day. All of these, to this reviewer, further cloud the results of the study, and conclusions without some reasonable doubts cannot be given.

The sponsor stated that percentage of instances where patients

were unable to stand is also a clinical efficacy endpoint (secondary). The difference between midodrine and ephedrine in this endpoint was reported not significant: 5.3% for midodrine and 10% for ephedrine, p=0.08. Clearly then this becomes an uninformative endpoint in this small active-controlled trial.

PROTOCOL 20,762-11/11A

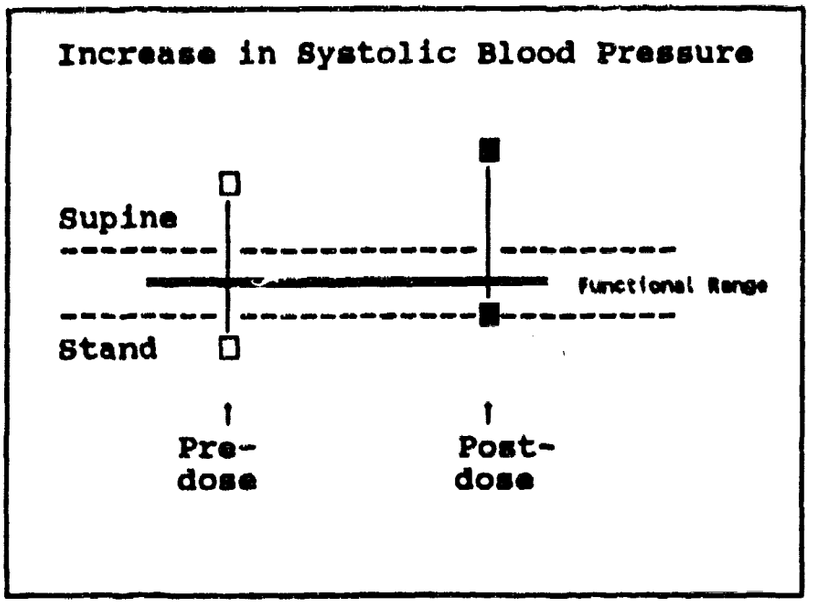
OBJECTIVE: To evaluate the efficacy and safety of midodrine 2.5, 5, and 10 mg t.i.d. in treating patients with orthostatic hypotension.

DESIGN: Randomized, double-blind, parallel, placebo-controlled.

Ninety-seven (97) patients over 18 centers with moderate to severe orthostatic hypotension associated with autonomic failure were randomized to receive either placebo, 2.5 mg, 5 mg or 10 mg of midodrine t.i.d. After a one-week placebo run-in, midodrine doses were titrated up weekly until week 5 when all patients received their assigned dose. The sponsor's analysis for efficacy was based on a 'last visit analysis", referred to as 'visit 7' in the NDA, and represented the available evaluation for the 5th or 6th visit, whichever was later.

There were two primary efficacy endpoints in terms of blood pressures: 1) the change (increase) in standing systolic blood pressure at peak from trough (1 hour post-dose minus pre-dose); 2) the "delta of the deltas" defined as the difference in the drop of systolic pressure from supine to standing, i.e., (supine minus standing systolic prior to dosing)-(supine minus standing systolic one hour post dosing) at evaluation period.

REVIEWER COMMENT: It appears that what the sponsor termed "delta of the deltas" is simply a peak/trough difference in the drop of the systolic blood pressure from supine to standing position (Fig. 2) after 4 or 5 weeks of treatment (at visit 5 or 6). In terms of this peak/trough difference this reviewer concurs with the sponsor's conclusion that there were no statistically distinguishable differences between the midodrine groups and the placebo group. The reason for this given by the sponsor was that midodrine apparently elevates both supine and standing blood pressures (by approximately the same amount). The sponsor therefore proposed (in the protocol) that the change in the standing systolic blood pressure (item 1 above) be the key efficacy variable. This also can be recognized as a peak/trough difference after 4 or 5 weeks of treatment (in the standing systolic blood pressure). This appears logically reasonable as illustrated in the following figure.



This figure is intended to illustrate that it may be possible for a chemical agent to elevate both the supine and standing systolic blood pressures and the result is that the difference between the two remain the same from before the dosing. However the absolute level of the standing systolic blood pressure is higher post-dose than pre-dose. Clearly the same situation can also occur with the supine systolic blood pressure (and thus resulting in the no change in the difference between supine and standing systolic blood pressure, pre- and post- dose).

Therefore it would appear that the action of midodrine may be seen by looking at the increase in standing systolic blood pressure. However in a situation where only increase in the standing systolic blood pressure is intended, but as a result of treatment, the supine blood pressures (systolic and diastolic) are also increased as well, it would seem that any benefit of the treatment must be carefully (by clinicians) balanced against the risk it brings.

For the 97 patients randomized, they were balanced in age, weight, height and diagnostic factors (IOH, Shy-Drager, Parkinson's Diabetes). For the standing systolic blood pressure, the sponsor reported no significant imbalance (pre- and post- placebo, Table 2.1). However, the pre-placebo systolic blood pressure drop from supine to standing position did show an imbalance between groups (38, 39, 39, 58 mmHg for 0, 2.5, 5, and 10 respectively, p=0.0329, also Table 2.1). (This perhaps reflects some imbalance of the systolic blood pressure in the supine position at baseline. Indeed a test shows that this was the case with the baseline supine blood

pressures 130, 140, 136, and 157 mmHg for the 0, 2.5, 5, and 10 mg midodrine respectively, p<0.001.)

According to the sponsor only 75 of these patients provided clinically evaluable efficacy data. The results on the peak/trough difference in these patients at the last visit are displayed in Table 2.2. This Table shows that the peak/trough difference in the standing systolic blood pressure in the midodrine patients was not statistically significant from the placebo patients except for the 10 mg group, at the one-sided 0.05 level. However because of the imbalance in the baseline supine systolic blood pressure it is not clear what is the correct interpretation of the significance.

COMMENT: It seems to this reviewer another valid efficacy analysis is to compare the increase (from baseline) in the peak (one hour post-dose) standing systolic blood pressure at the last visit. The following data are taken out of Appendix Table C4 of the NDA:

Standing Systolic Blood Pressure

Group (mg)	Baseline N	Baseline Mean	Baseline SD	Last Visit N	Last Visit Mean	Last Visit SD	Increase in Mean
0	21	91	20	18	108	23	17
2.5	20	109	26	17	114	24	5
5	20	101	29	19	104	34	3
10	21	100	27	21	116	31	16

Appendix Table C4 of the NDA

It should be clear from this table that in terms of the increase from baseline in peak standing systolic blood pressure at the last visit the placebo group had the largest increase from baseline and that no significant differences in increase between the midodrine groups and the placebo group can be detected.

SUMMARY OF BLOOD PRESSURE ENDPOINTS FOR STUDY:

In terms of the peak/trough difference in the supine to standing systolic blood pressure change (delta of deltas) at the last visit, there is no discernable effect by midodrine. In terms of the peak/trough difference in the standing systolic blood pressure at the last visit, the difference for the 10 mg midodrine group was larger than the placebo group. However, this difference in effect was confounded with the baseline imbalance in the supine systolic blood pressure, and so the validity of the midodrine effect is unclear. In terms of the

increase from baseline in the peak standing systolic blood pressure at the last visit, there is no discernable effect by midodrine.

SYMPTOMATOLOGY RESULTS

It was stated in the NDA that in addition to blood pressure, the improvement in the syncopal symptoms (syncope and dizziness/lightheadedness) was also a primary efficacy endpoint. This was a quality of life endpoint which involved patients rating questionnaires for each visit. According to the sponsor, the three-point scores (often=1, sometimes=2, never=3, so that higher the score, the better the response) for each of the two questions syncope and dizziness/lightheadedness were averaged together and analyzed. The results for the change-from-baseline are displayed in Table 3. Clearly there were no significant differences between the midodrine groups and the placebo group in the change-from-baseline (increase) for the mean syncopal scores.

The sponsor also presented the results for the percent-change-from-baseline. These are given in Table 4. The sponsor claimed that in terms of the percent-change-from-baseline, the midodrine 10 mg group was statistically significantly separated from the placebo group. However this reviewer finds fault with this interpretation: Recall as mentioned in the last paragraph, by the sponsor's definition the higher a treatment group's score the better that group's response to the treatment. It is then pointed out that even though the sponsor would state that at baseline the groups were homogeneous with regard to the response scores, but the presence of statistically unbalanced groups cannot be ignored. A test for the homogeneity of the groups at baseline gave a p-value of 0.0056 for the syncopal symptoms score, with an apparently midodrine dose-related lowering of the score (see baseline values in Table 3). However, after 6 weeks of treatment, for the last visit the scores were all elevated essentially to the same level (p=0.47), but still with the placebo group having the highest score. That is there was no 'break-through' in the midodrine scores. Therefore the effect of the midodrine doses essentially parallelled that of the placebo--this is the result of the analysis of change-from-baseline given in the last paragraph. The higher percentage change of the 10 mg group was therefore the result of the significantly lower score of the group at baseline.

In addition it should also be pointed out that the (one-tailed) p-values in Tables 3 and 4 should be adjusted for multiple testing, and doing so would show that none of the percent changes of the midodrine groups were significantly different from that of the placebo group at the statistical 0.05 level.

OVERALL SUMMARY AND RECOMMENDATIONS:

Two studies on midodrine have been reviewed for orthostatic hypotension. The first one (Tarazi) was supposedly a multicenter study, but only one site collected data, and only for 7 patients. This is too few data for the results to be useful. Because of other difficulties with the study (see text), this reviewer feels that the medical reviewer's (negative) conclusion for the study should be heeded.

The other study (Protocol 20,762-11/11A) randomized 97 patients among four groups. Seventy-five of these provided analyzable data. The analyses of delta of the deltas by the sponsor and the one on the change from baseline in standing systolic blood pressure by this reviewer did not show midodrine treatment effect. The sponsor's result on the post-dose/pre-dose standing systolic blood pressure change was difficult to interpret because of a baseline imbalance in supine systolic blood pressure (page 6-7 and Table 2.2). Should this become an important endpoint for the submission, then the baseline imbalance in supine systolic blood pressure becomes relevant, and further analyses adjusting for the imbalance should be made. There was no midodrine treatment effect compared to placebo as measured by the syncopal symptoms endpoint (page 8, symptomatology results).

Stan Lin, Ph.D., Math. Statistician

Concur: Dr. Chi 6/20/91

for Dr. Dubey SBM 6-25-91

cc: NDA 19-815
HFD-110
HFD-110/Dr. Lipicky
HFD-110/Ms. Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Lin,S.
Chron.

S.Lin/(301)443-0263/SERB/06-17-91

This review consists of 9 pages of text, 5 tables, 2 appendices and 2 figures.

TARAZ:MEANS FOR THE ENTIRE TREATMENT PERIOD

VARIABLE ASID_S

WITHIN DRUG	N	MEAN	S.D.	MIN.	MAX.
GSLINE	8	[illegible]	[illegible]	[illegible]	[illegible]
MIDD_T	8	97.81	14.119	81.405	117.65
MIDD_M	8	[illegible]	[illegible]	94.825	122.25
PLACEBO	8	[illegible]	[illegible]	[illegible]	112.42
EPHED_T	8	[illegible]	[illegible]	[illegible]	[illegible]
EPHED_M	7	[illegible]	[illegible]	[illegible]	[illegible]
TOTAL	47	[illegible]	[illegible]	[illegible]	[illegible]

VARIABLE MSID_S

WITHIN DRUG	N	MEAN	S.D.	MIN.	MAX.
GSLINE	8	89.37	8.634	80.000	100.00
MIDD_T	8	95.12	16.626	74.000	120.00
MIDD_M	8	105.00	11.006	90.000	122.00
PLACEBO	8	85.50	16.274	60.000	112.00
EPHED_T	8	90.50	15.257	60.000	108.00
EPHED_M	7	91.57	16.652	70.000	120.00
TOTAL	47	92.87	15.093	60.000	122.00

TABLE 2.1

SUPINE AND STANDING SYSTOLIC BLOOD PRESSURES
BASELINE AND VISIT 7
(Protocol 20,762-11/11A)

	SUPINE SYSTOLIC								STANDING SYSTOLIC								SUPINE-STANDING											
	PRE-DOSE				POST-DOSE				PRE-DOSE				POST-DOSE				PRE-DOSE				POST-DOSE				DIFFERENCE			
*	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
VISIT 1																												
MEAN	130	140	136	157	130	149	140	155	91	101	97	100	91	109	101	100	38	39	39	58	39	39	39	56	1	-1	-1	-2
SD	23	24	21	19	21	21	22	22	16	26	25	28	20	26	29	27	24	23	23	32	30	19	25	29	16	16	14	17
N	21	21	21	24	21	21	20	21	21	20	21	24	21	20	20	21	21	20	21	24	21	20	20	21	21	20	20	21
VISIT 7																												
MEAN	138	143	147	161	136	150	150	174	105	106	100	94	108	114	104	116	33	37	47	67	28	36	45	58	-5	-2	-2	-9
SD	29	23	24	24	29	23	24	31	21	33	31	31	23	24	34	31	32	37	31	34	28	33	33	38	17	13	14	22
N	18	17	19	21	18	17	19	21	18	17	19	21	18	17	19	21	18	17	19	21	18	17	19	21	18	17	19	21

1='placebo', 2='2.5 mg', 3='5 mg', 4='10 mg'

Table 2.2

EFFECT OF MIDODRINE ON STANDING SYSTOLIC BLOOD PRESSURE (mm Hg) IN PATIENTS WITH ORTHOSTATIC HYPOTENSION

MIDODRINE STUDY 11 AND 11A

		PRE-DOSE		POST-DOSE		CHANGE (POST-PRE)		% CHANGE (POST-PRE/PRE)	
GROUP	N	MEAN	SEM	MEAN	SEM	MEAN	SEM	MEAN	SEM
0	18	105	5	108	5	3	4	4	4
2.5	17	106	8	114	6	9	3	14 (*)	6
5	19	100	7	104	8	4	3	5	4
10	21	94	7	116	7	22 ***	4	28 ***	6

LAST VISIT (VISIT 7) ANALYSIS. MEASUREMENT TAKEN 1 HR POST DOSE

P VALUES BASED ON ONE TAILED T-TEST OR F-TEST VS. PLACEBO:

(*) P < 0.1; *** P< 0.001

CHANGE AND % CHANGE:

LINEAR DOSE RESPONSE (p<0.001)

5 AND 10 MG (P<.05)

2.5, 5 AND 10 MG (P<.05)

TABLE 3
(Protocol 20,762-11/11A)

Syncopal Symptoms
Change from baseline analysis of mean scores

Group (mg)	N	Baseline Mean	Baseline SD	Last Visit Mean	Last Visit SD	Change Mean	Change SD	P-Values vs Plbo
Plbo	14	2.2	0.1	2.6	0.2	0.36	0.11	
2.5	14	1.9	0.1	2.4	0.2	0.46	0.16	0.623
5	17	1.8	0.1	2.3	0.2	0.56	0.17	0.334
10	18	1.6	0.1	2.3	0.1	0.67	0.13	0.135

Table 14a of the NDA, Vol 5.2, page 36

TABLE 4
(Protocol 20,762-11/11A)

Syncopal Symptoms
% Change from baseline for the mean scores

Group (mg)	N	Baseline Mean	Baseline SD	Last Visit Mean	Last Visit SD	% Change Mean	% Change SD	P-Values vs Plbo*
Plbo	14	2.2	0.1	2.6	0.2	17	5	
2.5	14	1.9	0.1	2.4	0.2	30	12	0.225
5	17	1.8	0.1	2.3	0.2	38	14	0.113
10	18	1.6	0.1	2.3	0.1	53	13	0.018

Table 14a of the NDA, Vol 5.2, page 37
* One-tailed test

TABLE B, continued

Analyzable Patients--Early Removals
(Included in efficacy analysis)

SCN	Reason for Removal	Location at Removal	Hours TTS Worn	Serum Fentanyl (ng/ml)
249	Respiratory depression, (3-8 breaths/min; pCO_2 60). No further sequelae after treatment with naloxone.	WARD	11.5	3.0 at 12 hrs
255	Required naloxone for extubation. Mild hypotension, lethargy, pCO_2 53. No further sequelae after treatment with naloxone.	PAR	6.0	2.1 at 8 hrs

TREATMENT: TTS (PLACEBO)

No early removals

Reference: Section 3.3, Appendix I

3.1.3 Patient Demographics

Table C summarizes the demographics of all patients randomized to treatment and Table D summarizes their pre-treatment vital signs. (A second demographic analysis was performed excluding non-analyzable patients and is included in Table 1.)

Information for individual patients, including patients excluded from analysis, is listed in Appendix I. No statistically significant differences were found between groups on any of the demographic variables analyzed. In the group randomized to, fentanyl, mean age was 55.1 years, 60% of the patients were men, and 70.8% had an ASA rating

C. Open-Dose Titration Phase - Response to Single Incremental Doses

Day 1 -- successive incremental dosages of 2.5 mg Midodrine or 5.0 mg Ephedrine will be given to the patient until a safe maximal pressure response as defined below is observed. A maximum of two doses will be given each day. The first dosage at 7:30 a.m. the second at 12:30 p.m. If additional dosages are required, a maximum single dose will be 10 mg Midodrine or 12 mg Ephedrine on day 2.

Supine and upright blood pressures will be obtained just prior to the drug administration, one-half hour after dosing and at hourly intervals thereafter until 4:00 p.m. The dosages will be given approximately one-half hour prior to meals. A safe maximal pressure response, for instance, is defined as a supine blood pressure of 140-180 mm Hg systolic pressure, with a diastolic pressure of 100 or less, along with or concomitant with a standing blood pressure of greater than 80 mm Hg systolic. The dosage which is found to produce this safe maximal pressure response will then be given to the patient on a TID schedule beginning the following day.

D. Crossover Phase

Each leg of the crossover will last four days with a [illegible] day placebo washout in between the Midodrine or Ephedrine. A dose of Midodrine or Ephedrine determined in C. will then be administered to the patient three times a day at 7:30 a.m., 12:30 p.m. and 5:30 p.m. for 4 consecutive days. The timing for meals, frequency of blood pressure measurements will be as previously described under the Open-Dose Titration Phase. Family members or other suitable personnel trained in blood pressure technique will be asked to record the blood pressures in the evening [illegible] p.m. and at 7:00 a.m. each day.

During the period of the TID dosage administration any symptoms assigned to orthostatic hypotension or any adverse side effects of Midodrine should be recorded. If severe supine hypertension develops, that is, blood pressure is greater than [illegible] systolic over [illegible] diastolic [illegible] that [illegible] the patient [illegible]

Introduction

'OSTURAL hypotension is a disabling feature of ...nic autonomic failure. Autonomic failure may occur ...an isolated disturbance (idiopathic or neurogenic ...ostatic hypotension[1]) or in association with idio... parkinsonism or more widespread neurological ...se (Shy-Drager syndrome[2] or multiple-system atro... Orthostatic hypotension in all these patients ...s to be the result of lesions of the efferent sympa... pathway, caused by loss of sympathetic interme... ...teral column cells in the spinal cord and varying ...es of ganglionic and post-ganglionic degeneration, ...consequent failure of noradrenaline release.[4,5] Sug... ...d therapy includes blood-volume expansion by body ...g or mineralocorticoids, reduction of pooling in the ...by mechanical aids, and the use of pressor drugs to ...note vasoconstriction. Since all of these measures ...their limitations,[6-8] reports[9-12] that postural hypo... ...on was much improved by *p*-tyramine and a mono... ...e-oxidase inhibitor prompted further study. We ...compared the effects of *p*-tyramine and a mono... ...e-oxidase inhibitor with those of the pressor drugs ...ylephrine and ephedrine in four patients with ...ral hypotension caused by autonomic failure.

Patients and Methods

... male (cases 1 and 2) and 2 female (cases 3 and 4) pa... ...ged 59–69 were treated. The patients had had symp... ...al postural hypotension for 7 months – 12 years. Cases ... 3 had no clinical evidence of any other neurological defi... ...diopathic postural hypotension). Case 1 had signs of cere... ...r degeneration and case 4 had pyramidal signs and ...insonism (multiple-system atrophy). Testing of autonomic ...ion revealed pronounced postural hypotension, loss of the ...ic overshoot in the Valsalva response, and loss of a pres... ...response to stress, indicating an efferent sympathetic ...n.[13] All patients were admitted to hospital for the study. ...e patients were receiving fludrocortisone, which was dis... ...tinued 7 days before any pressor amines were used; case 1 had received no drugs. *p*-Tyramine hydrochloride and phenylephrine were made up in gelatin capsules.

Before the study *p*-tyramine alone was given to case 3 and the dose was increased to 12 mg. All subjects were treated for 5 days with the standard therapeutic dose of phenelzine (15 mg, 3 times daily), and on the 5th, 6th, and 7th days single oral doses of *p*-tyramine (2 mg, 4 mg, 6 mg, respectively) were administered until a pressor response was observed. Case 3 was given 12 mg of *p*-tyramine on the 8th day. For all subjects, treatment with regular doses of phenelzine plus *p*-tyramine was carried out for 2 days only. Sufficient time (6 days to 2 months) elapsed between the termination of phenelzine therapy and use of phenylephrine or ephedrine for monoamine-oxidase activity to return to normal. Clinical evidence suggests that this process, which occurs mainly by synthesis of new enzyme, requires only a few days.[14,15]

Successive test doses of phenylephrine or ephedrine were given to each subject until a pressor response was detected. Regular doses of phenylephrine (30 mg 3 times daily) and then ephedrine (30 mg 3 times daily) were given for 2 days to patients 3 and 4; only one dose of phenylephrine and 2 of ephedrine were given to patients 1 and 2 because of dramatic hypertensive responses. Smaller doses of ephedrine or phenylephrine did not produce a pressor response.

Blood-pressure and heart-rate responses to single doses of drugs given to each subject were monitored at 1 min intervals by means of a 'Biosemat II' automatic blood-pressure recorder (Bosch and Sohn, Fabrik Medizinischer Apparate D.7455, Jungingen). The instrument was calibrated against a sphygmomanometer and by auscultation at frequent intervals during the tests. During the studies of the effects of regular doses of all drugs, recumbent and 45° tilt pressures were recorded by sphygmomanometer at hourly intervals from 6 A.M. to 10 P.M. After each dose of drug, more frequent observations of blood-pressure were made until it had returned to stable, pre-treatment levels.

Results

Single-dose Studies

The results with single doses of *p*-tyramine, *p*-tyramine plus phenelzine, phenylephrine, or ephedrine are shown in the accompanying figure for case 3. The re-

BLOOD-PRESSURE RESPONSES TO PRESSOR AMINES

Case	Drug	Dose (mg)	Dosage frequency (daily)	Onset* (min)	Duration	B.P. before treatment		B.P. after treatment	
						Supine	Tilt	Supine	Tilt
1	Phenelzine + *p*-tyramine	15 + 6	×3	89	70	120/70	90/60	170/110	85/60
	Phenylephrine	30	×1	15	120	130/90	90/60	210/115	170/90
	Ephedrine	30	×2	12	73	120/80	95/60	185/110	180/100
2	Phenelzine + *p*-tyramine	15 + 6	×3	42	73	130/90	85/65	180/115	90/65
	Phenylephrine	30	×1	11	133	130/90	85/55	200/120	160/115
	Ephedrine	30	×2	11	139	130/90	90/60	185/120	130/100
3	*p*-Tyramine	12	×1	44	50	130/80	80/50	200/120	80/50
	Phenelzine + *p*-tyramine	15 + 6	×3	36	69	130/80	90/50	210/130	90/50
	Phenelzine + *p*-tyramine	15 + 12	×1	32	118	125/80	70/40	210/125	60/40
	Phenylephrine	30	×3	16	109	130/80	80/50	190/115	110/85
	Ephedrine	30	×2	45	120	120/80	85/50	170/110	110/80
4	Phenelzine + *p*-tyramine	15 + 6	×3	42	68	115/80	70/40	165/105	70/40
	Phenylephrine	30	×3	17	113	120/85	60/40	185/115	120/90
	Ephedrine	30	×3	22	100	115/80	60/40	180/120	115/80

* Time after ingestion.

FIGURE 1

MIDODRINE STUDY DESIGN
(20,762-1)

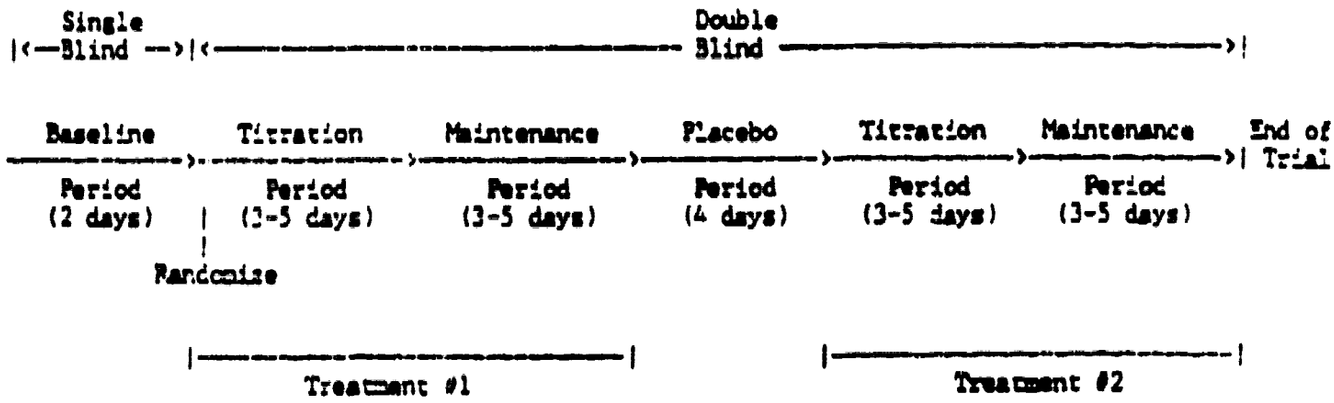
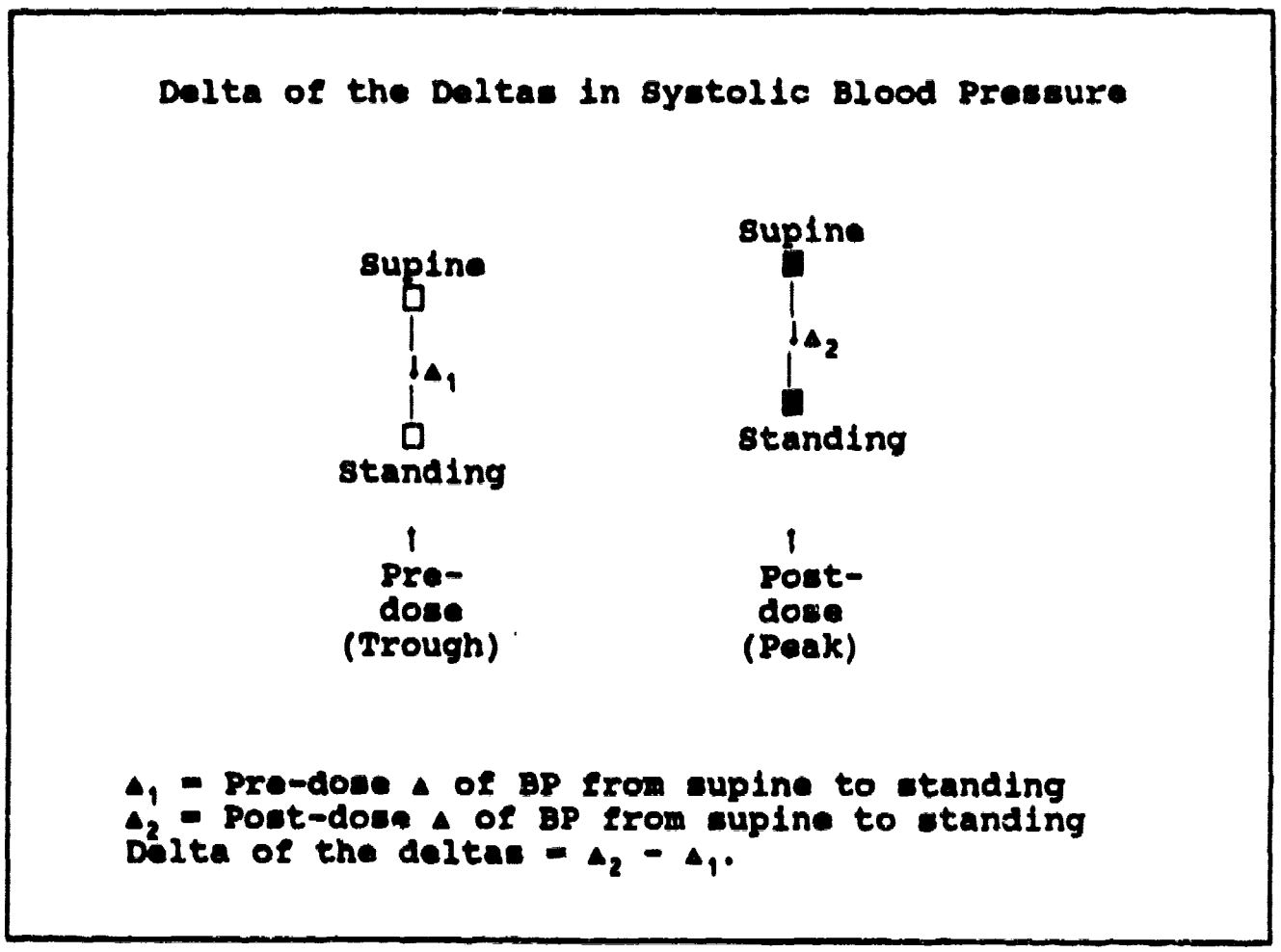


FIGURE 2


Delta of the Deltas in Systolic Blood Pressure
Supine
Standing
Pre-dose (Trough)
Supine
Standing
Post-dose (Peak)
Δ_1 = Pre-dose Δ of BP from supine to standing
Δ_2 = Post-dose Δ of BP from supine to standing
Delta of the deltas = $\Delta_2 - \Delta_1$.

Chemist Review