

Data Report: Site 3

Protocol:

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

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ABSTRACT

Two hundred sixteen (216) healthy normotensive volunteers (mean age = 32.3) 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 = 36), mildly overweight (15-30%, n = 72), moderately overweight (31-45%, n = 72), and severely overweight (over 46%, n = 36). 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.

Mixed design analysis of variance revealed no main effects for drug treatment on any of the measures. 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. 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. These changes were not, however, related to the drug treatment condition. These findings are consistent with previous studies of PPA at this dose level.

Data Report: Site 3 (San Francisco)

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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 pre-diabetic hyperglycemic 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 formation. 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 216 healthy normal volunteers (mean age = 32.3) (both male and female). The study population consisted of 174 caucasians, 28 blacks, 6 orientals, 2 American Indians, and 6 "others." Ninety-seven (44.90%) 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)
36 normal weight

- 72 mildly overweight (15-30%)
- 72 moderately overweight (31-45%)
- 36 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 864 subjects (216/site) are tested at four sites under treatment conditions as detailed below. This portion of the report describes the results obtained at the San Francisco site under the medical direction of Dr. Rudolf Noble.

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 the 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 <u>(approx. 8:00 am)</u>	Dose 2 <u>(approx. 12 noon)</u>	Dose 3 <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 measurements. Measures 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). The ARCI 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) MEG: 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.

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 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 (Mean difference 3.51 bpm, 3.45 bpm; $F = 5.15, 5.46$, respectively, $p < .01$ for both). Standing, but not supine, pulse showed significant changes over the course of the session which reflected a small (albeit statistically reliable) increase in pulse rate during the mid-day portion of the session of approximately 1 bpm. No main effects for or interactions with drug treatment group were identified. Pulse effects are shown in Table 1.

Standing systolic blood pressure was slightly (approximately 1.5 mm Hg), but reliably, higher during the mid-day portion of the session for all treatment groups ($F = 3.90, p < .05$). Subjects in the two higher weight categories showed higher overall standing systolic blood pressures than did subjects in the two lower weight categories (128.75 mm Hg vs 120.59 mm Hg; $F = 6.89, p < .01$). No main effects for or interactions with drug treatment group were identified. The mean difference between placebo and either of the active drug treatments was less than 1 mm Hg. These effects are summarized in Table 2.

Standing diastolic blood pressure was higher for subjects in the two higher weight categories as compared with those in the two lower weight categories (81.28 mm Hg vs 76.00 mm Hg; $F = 11.97$, $p < .01$). No significant fluctuations were observed over the course of the session. No main effects for or interactions with drug treatment group were identified. The mean difference between placebo and either of the active drug treatments was less than 1 mm Hg. These effects are summarized in Table 3.

Analysis of the various individual response variables did not identify any statistically significant effects attributable to drug treatment condition. Only two individuals (1 treated with placebo, 1 treated with 75 mg SR) showed standing diastolic blood pressure readings > 94 mm Hg at any point in the session. Peak changes from baseline for individuals in the various drug treatment groups also showed no systematic differences related to drug treatment. Mean peak difference between drug treatment groups—in both absolute and change score measures—was less than 1 mm Hg. Subjects in the heavier weight categories showed reliably higher peak readings than did subjects in the normal or mildly overweight categories (84.41 mm Hg vs 79.85 mm Hg; $F = 8.48$, $p < .01$). Change from baseline, however, tended to be greater in subjects of normal or near normal weight as compared with subjects in the heavier weight categories (4.00 mm Hg vs 2.68 mm Hg; $F = 4.00$, $p < .01$). These results are detailed in Appendix III (Tables 1, 2, 3, 4, 7, and 8).

Supine systolic blood pressure was slightly (approximately 1 mm Hg), but reliably, higher during the mid-day portion of the session for all treatment groups ($F = 3.20$, $p < .05$). Subjects in the two higher weight categories

showed higher overall readings than did subjects in the two lower weight categories (127.31 mm Hg vs 119.22 mm Hg; $F = 6.64$, $p < .01$). No main effects for or interactions with drug treatment group were identified. The mean difference between placebo and either of the active drug treatments was less than 1 mm Hg. These effects are summarized in Table 4.

Supine diastolic blood pressure was higher for subjects in the two higher weight categories as compared with those in the two lower weight categories (80.17 mm Hg vs 75.05 mm Hg; $F = 11.38$, $p < .01$). No significant fluctuations were observed over the course of the session. No main effect for or interactions with drug treatment group were identified. The mean difference between placebo and either of the active drug treatments was less than 1 mm Hg. These effects are summarized in Table 5.

Analysis of the various individual response variables did not identify any statistically significant effects attributable to drug condition. Only two individuals (1 treated with placebo, 1 treated with 75 mg SR) showed supine diastolic blood pressure readings > 94 mm Hg at any point in the session. Peak change from baseline for individuals in the various drug treatment groups also showed no systematic differences related to drug treatment. Mean peak differences--in both absolute and change score measures--was less than 1 mm Hg. Subjects in the heavier weight categories showed reliably higher peak readings than did subjects in the normal or mildly overweight categories (83.32 mm Hg vs 78.63 mm Hg; $F = 8.85$, $p < .01$). Change from baseline, however, tended to be greater in subjects of normal or near-normal weight as compared with subjects in the heavier weight categories (3.96 mm Hg vs 2.88 mm Hg; $F = 3.47$, $p < .02$). These results are detailed in Appendix III (Tables 1, 2, 5, 6, 9, 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 five subjects were excluded from the analysis of subjective effects due to incomplete data on these self-report forms. This data loss is minimal 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 session for subjects in all treatment groups. Scores on the AMP and BNG scales were generally higher early in the session and decreased later in the session ($F = 12.05$ and 11.32 , respectively, $p < .01$ for both). Scores on the MBG, PCAG, and LSD scales were generally lower early in the session and increased later in the session ($F = 23.35$, 10.42 , and 3.54 , respectively, $p < .01$, $.01$, and $.05$). 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.

No significant main effects for drug treatment were observed on any of the measures. Differences in blood pressure between drug treatment groups was very small, averaging less than 1 mm Hg. No consistent pattern of differences between drug treatments was observed. On some measurement occasions, subjects receiving active drug treatments showed slightly higher mean blood pressures than did subjects receiving placebo treatment. On other occasions, this effect was reversed. No statistically significant differences between drug treatments were found on any of the measurement occasions. In contrast, weight category 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 subjects of normal or near normal weight. No interaction between drug effect and weight category was found.

Results from the analysis of various individual response parameters were consistent with those from the overall analysis. No statistically reliable differences in pattern of peak response due to drug treatment were found for any of the measures. Weight category, however, showed strong and statistically reliable effects on blood pressure. As in the overall analysis, subjects in the heavier weight categories consistently showed higher mean diastolic blood pressure peaks than those subjects of normal or near-normal weight. These overall differences between the weight categories were not affected by drug treatment.

Statistically significant differences in systolic blood pressure were found over the course of the daily session in both standing and supine positions. These changes were extremely small and were not related to either

drug treatment condition or weight category. We interpret such changes to be due to normal circadian variation in blood pressure (see, e.g., Millar-Craig et al., 1978).

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 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). As was the case with systolic blood pressure, 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 results are generally consistent with those conducted at the Behavioral Pharmacology Research Unit (Johns Hopkins School of Medicine; Funderburk et al., 1982a, 1982b, 1982c).

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Table 1

Pulse - Standing

Weight Category

<u>Medication Dose</u>	<u>Normal Weight</u>	<u>Mildly Overweight</u>	<u>Moderately Overweight</u>	<u>Severely Overweight</u>	<u>Marginal Mean</u>
75 mg SR	66.86	68.23	70.38	71.14	69.15
25 t.i.d.	70.39	67.53	73.86	70.42	70.55
Placebo	65.26	67.70	71.51	69.70	68.54
Marginal Mean	67.50	67.82	71.92	70.42	

Pulse - Supine

<u>Medication Dose</u>	<u>Normal Weight</u>	<u>Mildly Overweight</u>	<u>Moderately Overweight</u>	<u>Severely Overweight</u>	<u>Marginal Mean</u>
75 mg SR	66.42	67.77	70.10	70.58	68.72
25 t.i.d.	69.83	66.93	73.44	69.77	69.99
Placebo	64.94	67.11	71.14	68.65	67.96
Marginal Mean	67.06	67.27	71.56	69.67	

Table 2

Standing Systolic Blood Pressure

<u>Medication Dose</u>	<u>Weight Category</u>				
	<u>Normal Weight</u>	<u>Mildly Overweight</u>	<u>Moderately Overweight</u>	<u>Severely Overweight</u>	<u>Marginal Mean</u>
75 mg SR	119.74	118.48	127.65	131.55	124.36
25 t.i.d.	117.96	125.27	132.19	123.84	124.82
Placebo	121.06	120.99	127.82	129.42	124.82
Marginal Mean	119.59	121.58	129.22	128.27	

Table 3

Standing Diastolic Blood Pressure

<u>Medication Dose</u>	Weight Category				<u>Marginal Mean</u>
	<u>Normal Weight</u>	<u>Mildly Overweight</u>	<u>Moderately Overweight</u>	<u>Severely Overweight</u>	
75 mg SR	75.54	76.68	80.64	83.08	78.99
25 t.i.d.	74.03	77.83	81.39	80.18	78.36
Placebo	75.58	76.38	80.13	82.27	78.59
Marginal Mean	75.05	76.96	80.72	81.84	

Table 4

Supine Systolic Blood Pressure

<u>Medication</u> <u>Dose</u>	Weight Category				
	<u>Normal</u> <u>Weight</u>	<u>Mildly</u> <u>Overweight</u>	<u>Moderately</u> <u>Overweight</u>	<u>Severely</u> <u>Overweight</u>	<u>Marginal</u> <u>Mean</u>
75 mg SR	118.27	116.91	125.88	130.46	122.88
25 t.i.d.	116.71	123.96	130.40	122.74	123.45
Placebo	119.89	119.54	126.11	128.25	123.45
Marginal Mean	118.29	120.14	127.46	127.15	

Table 5

Supine Diastolic Blood Pressure

<u>Medication Dose</u>	<u>Weight Category</u>				
	<u>Normal Weight</u>	<u>Mildly Overweight</u>	<u>Moderately Overweight</u>	<u>Severely Overweight</u>	<u>Marginal Mean</u>
75 mg SR	74.80	75.68	79.40	82.09	77.99
25 t.i.d.	73.05	76.78	80.23	79.27	77.33
Placebo	74.61	75.36	78.81	81.22	77.50
Marginal Mean	74.15	75.94	79.48	80.86	