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February 14, 1984

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

1984 FEB 16 PM 1:50
ADMINISTRATIVE CENTER

CITIZEN PETITION

The undersigned submits this petition on behalf of Thompson Medical Company, Inc. under 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-0052N) to accept the enclosed materials relating to the recently-completed study conducted by Paul Robertston, M.D., at the Department of Medicine, University of Washington, Seattle, Washington.

A. Action Requested

The undersigned respectfully requests that the administrative record be opened to permit the enclosed materials to be considered in the referenced OTC Drug Review.

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

76N-052N

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Dockets Management Branch
February 14, 1984
Page 2

OTC weight control and oral nasal decongestant use in the specified dosages. The Tentative Final Monograph has not yet been published in either Review. 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.

The enclosed materials summarize a study demonstrating the safety of PPA in weight control products. Since the same ingredient is involved in both types of products, the enclosed materials are highly significant to the agency's OTC Drug Reviews of both weight control and cough/cold drug products. Therefore, these materials should 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.



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THOMPSON MEDICAL COMPANY, INC.
919 THIRD AVENUE • NEW YORK, N.Y. 10022 • (212) 688-4420

February 13, 1984

Dr. Mark Novitch
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Novitch:

Enclosed please find the results of a recently completed clinical study conducted at the Department of Medicine; University of Washington; Seattle, Washington, by Paul Robertson, M.D. This study evaluated blood pressure, pulse, and subjective mood changes for possible adverse symptoms attributable to phenylpropanolamine.

The results are consistent with those reported to you on January 3, 1983 in the study of phenylpropanolamine conducted at Johns Hopkins School of Medicine, as well as the study on phenylpropanolamine reported to you in September of 1983 conducted by Rudolf E. Noble, M.D., Ph.D., at the Cathedral Hill Obesity Clinic.

In this current study, two hundred twenty four (224) healthy normotensive volunteers participated in a double-blind placebo-controlled evaluation of the effects of phenylpropanolamine HCl (PPA) on blood pressure, pulse and mood.

The results of this study clearly indicated that:

- A. Phenylpropanolamine does not affect blood pressure.
- B. Phenylpropanolamine does not raise pulse rate.
- C. Phenylpropanolamine does not have abuse or addictive potential.
- D. Phenylpropanolamine does not affect mood.
- E. Phenylpropanolamine is not a stimulant.

This study reconfirms not only the data from the Johns Hopkins and the Cathedral Hill studies, but also the numerous previously submitted clinical studies which support the claim of safety of phenylpropanolamine in the recommended dose.

We feel that these data definitely support the continued confidence of the agency in maintaining phenylpropanolamine as a Category I drug to help suppress appetite and aid in weight loss.

Thank you for your courtesy and attention.

Sincerely yours,

Edward L. Steinberg, M.Sc., O.D.
Vice Chairman of the Board

ELS:kj
Encl.

Data Report: Site 4

Protocol:

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

Principal Investigator: Dr. Paul Robertson

Study Site: Department of Medicine
University of Washington
Seattle, WA

Protocol Design and
Data Report by: The Clinical Consulting Group
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Date: September 6, 1983
Revised November 18, 1983

TABLE OF CONTENTS

ABSTRACT	
INTRODUCTION	1
OBJECTIVE	2
RATIONALE	2
INVESTIGATIVE METHODS	3
Subjects	3
Design and Procedure	4
1. General Procedures	5
a. Subject control	5
b. Meals and food restrictions	5
c. Drug administration	5
d. Clinical measurements	6
e. Subjective drug effects	6
f. Physical procedures	7
2. Design	8
RESULTS	8
DISCUSSION	11
REFERENCES	14
TABLES	17

TABLES

APPENDIX I

Analysis of Variance, Means, and Standard Deviations for
Blood Pressure and Pulse Variables.

APPENDIX II

Analysis of Variance, Means, and Standard Deviations for
Addiction Research Center Inventory (ARCI) Variables.

APPENDIX III

Supplemental Analysis of Individual Effects

APPENDIX IV

Figures

APPENDIX V

Individual Case Data - ARCI

APPENDIX VI

Individual Case Data - BloodPressure - Pulse

ABSTRACT

Two hundred twenty-four (224) healthy normotensive volunteers (mean age = 31.6) 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 = 46), mildly overweight (15-30%, n = 72), moderately overweight (31-45%, n = 71), and severely overweight (over 46%, n = 35). 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 received 25 mg doses at each medication occasion (Group B). 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.

Data were analyzed using mixed design analysis of variance. Pulse was more rapid in subjects in the heavier weight categories compared with those in

the lower weight categories. In addition, subjects in the higher weight categories showed higher blood pressure readings than did those in the lower weight categories (in both standing and supine body positions). Overall, subjects treated with the 75 mg sustained release PPA showed a small but reliable increase in supine blood pressure as compared with placebo or the 25 mg t.i.d. condition. The mean difference from placebo was 4.48 mm Hg for supine systolic and 3.73 mm Hg for supine diastolic. In both of the supine measures and in the standing systolic measure the difference between the treatment groups was reliably larger early in the session as compared with later in the session. All of the blood pressure and pulse measures showed normal circadian variation. No significant differences in drug effect as a function of weight classification were observed. The subjective measures revealed no significant changes as a function of either drug condition or weight class. Like the physiologic measures, the subjective measures showed characteristic circadian variations. The present findings are consistent with previous reports indicating no clinically significant effects of PPA at the doses studied.

Data Report: Site 4 (Seattle)

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 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 formation 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 proposed research 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 form. 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 = 31.6) (both male and female). The study population was predominantly caucasian (86%). Approximately 47% of the subjects were men. All had given informed consent and had been screened to meet the following criteria:

- a. between 18 and 65 years of age
- b. weight stratification (according to the Metropolitan Life Insurance Scales)
46 normal weight

- 72 mildly overweight (15-30%)
- 71 moderately overweight (31-45%)
- 35 severely overweight (46+%)
- c. no current use of medications which would compromise the validity of the evaluation of the test products.
 - d. no physical or allergic contraindications to consumption of PPA at the dose levels used in this study.
 - e. no hypertensive history defined as a diastolic blood pressure greater than 94mmHg.
 - f. no diabetics.
 - g. no history of severe emotional disturbance (severe depression, etc.), chronic alcoholism, or drug abuse.
 - h. evidence that the subject would participate in the research and be cooperative.
 - i. good general health based on a medical history interview conducted within one month of the study start and a recent physical examination.
 - j. 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 Seattle site under the medical direction of Dr. Paul Robertson.

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. 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 medication was taken with a full glass of water.

Dosing Schedule on a Test Day

	Dose 1	Dose 2	Dose 3
	<u>(approx. 8:00 am)</u>	<u>(approx. 12 noon)</u>	<u>(approx. 4:00 pm)</u>
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 hour, 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 interpreted 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).

RESULTS

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

Pulse tended to be slightly more rapid in subjects in the two higher weight categories as compared with subjects in the two lower weight categories. This effect was evident in both the standing and supine body

positions ($F = 7.70, 6.37$, respectively, $p < .01$). Both standing and supine pulse showed significant changes over the course of the session which reflected a small but statistically reliable decrease in pulse rate during the mid-day portion of the session. No main effects for or interactions with drug treatment group were identified. Pulse effects are shown in Table 1.

Standing systolic blood pressure was significantly higher for subjects in the heavier weight categories as compared with subjects of normal weight ($F = 7.19, p < .01$). Statistically significant fluctuations over the course of the session were observed in all treatment groups ($F = 19.50, p < .01$). In general, blood pressure tended to increase during the first few hours of the session, to decrease during the middle portion of the session, and to increase again in the latter portion of the session. In addition, a significant condition-x-time interaction was detected ($F = 6.04, p < .01$). This result reflects the fact that blood pressure fluctuations over the session were greater (especially early in the session) in subjects who had received the 75 mg sustained release product as compared with those who received the other treatments. No other main effects or interactions were statistically significant. Table 2 and Figure 1 illustrate these effects.

Standing diastolic blood pressure was significantly higher for subjects in the heavier weight categories as compared with subjects in the more normal weight categories ($F = 12.62, p < .01$). Statistically significant fluctuations over the course of the session were observed in all treatment groups ($F = 15.27, p < .01$). These fluctuations followed the pattern observed in standing systolic blood pressure. No other main effects or interactions were statistically significant. Table 2 and Figure 1 illustrate these effects.

Supine systolic blood pressure was significantly higher for subjects in the heavier weight categories as compared with those of normal weight ($F = 7.69, p < .01$). Overall, subjects in the 75 mg sustained release condition showed slightly higher supine systolic blood pressure readings as compared with the subjects in the placebo or the 25 mg t.i.d. treatments ($F = 3.42, p < .05$). The mean difference between placebo and the 75 mg sustained release treatment was 4.48 mm Hg. Differences between the treatment conditions tended to be higher during the early part of the session as compared with later in the session ($F = 8.10, p < .01$). All groups showed normal circadian fluctuations in blood pressure over the course of the session ($F = 12.98, p < .01$). Table 3 and Figure 2 illustrate these effects.

Supine diastolic blood pressure was significantly higher for subjects in the heavier weight categories as compared with those in the more normal weight categories ($F = 9.85, p < .01$). Overall subjects in the 75 mg sustained release condition showed slightly higher supine diastolic blood pressure readings as compared with subjects in the placebo or the 25 mg t.i.d. treatments ($F = 3.87, p < .05$). The mean difference between placebo and the 75 mg sustained release treatment was 3.73 mm Hg. Differences between the treatment conditions tended to be higher during the early part of the session as compared with later in the session ($F = 3.32, p < .05$). All groups showed normal circadian fluctuations in blood pressure over the course of the session ($F = 6.42, p < .01$). Table 3 and Figure 2 illustrate these results.

Subjective effects were measured using the Addiction Research Center Inventory (ARCI). As described previously, a version of the ARCI containing the AMP, BG, MBG, and LSD scales was used. Data from seven subjects were

excluded from the analysis of subjective effects due to incomplete or invalid data on the self-report forms. This data loss is minimal (3%) and 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 12-hour session for subjects in all treatment groups. Scores on the AMP, BG, and MGB scales were generally higher early in the session and decreased later in the session ($F = 2.60, 3.07, \text{ and } 5.85$, respectively; $p < 0.05$ for all three variables). Scores on the PCAG and LSD scales were generally lower early in the session and increased later in the session ($F = 4.17 \text{ and } 3.60$, respectively; $p < 0.05$, for both variables). Such changes are consistent with the general "mood" effects which might be expected over the course of a 12-hour experimental session.

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

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 period.

Statistical analysis indicated that weight classification (in terms of degree overweight) was significantly related to measures of blood pressure and

pulse. Subjects in the heavier weight categories consistently showed more rapid pulse rates and higher blood pressure readings than did those subjects of normal or near normal weight. All measures showed main effects for measurement time (circadian effects), indicating, as expected, that subjects' physiological state changed over the course of the session. These changes were not, however, related to drug treatment condition.

The 75 mg sustained release product was associated with small but statistically reliable increases in supine blood pressure. Supine systolic blood pressure in the 75 mg sustained release group was approximately 4.5 mm Hg higher than that in the placebo group. The 25 mg t.i.d. dosing group was approximately equal to the placebo group (mean difference equal to 0.81 mm Hg). A similar result was found with the supine diastolic measure. The subjects receiving the 75 mg sustained release product showed mean supine diastolic readings approximately 3.7 mm Hg greater than those shown by subjects treated with placebo. The 25 mg t.i.d. dosing group was approximately equal to the placebo group (mean difference equal to 1.06 mm Hg). Although no overall differences between the drug treatment groups was observed on the measures of standing blood pressure, a statistically reliable interaction between measurement occasion and drug treatment suggested that subjects receiving the 75 mg sustained release PPA treatment showed larger increases in standing systolic blood pressure early in the session than did subjects in the other drug treatments. This same interaction effect was also noted for the supine blood pressure readings.

The present results also suggest that PPA, in the dosage forms studied, had no systematic effect on subjective ratings of drug effects, as measured by

the standardized drug inventory, the ARCI. No statistically reliable difference 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 Korttila (1981) in that no significant 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). As was the case with the physiologic 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 to later in the session. Thus, this study indicated that at the dose levels studied, PPA is not psychoactive, and does not have the profile of either a drug likely to be abused or one likely to produce adverse psychologic effects.

The present results are quite consistent with those found in previous investigations of PPA at this dose level (e.g., Funderburk et al., 1982a, b). Although some statistically reliable blood pressure differences were observed between subjects treated with the 75 mg sustained release product and those who received placebo, the magnitude of this difference was small and was not regarded as clinically significant. Overall the present findings support previous studies which suggest that phenylpropanolamine (in the dosage forms studied) is not associated with adverse effects on blood pressure, pulse or subjective effects.

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