Nixon, Hargrave, Devans & Doyle
Attorneys and Counselors at Law
A PARTNERSHIP INCLUDING PROFESSIONAL CORPORATIONS
SUITE 800, ONE THOMAS CIRCLE
WASHINGTON, D.C. 20005
(202) 223-7200

LINCOLN FIRST TOWER
POST OFFICE BOX 1051
ROCHESTER, NEW YORK 14603
(716) 546-8000
CABLE: NIXONHARG ROCHESTER
TELEX: 978450

30 ROCKEFELLER PLAZA
NEW YORK, NEW YORK 10112
(212) 586-4100
CABLE: NIXONHARG NEW YORK
TELEX: 66521

REYNOLDS PLAZA
1061 EAST INDIANTOWN ROAD
JUPITER, FLORIDA 33458
(305) 746-1002
(305) 283-5004 (MARTIN COUNTY)

June 20, 1985

1985 JUN 21 PM 12:44

Dockets Management Branch
Food and Drug Administration
Department of Health and
Human Services
Room 4-62
5600 Fishers Lane
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this petition on behalf of Thompson Medical Company, Inc. pursuant to 21 CFR 10.30 to request the Commissioner of Food and Drugs to open the administrative records in the Over-the-Counter Drug Reviews of Weight Control Drug Products (Docket No. 81N-0022) and Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (Docket No. 76N-052N) to accept the enclosed report of the recently-completed study conducted by John P. Morgan, M.D., at the School of BioMedical Education, C.C.N.Y., New York, New York.

A. Action Requested

The undersigned respectfully requests that the administrative records be opened to permit the enclosed report to be considered in the referenced OTC Drug Reviews.

B. Statement of Grounds

The grounds on which petitioner relies are that phenylpropanolamine hydrochloride (PPA) is one of the ingredients of weight control products and nasal decongestants which are the subjects, respectively, of the above-referenced proposed OTC Drug Products Monographs. The Panel Monographs concluded that PPA and its salts are safe and effective for OTC weight control and oral nasal decongestant use in the specified dosages. The Tentative Final Monograph has not yet been published in either Review with regard to PPA.

76N-052N

C
CP0009

In the preamble to the Advance Notice of Proposed Rulemaking in the Weight Control Drug Products Review (47 Fed. Reg. 8466, et seq., February 25, 1982), the Commissioner requested further studies regarding the safety of PPA for use in weight control products.

In the preamble to the Notice of Proposed Rulemaking in the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products Review (50 Fed. Reg. 2220, 2221, January 15, 1985) the Commissioner commented on the safety of PPA for use in weight control and nasal decongestant products and stated that the agency has decided to address the safety of PPA in both weight control and nasal decongestant products in the near future.

The enclosed report summarizes a study, involving 224 patients, which demonstrates the safety of PPA in weight control products. Since the same ingredient is involved in both types of products, the enclosed report is highly significant to the agency's OTC Drug Reviews of both weight control and cough/cold drug products and should therefore be considered in both Reviews at the earliest possible time.

In view of the size of the study report, two copies are enclosed for your convenience, one for each administrative record.

C. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Stephen Kurzman, P.C.
Nixon, Hargrave, Devans & Doyle
Suite 800
One Thomas Circle, N.W.
Washington, D.C. 20005
(202) 223-7200

FINAL REPORT

A MULTISITE EVALUATION OF THE ACUTE EFFECTS OF PHENYLPROPANOLAMINE IN NORMAL VOLUNTEERS

SPONSOR: Thompson Medical Company, Inc.
919 Third Avenue
New York, New York 10022

INVESTIGATOR: John P. Morgan
School of BioMedical Education
C.C.N.Y.
138th St. and Convent Street
New York, New York 10031

CONTACT: Frank R. Funderburk
Director, Clinical Consulting Group
ANTECH, Inc.
P.O. Box 2193
Columbia, Maryland 21045
(301) 997-0880

DATE: March 5, 1985

TABLE OF CONTENTS

ABSTRACT

INTRODUCTION 1

OBJECTIVE 2

RATIONALE 2

INVESTIGATIVE METHODS 3

Subjects 3

Design and Procedure 5

1. General Procedures 5

a. Subject control 5

b. Meals and Food Restrictions..... 5

c. Drug Administration..... 6

d. Clinical Measurements 7

e. Subjective Drug Effects 7

f. Physical Procedures 9

2. Design..... 9

RESULTS 11

DISCUSSION 16

REFERENCES 20

ABSTRACT

Two hundred twenty four (224) healthy normotensive volunteers (mean age = 27.9), presenting with various degrees of overweight participated in a double blind, placebo-controlled evaluation of the effects of phenylpropanolamine HCL (PPA) on blood pressure, pulse, and mood. Two dosage forms of PPA were studied (75 mg sustained release and 25 mg t.i.d.) in comparison with placebo. Subjects in each of four weight categories were randomly assigned to one of the three drug conditions. The weight categories were normal weight (n=67), mildly overweight (15-30%, n=66), moderately overweight (31-45%, n=54), and severely overweight (over 46%, n=37). Subjects received a test medication (either an active product or placebo) 3 times during a 12 hour testing session. Subjects in one group (Group A) received a 75 mg sustained release dose on their first medication occasion and placebo capsules on the other two dosing occasions. Subjects in another group (Group B) received 25 mg doses at each medication occasion. Subjects in the other group (Group C) received placebo at each medication occasion. Subjects were studied for a 12 hour testing session.

Measurements of blood pressure (both standing and supine), pulse, and subjective drug effect (using the Addiction Research Center Inventory- ARCI) were obtained 11 times during the session at baseline (prior to drug administration) and at 1/2 hour, 1 hour, 2 hours, 4 hours, 4-1/2 hours, 6 hours, 8 hours, 8-1/2

hours, 10 hours, and 12 hours post initial dosing.

Mixed design analysis of variance revealed no overall main effects for drug treatment on measure of pulse or blood pressure in either body position. This finding is quite consistent with research conducted at a number of other well-established clinical sites. Subjects in the heavier weight categories consistently showed more rapid pulse rates and higher blood pressure values than did those subjects of normal or near normal weight. However, no significant differences in drug effect as a function of weight classification were observed. As expected, most measures showed main effects for measurement time (circadian effects), indicating that subjects' physiological and subjective state changed over the course of the session. Significant interactions for drug treatment and measurement time were obtained for standing systolic blood pressure only.

One way analysis of variance of peak diastolic blood pressure during the course of the session did not indicate a main effect for drug treatment in either body position. Weight class, however, was reliably related to peak diastolic blood pressure in both body positions. Heavier subjects consistently showed higher peak diastolic values as campared with subjects of normal weight. Subjective effects, as measured by the Addiction Research Center Inventory, did not differentiate the drug treatment conditions but did show normal circadian variation. The present results are consistent with much previous research indicating that no clinically significant increases in blood

pressure or pulse are associated with PPA at the currently recommended dose.

Data Report: Site 1 New York

Protocol:

A MULTISITE EVALUATION OF THE ACUTE EFFECTS OF PHENYLPROPANOLAMINE IN NORMAL VOLUNTEERS

INTRODUCTION

Phenylpropanolamine hydrochloride (PPA) is a synthetic compound with actions similar to ephedrine. However, PPA is generally believed to produce less CNS stimulation than ephedrine. PPA is currently marketed over-the-counter (OTC) in the United States both as a nasal decongestant and as a weight control aid. Recently FDA and others have raised questions about the safety and appropriateness of OTC availability of PPA (Federal Register, Vol. 47, No. 39, 1982). In their publication, the agency requested additional information on the effects of PPA on a variety of safety parameters including blood pressure, pulse, and self-reported side effects. Previous work sponsored by the Thompson Medical Company investigated the effects of two dosage forms of PPA (75 mg sustained release and 25 mg t.i.d) in comparison with placebo. Measures of blood pressure, pulse, mood, and subjective drug effects were taken over the course of a 12 hour session in a group of 150 normal volunteers. No adverse

effects on any of the measures were observed. This result was replicated in a crossover design using 59 normal volunteers exposed to both the 75 mg sustained release formulation and placebo. The present study is part of a multi-site extension of this work (Funderburk et al., 1982a, 1982b, 1982c) designed to provide an independent evaluation of the effects of PPA in normal volunteers. In addition, the present study was also designed to evaluate weight classification (in terms of degree of overweight) as a variable which could influence the physiological and subjective effects of PPA at recommended dose levels.

OBJECTIVE

The present study aims to provide an objective characterization of the effects of PPA on various behavioral and physiological parameters over a 12 hour testing session. Normal volunteers in four weight classes (normal weight, mildly overweight, moderately overweight and severely overweight) were studied to evaluate the effects of PPA over a wide range of weight classes.

RATIONALE

PPA has been used as an anorexiant for over 40 years and has long been an ingredient in many over-the-counter cough-cold products (see, e.g., Silverman, 1980). Recently, however, some reports have appeared suggesting that PPA--generally in doses higher than those approved for over-the-counter use in the United States--may be associated with adverse hypertensive effects or

other amphetamine-like side effects (e.g., Horowitz, 1980; Dietz, 1981). In contrast, a number of well controlled studies of PPA at recommended dose levels have been conducted which suggest that PPA (at recommended dose levels) is not associated with adverse effects. Silverman et al. (1980) reported no adverse hypertensive effects of a 25 mg dose of PPA either alone or in combination with 100 mg of caffeine. Hoebel (paper in preparation, 1982) noted no adverse hypertensive effects of 150 mg PPA (75 mg b.i.d.) in a group of six normotensive individuals. Funderburk et al. (1982a, 1982b, 1982c) in a series of double-blind placebo controlled studies noted no adverse effects on blood pressure, pulse, mood or subjective state in 150 normal volunteers studied for a 12 hour period following doses of 75 mg sustained release PPA or a 25 mg t.i.d. dosage formulation. Similar results were found in a crossover comparison (n=59) of 75 mg sustained release PPA and placebo.

The present study was undertaken to extend the examination of PPA effects on blood pressure, pulse, and subjective state in another large, carefully controlled clinical investigation.

INVESTIGATIVE METHODS

Subjects

Subjects were 224 healthy normal volunteers (mean age= 27.9) 51% male. The study population consisted of 86 Caucasians, 108 Blacks, 1 American Indian, 5 Orientals, 9 Puerto Ricans and 5

"others". Ten cases had missing data on this variable. All had given informed consent and had been screened to meet the following criteria:

1. between 18 and 65 years of age

2. weight stratification (according to the Metropolitan Life Insurance Scales) 67 normal weight 66 mildly overweight (15-30%) 54 moderately overweight (31-45%) 37 severely overweight (46+%)

3. no current use of medications which would compromise the validity of the evaluation of the test products.

4. no physical or allergic contraindications to consumption of PPA at the dose levels used in this study.

5. no hypertensive history defined as a diastolic blood pressure greater than 94mmHg.

6. no diabetics.

7. no history of severe emotional disturbance (severe depression, etc.), chronic alcoholism, or drug abuse.

8. evidence that the subject would participate in the research and be cooperative

9. good general health based on a medical history interview conducted within one month of the study start and a recent

physical examination.

10. female subjects certified that they were not pregnant or nursing a baby for the duration of the protocol.

Design and Procedure

This investigation is a large-sample parallel group design in which approximately 864 subjects (approximately 216 site) are tested at four sites under treatment conditions as detailed below. This portion of the report describes the results obtained at the New York site under the medical direction of Dr. John Morgan.

1. General Procedures

a. Subject control. Subjects were instructed to be free of all medications for the week prior to the administration of a test product. Subjects who ingested substances which compromised the validity of the study were excluded. Study medications were administered under clinical supervision. Subjects remained at the test facility for the entire testing period during test days.

b. Meals and food restrictions. On test days subjects were provided with a choice of standard noontime meals. Foods containing xanthines (e.g., coffee, tea, cola) were not permitted on study day, and subjects were instructed not to use these foods in their breakfast before coming to the test facility.

c. Drug administration. In this investigation two currently marketed dose forms of a test product containing PPA (PPA, 75 mg sustained - release and 25 mg t.i.d. were compared with placebo. Medications were administered following double-blind procedures. On each test day subjects received the test product at approximately 8:00 am, 12 Noon, and 4 pm, or equivalent spacing if test day started early (e.g., 7 am, 11 am, 3 pm).

Subjects were randomly assigned to one of three drug treatment conditions stratified by weight. One group of subjects (Condition A) received the 75 mg sustained release product at their first dosing and placebo capsules on subsequent dosings. Another group of subjects (Condition B) received 25 mg t.i.d. and a third group of subjects (Condition C) received placebo, as illustrated below. All medications were taken with a full glass of water.

Dosing Schedule on a Test Day

	Dose 1 (approx. 8:00 am)	Dose 2 (approx. 12 noon)	Dose 3 (approx. 4:00 p
Condition A	75 mg sustained	placebo	placebo
Condition B	25 mg PPA	25 mg PPA	25 mg PPA
Condition C	placebo	placebo	placebo

d. Clinical measures. Clinical measures of subjective state of blood pressure and pulse were obtained 11 times during each experimental session: once prior to initial drug administration (0 hr) and at 1/2 hr, 1 hr, 2 hr, 4 hr, 4-1/2 hr, 6 hr, 8 hr, 8-1/2 hr, 10 hr, and 12 hr following initial drug administration.

Blood pressure (after standing for 2 minutes and after being supine for 5 minutes) was measured using procedures recommended by the American Heart Association (Kirkendall et al., 1980). Clinical measures of subjective states were obtained using a self-administered standardized drug effect scale at each measurement interval (Addiction Research Center Inventory; ARCI). These measures were supplemented by subjective reports of subjects and the observations of research staff.

e. Subjective drug effects were measured using the short version of the Addiction Research Center Inventory (ARCI). This is a standardized, self-administered inventory which compares the

subjective effects of a test compound with those of a variety of CNS-active drugs (see Haertzen, 1974, for a detailed description). The inventory requires approximately 5 minutes to complete. The scales used in this study, and the characteristics they reflect, are:

1. AMP: empirical scale which measures similarity to amphetamine effects.

2. BG: group variability scale which measures similarity to benzedrine effects. Interpreted as a measure of intellectual efficiency and energy.

3. MBG: group variability scale which measures a morphine-benzedrine effect. Interpreted as a measure of euphoria.

4. PCAG: group variability scale which measures pentobarbital-chlorpromazine-alcohol effects. Interpreted as a measure of sedation, fatigue, and low motivation.

5. LSD: empirical scale which measures similarity to LSD effects. Interpreted as a measure of anxiety, tension, difficulty in concentration, depersonalization, and psychomimetic changes. Also interpred as a measure of dysphoria.

This inventory was administered in association with each of the 11 clinical measurement occasions. This version of the ARCI

contains empirically derived scales which have been validated in thousands of subjects since its initial use in the 1950s. The scales are known to be sensitive to the subjective changes produced by a wide variety of drug and non-drug stimuli. It is particularly useful for characterizing the psychoactive effects of drugs (Haertzen & Hickey, 1984; Jasinski et al., 1984).

f. Physical procedures. All subjects were kept in the test facility throughout the test day. All activity was sedentary, e.g., watching tv, reading, etc., or generally non-stressful.

2. Design

The overall study design may be viewed as a parallel groups study in which 864 subjects (216/site) were randomly assigned to one of the three treatment conditions (stratified according to weight). This report focuses on one of the four study sites.

This portion of the overall multisite study may be viewed as a 3 (drug treatment conditions) x 4 (weight classes) x 11 (measurement occasions) mixed design. Mixed design analysis of variance procedures were used to evaluate data from this component of the study. Separate analyses were conducted for each of the dependent variables. Factors in the analysis were drug treatment assignment (Condition A vs B vs C), weight classification (normal, mildly overweight, moderately overweight, and severely overweight), and measurement occasion (0 hr, 1/2 hr, etc.). Treatment assignment and weight class were between-groups

factors while measurement occasion was a within-subjects factor. For all tests involving repeated measures factors, a conservative F test was used in evaluating statistical significance (see, e.g., Geisser & Greenhouse, 1958).

In addition to these traditional types of statistical analyses, special attention was given to individual changes in diastolic blood pressure observed during the course of the session. Four distinct analytical approaches were used to examine these individual effects:

1. Evaluation of the number of cases in each drug treatment group showing diastolic blood pressure > 94 mm Hg during the session, independent of baseline level of blood pressure.

2. Evaluation of the number of cases in each drug treatment group showing certain levels of change in diastolic blood pressure (<10 mm Hg, 11-25 mm Hg, > 25 mm Hg) during the course of the session.

3. Analysis of variance applied to the peak diastolic blood pressure observed in any individual, independent of baseline level.

4. Analysis of variance applied to peak change readings observed in any individual, relative to baseline level of blood pressure.

Each of these analyses was applied to observations of both standing and supine diastolic blood pressure.

RESULTS

Specific results of the analysis of variance for each of the variables studied are summarized below.

Pulse was not reliably affected by drug treatment. The largest mean difference between placebo and an active drug treatment in any body position was 1.74 bpm. Pulse tended to be more rapid in the heavier weight categories as compared to the more normal weight categories. This effect was evident in both the standing and supine body positions (mean difference = 6.07 bpm, 5.71 bpm; $F=4.42$, 5.58, respectively, $p < .01$ for both). Reliable changes in pulse were obtained over the course of the session for all treatment conditions in both body positions which reflected a decrease in pulse rate early in the session (of approximately 5 bpm) followed by a tendency to return towards the basal pulse rate at midday and generally higher pulse rates later in the session (standing $F=21.83$, $p < .01$; supine $F=28.94$, $p < .01$).

Standing systolic blood pressure showed no main effect for drug treatment. The mean difference between placebo and either of the active drug treatments was 1.36 mm Hg. Small but reliable

fluctuations in blood pressure were observed over the course of the session ($F=3.88$, $p < .05$). The general trend was for a small decrease from baseline during the first 2 hours of the session followed by an increasing trend during the remainder of the session. The maximum mean difference between observations was 4.27 mm Hg. Subjects in the 75 mg SR drug condition showed a tendency for increases from baseline values earlier in the session as compared with the other two drug treatment groups ($F=2.86$, $p < .05$). These differences, however, were reversed later in the session. A main effect for weight category was identified ($F=13.09$, $p <.01$) reflecting the fact that subjects in the heavier weight groups showed higher mean values than did those in the normal weight group. The relationship was linear with a maximum difference of 12.87 mm Hg between the most extreme weight categories.

Standing diastolic blood pressure showed no main effect for drug treatment. The maximum mean difference between placebo and either of the active drug treatments was 1.43 mm Hg. A small main effect was observed for time course($F=2.68$, $p < .05$). This reflects a small increase early in the session followed by a general decrease during the remainder of the session. A strong main effect for weight category was observed ($F=13.88$, $p < .01$). Subjects in the heavier weight groups consistently showed higher values than did subjects in the normal category. The relationship was linear with a maximum difference of 9.98 mm Hg

between the most extreme weight categories.

Analysis of individual peak response obtained during the course of the session did not identify main effects for or interactions with drug treatment condition. The largest difference between placebo and either active drug treatment condition was less than 1 mm Hg. Peak change from baseline also failed to differentiate the treatment groups. The largest mean difference between treatments was < 2 mm Hg. The relative frequency of diastolic readings > 94 mm Hg also did not differentiate the drug treatments. Weight class, however, was associated with statistically reliable differences in peak responses ($F = 6.37$, $p < .01$). Overall subjects in the heavier weight categories showed higher peak responses compared with those of normal weight. The relationship was linear with a maximum difference 8.01 mm Hg between the most extreme weight categories. These results are detailed in Appendix III (Tables 1,2,3,4,7, and 8).

Supine systolic blood pressure showed no main effect for drug treatment. The largest mean difference between drug treatment conditions was 1.38 mm Hg. A significant time course effect was observed ($F=6.95$, $p < .01$), reflecting a tendency for this measure to increase over the course of the session. The maximum increase from baseline was approximately 5 mm Hg. Subjects treated with the 75 mg sustained release product showed higher initial and lower midsession values compared with subjects in the other two drug treatment conditions ($F=2.87$, $p < .05$). A main

effect for weight category was observed ($F=5.45$, $p < .01$) reflecting a linear relationship between blood pressure and weight class. The mean supine systolic blood pressure of severely overweight subjects was 8.8 mm Hg higher than that of normal weight subjects.

Supine diastolic blood pressure did not differentiate the drug treatment groups. The largest difference between placebo and either of the active drug treatments was 1.45 mm Hg. A main effect for time course was observed ($F=5.07$, $p < .01$). Overall, this measure peaked 1 hour after drug administration, decreased during the midafternoon portion of the session, and increased prior to conclusion of the session. A main effect for weight class was also observed ($F=7.39$, $p < .01$), again reflecting the trend for heavier subjects to have higher blood pressure values than the more normal weight subjects. The mean difference between normal and severely overweight subjects was 6.48 mm Hg.

Analysis of the various individual response variables identified a small but statistically reliable effect attributable to drug condition in the measure of peak change from baseline ($F=3.43$, $p < .05$). Overall, the 75 mg sustained release condition was associated with a slightly larger peak change when compared with either the 25 mg tid or placebo condition (mean difference from placebo was 3.65 mm Hg). This effect, however, was qualified by an interaction with weight class ($F=2.16$, $p < .05$). This interaction effect reflects the fact that the pattern of results

within the various weight categories is not consistent. Thus, while the overall pattern in present in the normal and moderately overweight subjects, the 25 mg tid condition shows the largest change in the mildly overweight subjects while the placebo condition is associated with the largest change in the severely overweight group.

Analysis of mean peak diastolic blood pressure did not differentiate the drug treatment groups (largest difference between treatments was 2.85 mm Hg). A main effect for weight class ($F=4.94$, $p < .05$), however, was identified. This effect reflects an increase in mean peak diasolic blood pressure associated with increased body weight. The mean difference between normal and severely overweight subjects was 7.05 mm Hg. These results are detailed in Appendix III (Tables 1,2,5,6,9 and 10).

Subjective effects were measured using the Addiction Research Center Inventory (ARCI). As described previously, scales studied were AMP, BG, MBG, PCAG, and LSD. Data from 31 subjects were excluded from analysis of subjective effects due to missing data on these self-report forms. This data loss is considered a random event and therefore does not affect the interpretation of the results.

All of the ARCI variables showed significant and consistent changes over the course of the session. Scores on the AMP, BG,

and MBG scales were generally higher early in the session and decreased later in the session ($F=6.03$, 6.55, 13.53, respectively, $p < .01$ for all). Scores on the PCAG increased during the early portion of the session and returned to baseline levels late in the sesison ($F=6.23$, $p < .01$). Scores on the LSD scale increased over the session ($F=4.80$, $p < .01$). In addition, main effects for weight category were observed for the PCAG and LSD scales ($F=3.01$, 3.92, respectively, $p < .01$). These reflect lower overall scores on these scales for moderately overweight subjects. These time-related changes are consistent with the general "mood" effects which might be expected over the course of a 12 hour experimental session. No main effects for or interactions with drug treatment condition were identified.

Summary tables of means, standard deviations, and analysis of variance results for each variable studied are presented in the Appendix.

DISCUSSION

The present study evaluated the acute effects of two dosage forms of phenylpropanolamine (75 mg sustained release, 25 mg t.i.d.) in comparison with placebo. Measures of drug effect on pulse, blood pressure (both standing and supine) and subjective state (ARCI) were obtained over a 12 hour testing session.

No significant main effects for drug treatment were observed in the overall mixed-design analyses. Differences in blood pressure

between drug treatment groups were small and not statistically significant. They averaged 1.41 mm Hg. This result is very consistent with previous studies conducted at other well established clinical sites. Overall differences in pulse rate between treatment groups averaged less than 2 bpm. In contrast, weight class was significantly related to pulse. Subjects in the heavier weight categories consistently showed more rapid pulse rates (an average difference of 5.7-6.1 bpm) than did subjects of normal or near normal weight. In addition, blood pressure was reliably elevated in the heaviest subjects when compared with those of normal weight in all body positions (average difference of 9.53 mm Hg.). No interaction between drug effect and weight category was found.

Results from the analysis of various individual response parameters revealed only one statistically reliable difference in blood pressure response attributable to drug condition. This was obtained for the measure of peak change from baseline in the supine position. Analysis indicated that the 75 mg SR condition was associated with slightly higher values than the other drug treatments (mean difference from placebo of 3.65 mm Hg). This small effect was not consistent across weight classes, as evidenced by a statistically significant interaction effect. Both the small magnitude and lack of consistency of this effect indicate that it is not of clinical significance.

Weight category, on the other hand, was found to have a

significant effect on the individual response measures of peak diastolic blood pressure in both body positions. The average difference between the normal and severely overweight groups was 7.53 mm Hg.

Statistically significant differences were found over the course of the session in most of the physiological measures. These effects were present in both standing and supine positions. These effects were extremely small and were not related to weight category. Differences in circadian variation were obtained for systolic blood pressure and peak in both positions, and for diastolic blood pressure in the supine position only. None of these changes were related to drug treatment condition, and all fell well within the range of normal circadian variation for these variables (see, e.g., Funderburk et al., 1982a, b; Miller-Craig et al., 1978; Noble, 1983; Robertson, 1983; Blackburn, 1984; Mancia, et.al., 1983).

The present results also suggest that PPA, in the dosage forms studied, had no systematic effect on subjective ratings of drug effect as measured by a standardized drug inventory, the ARCI. No statistically reliable differences between drug treatments were observed on any of the measures of drug effect. The effects of the two PPA treatments were not differentiated from that of the placebo treatment. This finding is consistent with that of Seppala, Nuotto, and Dorttila (1981) in that no signifiant euphoric effects were noted for subjects treated with PPA, and

with the previous work sponsored by Thompson Medical Company (Funderburk et al., 1982c; Noble, 1983; Robertson, 1983; Blackburn, 1984). As was the case with the physiological measures, subjective state showed circadian changes over the course of the session. In general, subjects in all treatment groups reported feeling more energetic early in the session as compared with later in the session.

Overall, the present findings suggest that phenylpropanolamine, in the dosage forms studied, is not associated with adverse effects on blood pressure, pulse, or subjective drug experiences. The small but statistically reliable treatment effects which were obtained for the individual response variables are not considered to be of clinical significance. The results are generally consistent with those conducted at the Behavioral Pharmacology Research Unit (Johns Hopkins School of Medicine; Funderburk et al., 1982a, 1982b, 1982c; The University of California (Noble, 1983), the University of Washington (Robertson, 1983), and the Harvard Medical School (Blackburn, 1984).

REFERENCES

Blackburn, G.L. A multisite evaluation of the acute effects of phenylpropanolamine in normal volunteers. Report to Thompson Medical Company, July 28, 1984.

Dietz, A. J. Amphetamine-like reactions to phenylpropanolamine. Journal of the American Medical Association, 1981, 245, 601-602. Federal Register, Vol. 47, No. 39, 1982.

Funderburk, F., et al. Effects of phenylpropanolamine on blood pressure, pulse, and mood: Parallel groups design. Report to Thompson Medical Company, October, 8, 1982.

Funderburk, F., et al. Effects of phenylpropanolamine on blood pressure, pulse and mood: A crossover design. Report to Thompson Medical Company, October 22, 1982.

Funderburk, F., et al. Supplement to clinical protocols 82-8(A) and 82-8(B). Evaluation of phenylpropanolamine (75 mg) effects on standardized measures of drug effect and affective state. Repor to Thompson Medical Company, December 6, 1892.

Geisser, S., & Greenhouse, S.W. An extension of Box's results on the use of the F distribution in multivariate analysis. Annals of Mathematical Statistics, 1958, 29, 885-891.

Haertzen, C.A. Overview of Addiction Research Center's Scales (ARCI): An appendix and manual of scales. Washington, D.C.: National Institute on Drug Abuse, 1974. (DHEW Publication No. ADM 74-92).

Haertzen, C.A., & Hickey, J.E. Measurement of euphoria and other drug effects. In M.A. Bozarth (Ed.), Methods for assessing the reinforcing properties of abused drugs. Brunswick, Maine: Haer Institute, 1984, in press.

Hoebel, B.G., Effects of phenylpropanolamine (75 mg b.i.d.) on normotensive volunteers. Personal communication, Thompson Medical Company. Abstract to be published in Philadelphia Medicine, 1982.

Horowitz, J.D. et. al. Hypertensive responses induced by phenylpropanolamine in anorectic and decongestant preparations. Lancet, 1980, January 12, 60-61.

Jasinski, D.R., Johnson, R.E., & Henningfield, J.E. Abuse liability assessment in human subjects. Trends in Pharmacological

Sciences, 1984, in press.

Kirkendall, W.M. et al. Recommendations for human blood pressure determination by sphygmomanometers. Reports of the Postgraduate Education Committee, American Heart Association, 1980.

Mancia, G. et al. Blood pressure and heart rate variabilities in normotensive and hypertensive human beings. Circulation Research, 1983, 53, 96-104.

McNair-Craig, M.W., Bishop, C.N., & Raftey, E.B. Circadian variation of blood pressure. Lancet, 1978, April 15, 795-796.

Noble, R. Data Report: Site 3. A multisite evaluation of the acute effects of phenylpropanolamine in normal volunteers. Report to Thompson Medical Company, September 20, 1983.