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February 18, 1983

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

CITIZEN PETITION

The undersigned submits this petition under 21 CFR 10.30 to request the Commissioner of Food and Drugs to open the administrative record in the Over-the-Counter Drug Review of Drug Products (Docket No. 76N-0052N) to accept the enclosed materials relating to the recently-completed study conducted at Johns Hopkins University Medical School.

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 nasal decongestants which are the subject of the above-referenced Proposed OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products Monograph. (41 Fed. Reg. 38312, 38400, September 9, 1976.) The Panel Monograph concluded that PPA and its salts are safe and effective as oral nasal decongestants for OTC use in the specified dosages. The Tentative Final Cough/Cold Monograph has not yet been published.

76N-0052N

C
CP0003

The enclosed materials summarize a study demonstrating the safety of PPA in weight control products. Since the same ingredient is involved in the two products, the enclosed materials are highly significant to the agency's OTC Drug Review of cough/cold drug products as well as to its OTC Drug Review of weight control products. (47 Fed. Reg. 8466 et seq., February 26, 1982.) Therefore, these materials should be considered in both reviews at the earliest possible time. Please note that a parallel Citizen Petition dated January 11, 1983, was filed by the undersigned requesting that the administrative record in the Weight Control OTC Drug Review be opened to permit the enclosed materials to be considered in that review.

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

January 3, 1983

Dr. Mark Novitch
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Novitch:

Enclosed please find a just completed clinical study conducted at Johns Hopkins University Medical School by Ira Liebson, M.D. evaluating possible adverse symptoms attributable to phenylpropanolamine including but not limited to blood pressure, pulse, psychological and mood changes.

This study is in three parts a, b and c and has been completely evaluated using the most modern statistical methods.

The results of this study clearly indicate 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.

Following is a quick summary of this three part study:

A. A parallel group design study of 150 healthy normotensive volunteers who participated in a double-blind, placebo controlled comparison of the effects of phenylpropanolamine HCl on blood pressure, pulse and mood. Two dosage forms of phenylpropanolamine were studied (75 mg sustained-release and 25 mg t.i.d.) in comparison with placebo. Subjects were studied for a 12-hour testing session in which measurements of blood pressure, pulse and subjective drug effect (mood) were obtained nine times during the session.

B. A crossover design involving 59 healthy, normotensive patients in the evaluation of the effects of phenylpropanolamine HCl in normal volunteers. This study also measured blood pressure (sitting, standing and supine), pulse and subjective drug effect (mood) nine times during the 12-hour session. This study compared 75 mg sustained-release phenylpropanolamine with placebo. After one washout day the subjects returned to complete the second leg of the crossover. During this second session they received the alternate medication which was not administered on the first day.

Overall, the results of this present study are quite compatable with the results of Study A. No clinically relevant adverse effects were noted on pulse, blood pressure or subjective state

(mood), in phenylpropanolamine subjects compared to placebo subjects.

C. An additional analysis was undertaken on the data collected as part of Parts A & B as indicated above. These analyses focused on a comparison of possible subjective effects of phenylpropanolamine on affective state ("mood"), compared with those of potent CNS-active drugs.

These analyses clearly indicated that phenylpropanolamine in doses of 25 mg t.i.d. or 75 mg sustained-release, were not associated with euphoria, amphetamine-like reactions, sedation or stimulation in data derived from the 150 patients parallel group design study and the 59 patient crossover study.

This study reconfirms the numerous previously submitted clinical studies supporting the safety of phenylpropanolamine delivered to Dr. Arthur Hull Hayes by the Proprietary Association Task Force on Phenylpropanolamine.

The overwhelming conclusion of all of this data clearly substantiates the wide safety of phenylpropanolamine and definitely supports the continued confidence of the Agency in maintaining phenylpropanolamine as a Category 1 drug.

In view of all of this accumulation of scientific data and vast consumer usage over the past 40 years it would be highly detrimental to the consumer, the Agency and industry to consider changing the status of phenylpropanolamine at this time.

Considering the fact that more than five billion doses of phenylpropanolamine are consumed each year in cough and cold and diet aid products there are extremely small numbers of adverse reports and no reports confirming causative effects.

Ira Liebson, M.D. of the Johns Hopkins University who supervised this study will be available to personally report on this very important study to you at your convenience.

Thank you for your courtesy and attention.

Sincerely yours,

THOMPSON MEDICAL COMPANY, INC.

Ed Steinberg

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

ELS:fj
Enclosures (3)
cc:Dr. William Gilbertson

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

Study Site: Behavioral Pharmacology Research Unit
The Johns Hopkins University School of Medicine
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Baltimore, Maryland 21224

Contact: Frank R. Funderburk
Director, Clinical Consulting
ANTECH, Inc.
(301) 997-0880

Date: December 6, 1982

SUPPLEMENT TO CLINICAL PROTOCOLS
82-8(A) and 82-8(B)

Evaluation of Phenylpropanolamine Effects on Standardized Measures of Drug Effect and Affective State

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

Investigators: Ira Liebson
George Bigelow
Roland Griffiths
Frank Funderburk
Alistair MacKenzie

Protocol developed by: The Clinical Consulting Group
ANTECH, Inc. and the
Behavioral Pharmacology Research Unit

Contact: Frank Funderburk
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Date: December 6, 1982

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ABSTRACT

Additional analysis was undertaken on data collected as part of Clinical Protocols 82-8(A) and 82-8(B). These analyses focused on a comparison of subjective PPA effects with those of other CNS-active drugs and a more rigorous evaluation of PPA effects on affective state ("mood"). These analyses indicated that PPA, in doses of 25 mg t.i.d. or 75 mg sustained release, were not associated with euphoria, amphetamine-like reactions, or sedation. Some evidence was found which suggested that PPA functioned to reduce the fatigue and boredom associated with a 12 hour experimental session in a relatively unstimulating environment.

INTRODUCTION

Previous reports from our laboratory (Funderburk et al., 1982a, 1982b) examined the effects of phenylpropanolamine (PPA) on blood pressure, pulse, and mood (including subjective ratings of drug effect) in normal volunteers. In a large sample (N = 150) parallel groups design study, PPA doses of 25 mg t.i.d. and 75 mg sustained release were found to have minimal effects on clinical measurements of blood pressure, pulse, or subjective ratings of drug effect and drug liking over a 12-hour experimental session. The authors concluded that PPA at the dose levels studied was not associated with adverse effects on the clinical measures studied. This conclusion received further support in a statistically more powerful crossover study (N = 59) which compared the 75 mg sustained release formulation with placebo on these same measures.

The present report is a supplement to Protocols 82-8(A) and 82-8(B). It describes additional analysis undertaken to provide additional information on the subjective effects of PPA. Particular attention will be focused on two key issues of concern: (1) A comparison of PPA with other CNS-active drugs and (2) A more rigorous evaluation of PPA effects on affective state ("mood"). In both instances our measures will be derived from widely used and well standardized psychometric instruments which have been proven sensitive to the effects of CNS drugs.

INVESTIGATIVE METHODS

Subjects. Subject characteristics are identical to those described in our previous reports. In the parallel groups design 150 healthy normal

subjects participated (N = 50 in each of three experimental groups). In the crossover study 59 healthy normal subjects participated (each being exposed to each of two experimental conditions).

Design and Procedure.

The measures described in this report were obtained from subjects who participated in Clinical Protocols 82-8(A) [parallel groups design] and 82-8(B) [crossover design]. Two standardized test forms were administered to subjects prior to each clinical measurement occasion. One form was a short version of the Addiction Research Center Inventory (ARCI). This test allows comparison of PPA subjective effects with those of other CNS-active drugs. The other form was the Profile of Mood States (POMS). This test allows an evaluation of changes in affective state associated with drug treatment. Each form generally required less than 5 minutes to administer. More detailed descriptions of these tests follows:

Addiction Research Center Inventory (ARCI). Detailed description of the ARCI scales was given by Haertzen (1974). The empirical drug scales on this inventory were developed by selecting items which differentiated placebo from a variety of drugs including morphine, pentobarbital, chlorpromazine, LSD, amphetamine, pyrahexyl, and alcohol. In addition, clusters of items were developed (group variability scales) which combined items from the various scales to reflect patterns of drug effects. The scales used in this study, and the characteristics which 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.

Profile of Mood States (POMS). The POMS scales provide a means of assessing transient, fluctuating mood states. These scales were developed by factor analytic methods in a variety of subject populations including both normals and specialized patient populations (see, McNair, Lorr, and Droppleman, 1971, for a more detailed discussion of the development of these scales). The POMS has been found to be a sensitive measure of the effects of various experimental manipulations (including drug administration) in normal volunteers. The POMS measures six identifiable mood or affective

states as well as various specialized affective states and global mood. The scales used in this study were:

(1) Tension-Anxiety

(2) Depression-Dejection

(3) Anger-Hostility

(4) Vigor-Activity

(5) Fatigue-Inertia

(6) Confusion-Bewilderment

(7) "Friendliness"

(8) Total Mood Disturbance.

Statistical Analysis. Data were analyzed using mixed design analysis of variance. Separate analyses were conducted for each of the dependent variables. In the parallel groups design factors in the analysis were drug treatment assignment (placebo, 25 mg t.i.d., 75 mg sustained release) and measurement occasion (0 hr, ½ hr, etc.). Treatment assignment was a between-group factor while measurement occasion was a within-subjects factor. Factors in the crossover design were drug treatment assignment, order of treatment administration (placebo first *vs.* active drug first), and measurement occasion. Order of drug administration was a between groups factor while drug treatment and measurement occasion were within subject factors. In both analyses tests involving repeated measures were evaluated using a conservative *F* test (e.g., Geisser and Greenhouse, 1953).

Results: Parallel Groups Design

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

ARCI Variables

AMP. No main effect for drug treatment condition was identified. A significant main effect for measurement occasion was found ($F = 3.91$, $p<0.05$) reflecting a general decrease in AMP scores over the session for subjects in all treatment groups. No significant interactions were identified.

BG. No main effect for drug treatment condition was identified. A significant main effect for measurement occasion was found ($F = 4.80$, $p<0.05$) reflecting a general decrease in BG scores over the session for subjects in all treatmenr groups. No significant interactions were identified.

MBG. No significant main effects or interactions were identified.

PCAG. No main effects or interactions were found for drug treatment. A significant main effect for measurement occasion was identified ($F = 7.46$, $p<0.01$) which reflected a tendency for sedation (PCAG score) to be lowest early and late in the session as compared with the middle of the session. This general trend was present in all drug treatment groups. No other main effects or interactions were identified.
*

POMS Variables

Tension-Anxiety. No significant main effects or interactions were identified.

Depression-Dejection. No significant main effects or interactions were identified.

*LSD. No significant main effects or interactions were identified.

Anger-Hostility. No significant main effects or interactions were identified.

Vigor-Activity. No main effects or interactions were found for drug treatment. A significant main effect for measurement occasion was identified ($F = 10.37$, $p<0.01$) reflecting a general decrease in vigor over the course of the session. This general trend was present in all drug treatment groups. No other main effects or interactions were identified.

Fatigue-Inertia. No significant main effects or interactions were identified.

Confusion-Bewilderment. No significant main effects or interactions were identified.

"Friendliness." No main effect for drug treatment condition was identified. A significant main effect for measurement occasion was found ($F = 19.98$, $p<0.01$) reflecting a general decrease in "friendliness" over the course of the session for subjects in all drug treatment groups. No significant interactions were identified.

Total Mood Disturbance. No significant main effects or interactions were identified.

Results: Crossover Design

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

ARCI Variables

AMP. No significant main effects or interactions with drug treatment were identified. A significant main effect for time course was identified ($F = 3.14$, $p<0.05$) which reflected a general decrease in scores over the course of the session for subjects in both drug treatment groups.

BG. No significant main effects or interactions with drug treatment were identified. A significant main effect for time course was identified ($F = 3.56$, $p<0.05$) which reflected a general decrease in scores over the course of the session for subjects in both drug treatment groups.

MBG. No significant main effects or interactions with drug treatment were identified. A significant main effect for time course was identified ($F = 5.40$, $p<0.05$) which reflected a general decrease in scores over the session for subjects in both drug treatment groups.

PCAG. A significant main effect for drug treatment was identified ($F = 4.97$, $p<0.03$). Overall subjects reported lower PCAG scores (reflecting less fatigue) under the 75 mg PPA treatment as compared with placebo. This effect was strongest in subjects who received the 75 mg PPA dose in their second session ($F = 5.72$, $p<0.02$). A main effect for time course was also identified ($F = 2.57$, $p<0.05$) which reflected a general increase in PCAG scores over the course of the session for subjects in both drug treatment groups. No drug x time interaction was identified.

LSD. A significant main effect for drug treatment was identified ($F = 7.69$, $p<0.01$). Overall subjects reported lower LSD scores (reflecting less dysphoria) under the 75 mg PPA treatment as compared with placebo. No other main effects or interactions were identified.

POMS Variables

Tension-Anxiety. A main effect for drug treatment was identified ($F = 4.86$, $p<0.05$). Overall subjects obtained lower tension and anxiety scores under the 75 mg PPA treatment as compared with placebo treatment. No other main effects or interactions were identified.

Depression-Dejection. No significant main effects or interactions were identified.

Anger-Hostility. A main effect for drug treatment was identified ($F = 5.27$, $p<0.025$). Overall subjects obtained lower anger-hostility scores under the 75 mg PPA treatment as compared with placebo treatment. No other main effects or interactions were identified.

Vigor-Activity. No main effects or interactions for drug condition were identified. A main effect for measurement occasion ($F = 5.23$, $p<0.05$) was identified which reflected a general tendency for subjects to obtain lower vigor-activity scores over time. No other main effects or interactions were identified.

Fatigue-Inertia. No significant main effects for drug treatment, order, or time course were identified. A drug x order interaction ($F = 8.64$, $p<0.01$) was identified which reflected the fact that greater fatigue was reported under placebo as opposed to 75 mg PPA in

one group of subjects while the opposite trend was present in the other group of subjects. No other significant interactions were identified.

Confusion-Bewilderment. A significant main effect for drug condition was identified ($F = 7.00$, $p<0.01$). Overall subjects obtained lower Confusion-Bewilderment scores under the 75 mg PPA treatment than under placebo. No other main effects of interactions were identified.

"Friendliness." No significant main effects or interactions with drug treatment were identified. A significant time course effect was found ($F = 6.62$, $p<0.01$) which reflected a general tendency for "friendliness" to decrease over the course of the session, although friendliness scores did tend to increase at the last measurement occasion.

Total Mood Disturbance. No significant main effects or interactions were identified.

DISCUSSION

The present study evaluated the acute subjective effects of two dosage forms of PPA (75 mg sustained release, 25 mg t.i.d.) in comparison with placebo in a parallel groups design. These assessments were repeated in a crossover design which compared the 75 mg sustained release dose with placebo. Measures obtained included a comparison of PPA effects with those of a variety of CNS-active drug effects as well as an evaluation of PPA effects on various affective states.

In the parallel groups design PPA effects were not different from those of placebo on any of the measures studied. Subjects in all groups tended to feel more sedated or tired as the session progressed, with lessening of the sedative effect prior to the conclusion of the session. The extent and nature of this effect was not related to drug treatment.

In the more powerful crossover design some statistically reliable differences between the 75 mg sustained release PPA treatment and placebo were identified. In particular, on the ARCI scales the 75 mg PPA treatment was associated with less sedation-fatigue and less dysphoria during the course of the session as compared with placebo. However, no evidence of amphetamine-like effects or euphoria was found. As expected, most measures showed reliable circadian effects over the course of the session. As in our previous studies, these effects indicated that subjects generally felt "better" early in the sessions as compared with later in the session. The POMS measures provided further confirmation of these effects. Subjects reported feeling less tense or anxious, less hostile, and less confused under the 75 mg PPA treatment as compared with placebo.

The pattern of results in the present study is consistent with that found in our previous analysis of PPA mood effects (Funderburk et al., 1982a, 1982b) and with the findings of Seppala et al. (1981). Overall no reliable euphoric effects were noted for PPA, although there is some evidence that PPA functioned to reduce the dysphoria and boredom associated with a 12-hour experimental session in the restricted and relatively bland environmental setting of a research laboratory. Thus, it appears that PPA may serve to increase mental alertness and reduce fatigue in relatively unstimulating settings.

In the doses studied PPA did not produce a pattern of subjective effects which would be indicative of high abuse liability. The absence of euphoric or amphetamine-like effects or sedative-type effects suggest that PPA is not likely to be knowingly chosen as a drug for self-administration by someone seeking such psychological effects. Such an interpretation is consistent with our previous finding that ratings of "drug liking" for PPA were not different from those of placebo.

Overall the present findings suggest that PPA may have mildly beneficial effects on affective state in that it increases alertness and reduces dysphoria. The magnitude of these effects, however, is not large. Further, these findings may be limited to affective states measured under unusually low levels of environmental stimulation. At the same time, no evidence of amphetamine-like or euphoric effects were noted even in the more powerful crossover design.

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AN EVALUATION OF THE ACUTE EFFECTS OF PHENYLPROPANOLAMINE IN NORMAL VOLUNTEERS: (CROSSOVER DESIGN)

Study Site: Behavioral Pharmacology Research Unit
Johns Hopkins University School of Medicine
Baltimore City Hospitals D-5-West
4940 Eastern Avenue
Baltimore, Maryland 21224

Contact: Frank R. Funderburk
Director, Clinical Consulting
ANTECH, Inc.
(301) 997-0880

Date: October 22, 1982

FINAL REPORT OF
CLINICAL PROTOCOL NO. 82-8(A)

An Evaluation of the Acute Effects of Phenylpropanolamine in Normal Volunteers: (Crossover Design)

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

Investigators: Ira Liebson
George Bigelow
Roland Griffiths
Frank Funderburk

Protocol developed by: The Clinical Consulting Group
ANTECH, Inc. and the
Behavioral Pharmacology Research Unit

Contact: Frank Funderburk
(301) 997-0880

Project Start Date: 25 June 82

Project Completion Date: 31 August 82

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ABSTRACT

Fifty-nine (59) healthy normotensive volunteers (mean age = 25.5) participated in a double blind, placebo controlled crossover evaluation of the effects of a 75 mg sustained release dosage form of phenylpropanolamine HCl on blood pressure, pulse, and mood. Each subject participated in two experimental sessions, one under placebo and the other under the active drug treatment. Order of exposure to treatment conditions was randomly determined.

Measurements of blood pressure (sitting, standing, and supine), pulse, and subjective drug effect ("mood") were obtained 9 times during the session - at baseline (prior to drug administration) and at 1/2 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr, and 12 hr post-initial dosing.

Mixed design analysis of variance revealed no statistically significant main effects for drug treatment on measure of pulse or mood. Nearly all blood pressure measures (the standing systolic measure was an exception) showed statistically reliable - but clinically insignificant - differences between placebo and the active drug condition. In all cases, the mean blood pressure was slightly higher under the active drug treatment. The magnitude of this effect, however, was extremely small (the mean differences ranged between .83 and 3.37 mm Hg).

As anticipated, most measures showed main effects for time of day (circadian effects), indicating that the subjects' physiological and subjective state changed over the course of the session. These changes were, however, generally independent of the drug treatment condition. This study suggests that the 75 mg sustained release dosage form of phenylpropanolamine has minimal - and clinically insignificant - effects on the blood pressure, pulse, or mood of normotensive individuals.

An Evaluation of the Acute Effects of Phenylpropanolamine in Normal Volunteers: (Crossover Design)

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 in both as a nasal decongestant and as a weight control aid. Recently the FDA and others have raised questions about the safety and appropriateness of OTC availability of PPA (Federal Register, Vol. 47, No. 39, 1982; Horowitz, 1980; Dietz, 1981; Lancet, 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. In the present report, crossover experimental design was used to compare the effects of 75 mg sustained release PPA with placebo on these parameters. Fifty-nine normotensive adults were studied over a time course of 12 hours.

OBJECTIVE AND RATIONALE

This study was designed to extend previous research conducted in our laboratory (Funderburk et al., 1982). In that investigation, 150 normotensive adults participated in a study comparing the effects of two dosage forms of PPA (25 mg t.i.d., 75 mg sustained release) with placebo. No significant main effects for drug treatment were found on any of the measures of blood pressure, pulse, or mood. Although the relatively large sample size in that

study provided considerable statistical power, it was believed that an even more sensitive comparison would be afforded by a crossover study in which each subject would serve as his own control.

Several studies have investigated the acute effects of PPA in normal subjects (e.g., Silverman et al., 1980; Hoebel, 1982). However, these studies have generally involved rather small subject samples and have, therefore, had relatively low statistical power. The recent study in our laboratory, however, (Funderburk et al., 1982) which employed 150 subjects in a parallel groups design provided a rather powerful test of the effects of PPA on normal subjects. The present study, using a crossover design, was implemented to provide an even more powerful evaluation of PPA effects in a large group of normal volunteers.

INVESTIGATIVE METHODS

Subjects

Subjects were 59 normal volunteers (both male and female, mean age = 25.5). The study population consisted of 33 caucasians, 25 blacks, and 1 American Indian. All had given informed consent and had been screened to meet the following criteria:

a. between 18-55 years of age

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

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

d. no history of severe emotional disturbance, chronic alcoholism, or drug abuse

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

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

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

Design and Procedure

Subjects were randomly assigned to one of two treatment sequences. One group (n = 30) received the placebo treatment on their first testing occasion and the 75 mg sustained release treatment on the second testing session. This order of treatment was reversed for subjects in the other group (n = 29). The two treatment sessions were always separated by at least one washout day to minimize any possible treatment carryover effects. The basic investigative procedures followed for each subject are detailed below.

1. General Procedures

a. Subject control. Subjects were instructed to be free of all medications for the week prior to the first administration of a test product. Subjects who had 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 days.

c. Drug administration. In this investigation a currently marketed dose of a test product containing PPA (75 mg sustained release PPA) was compared with placebo. On each test day subjects received three administrations of a test product (either active medication or placebo). Doses were given at 4 hour intervals (e.g., approximately 8:00 am, 12:00 noon, and 4:00 pm).

Subjects were randomly assigned to one of two treatment conditions on the first test day. One group of subjects (Group A) received the 75 mg sustained release product at their first dosing and matching placebo capsules on subsequent dosings. The other group (Group B) received placebo at all three dosings. After at least one washout day, the subjects returned to complete the second leg of the crossover. During this session, they received the treatment not administered on the first day. This dosing schedule is illustrated in Table 1.

Table 1

Dosing Schedule

		Dose 1 (approx. 8:00 am)	Dose 2 (approx. 12 noon)	Dose 3 (approx. 4:00 pm)
Session One	Group A	75 mg sustained	placebo	placebo
	Group B	placebo	placebo	placebo
Session Two	Group A	placebo	placebo	placebo
	Group B	75 mg sustained	placebo	placebo

d. Clinical measurements. Measures of blood pressure and pulse were obtained 9 times during each experimental session: Once prior to initial drug administration (0 hr) and at 1/2 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr, and 12 hr following initial drug administration. Blood pressure (sitting, standing, supine) was measured using procedures recommended by the American Heart Association (Kirkendall et al., 1980). Clinical measures of subjective state were obtained using analogue ratings of drug effects. These measures were supplemented by subjective reports of subjects and the observations of research staff.

2. Design

This study may be viewed as a 2(drug treatment conditions) x 2(orders of treatment administration) x 9(measurement occasions) mixed design. Mixed design analysis of variance procedures were used to evaluate data from this component of the investigation. Separate analyses were conducted for each of the dependent variables. Factors in the analysis were drug treatment condition (75 mg sustained release vs. placebo), order of treatment administration (active drug first vs. placebo treatment first), and measurement occasion (0 hr, 1/2 hr, etc.). Order of treatment administration was a between groups factor while drug treatment and measurement occasion were within subject factors. 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 increase slightly over the session showing a peak at approximately 6 hours post-dosing ($F = 9.45$, $p < .01$). This effect occurred under both drug treatment conditions. No main effect for drug treatment was identified. No other main effects or interactions were identified.

Standing systolic blood pressure was relatively stable for subjects in both drug treatment groups. No main effects or interactions were identified.

Standing diastolic blood pressure tended to be slightly higher under the active drug treatment than under placebo. Although this effect was statistically reliable ($F = 7.41$, $p < .01$), the overall magnitude of the effect was small (mean difference between treatments = 2.26 mm Hg). Under both treatment conditions, standing diastolic blood pressure tended to show peaks at 4 and 12 hours post-initial dosing ($F = 6.81$, $p < .01$).

Sitting systolic blood pressure tended to be slightly higher under the active drug treatment than under placebo ($F = 4.46$, $p < .05$). The mean difference between treatments was 2.09 mm Hg. No other main effects or interactions were identified.

Sitting diastolic blood pressure tended to peak at 4 and 12 hours post-initial dosing under both treatment conditions ($F = 5.26$, $p < .05$). Overall, sitting diastolic blood pressure tended to be higher under the active drug treatment than under placebo ($F = 11.28$, $p < .01$). The mean difference between treatments was 2.75 mm Hg. No other main effects of interactions were identified.

Supine systolic blood pressure tended to peak at 4 and 12 hours post-initial dosing under both treatment conditions ($F = 7.33$, $p < .01$). The peak effect at 4 hours was most evident for subjects under the active drug

treatment (resulting in a drug x time interaction, $F = 4.10$, $p < .05$). Overall, supine systolic blood pressure tended to be higher under the active drug treatment than under placebo ($F = 7.35$, $p < .01$). The mean difference between treatments was 2.52 mm Hg. No other main effects or interactions were identified.

Supine diastolic blood pressure tended to peak at 4 and 12 hours post-initial dosing under both treatment conditions ($F = 6.22$, $p < .05$). Overall, supine diastolic blood pressure tended to be higher under the active drug treatment than under placebo ($F = 11.91$, $p < .01$). The mean difference between treatments was 3.37 mm Hg. The time course of this drug effect was slightly different for the two treatment orders (4.15, $p < .05$). No other main effects or interactions were identified.

Subjective measures of drug effect and mood revealed no significant differences between the drug treatment conditions on any of the measures studied (rating of "drug effect," rating of "feeling good," rating of "feeling bad," and rating of "drug liking"). Ratings of "drug effect" tended to peak at approximately 6 hours post-initial dosing under both treatment groups. No other main effects or interactions were identified for any of the subjective measures.

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 a 75 mg sustained release dosage form of phenylpropanolamine in comparison with placebo. A crossover design, in which each subject served as his own control, was used. Measures of

drug effect on blood pressure (sitting, standing, and supine), pulse, and subjective state ("mood") were obtained over a 12-hour testing period.

As in our previously reported study (Funderburk et al., 1982), overall differences between phenylpropanolamine and placebo on measures of blood pressure were very small. In the present study, however, statistically reliable differences between the active drug and placebo were identified. This result can be attributed to the increased statistical power of the present design. As compared with our previous investigation, the present study had both a larger sample size per group (n = 59 vs. n = 50) as well as a lower overall error variance (a result of using each subject as his own control). Both of these features of the design served to increase statistical power. Under such conditions, it is quite possible to identify statistically reliable effects which are clinically trivial (see, e.g., Cohen, 1969). In the present study, for example, mean blood pressure differences between drug treatment conditons ranged from .83 mm Hg (standing systolic) to 3.37 mm Hg (supine diastolic) with an average overall difference of less than 2 mm Hg. Obviously, such small overall effects are not regarded as clinically significant.

As expected, statistically significant differences in blood pressure were generally found over the course of the daily session. This finding is consistent with the literature on circadian variation of blood pressure (see, e.g., Bock & Kreuzenbeck, 1966; Millar-Craig et al., 1978; Richardson et al., 1964; Rose, 1980). Drug treatment did not appear to affect these normal circadian variations. This result is consistent with our previous report.

The present study also replicated our previous investigation with respect to subjective drug effects. Overall our analysis failed to reveal any

systematic differences between the drug treatments on subjective ratings of drug effect or drug liking. The effect of the active drug was not rated as any better or any worse than that of the placebo. Somewhat less circadian variability in subjective effect was observed in this study as compared with our previous investigation.

Overall, the results of the present study are quite compatible with the results presented in our previous report. Although statistically reliable effects on blood pressure were noted for the 75 mg sustained release dosage form of phenylpropanolamine, these effects were extremely small and were not considered clinically relevant. Likewise, no adverse effects were noted on pulse or subjective state.

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APPENDIX

KEY:

O = ORDER OF DRUG ADMINISTRATION (A = 75MG SUSTAINED RELEASE ON FIRST SESSION, PLACEBO ON SESSION TWO; B = PLACEBO ON FIRST SESSION, 75MG SUSTAINED RELEASE ON SESSION TWO.)

D = DOSE ADMINISTERED. 1 = 75MG SUSTAINED RELEASE, 2 = PLACEBO.

T = TIME OF MEASUREMENT. (1=BASELINE, 2=30 MINUTES, 3=1HOUR, 4=2HOUR, 5=4 HOUR, 6=6HOUR, 7=8HOUR, 8=10 HOUR, 9=12 HOUR).

FOR EACH VARIABLE STUDIED, MEANS AND STANDARD DEVIATIONS AT EACH MEASUREMENT OCCASION ARE PRESENTED IN ONE TABLE, WHILE ANALYSIS OF VARIANCE RESULTS ARE PRESENTED IN ANOTHER. A CONSERVATIVE F-TEST WAS USED TO EVALUATE THE RESULTS OF ALL FACTORS INVOLVING REPEATED MEASURES.

VARIABLE 1: PULSE

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

	ORDER =		A	B	MARGINAL
	DOSE	TIME			
PUL0	1	1	76.75862	79.86667	78.33898
PUL5	1	2	76.62069	78.06667	77.35593
PUL10	1	3	74.55172	77.60000	76.10169
PUL20	1	4	76.06896	79.13333	77.62712
PUL40	1	5	76.75862	77.06667	76.91525
PUL60	1	6	84.41379	81.00000	82.67797
PUL80	1	7	78.06896	79.66667	78.88136
PUL0	1	8	74.82759	76.20000	75.52542
PUL120	1	9	73.93103	77.73333	75.86441
PUL02	2	1	78.89655	76.06667	77.45763
PUL52	2	2	77.17241	77.33333	77.25424
PUL102	2	3	76.89655	77.13333	77.01695
PUL202	2	4	78.06896	77.53333	77.79661
PUL402	2	5	74.13793	77.40000	75.79661
PUL602	2	6	82.82759	84.53333	83.69491
PUL802	2	7	79.24138	81.46667	80.37288
PUL02	2	8	78.00000	78.53333	78.27119
PUL1202	2	9	77.17241	78.06667	77.62712
	MARGINAL		77.46743	78.57778	78.03201
	COUNT		29	30	59

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

	ORDER =		A	B
	DOSE	TIME		
PUL0	1	1	10.00591	12.21569
PUL5	1	2	13.20285	8.68988
PUL10	1	3	11.09564	10.01241
PUL20	1	4	11.78962	9.89160
PUL40	1	5	10.95985	7.55181
PUL60	1	6	10.23131	8.64232
PUL80	1	7	10.50827	10.18563
PUL0	1	8	9.95012	10.79400
PUL120	1	9	9.26565	9.85037
PUL02	2	1	9.00137	11.33178
PUL52	2	2	8.95253	11.71304
PUL102	2	3	9.58550	13.44909
PUL202	2	4	9.97830	12.62382
PUL402	2	5	10.39136	12.39744
PUL602	2	6	11.89859	14.37367
PUL802	2	7	8.59258	12.53886
PUL02	2	8	10.91526	12.71364
PUL1202	2	9	9.20430	11.87850

VARIABLE 1: PULSE

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - PUL0 PUL5 PUL10 PUL20 PUL40 PUL60
PUL120 PUL02 PUL52 PUL102 PUL202 PUL402
PUL02 PUL1202

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	6463093.75000	1	6463093.75000	5887.77893	.000
D	327.23193	1	327.23193	.29810	.587
ERROR	62569.66309	57	1097.71338		
D	120.87634	1	120.87634	.84963	.361
DO	61.72772	1	61.72772	.43388	.513
ERROR	8109.38129	57	142.26985		
T	4468.65552	8	558.58194	9.45550	.000
TO	231.73096	8	28.96637	.49033	.863
ERROR	26938.13086	456	59.07485		
DT	376.30029	8	47.03754	.91872	.501
DTO	692.26245	8	86.53281	1.69013	.098
ERROR	23346.72217	456	51.19895		

VARIABLE 2: STANDING SYSTOLIC BLOOD PRESSURE

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

	ORDER =		A	B	MARGINAL
	DOSE	TIME			
STBPS0	1	1	99.65517	100.50000	100.08475
STBPS5	1	2	100.82759	99.86667	100.33898
STBPS10	1	3	101.44828	102.30000	101.88136
STBPS20	1	4	100.06896	101.46667	100.77966
STBPS40	1	5	102.41379	102.53333	102.47458
STBPS60	1	6	100.13793	100.60000	100.37288
STBPS80	1	7	96.75862	101.80000	99.32203
STBPSC	1	8	96.82759	102.53333	99.72881
STBPS12	1	9	100.48276	105.60000	103.08475
STBPS02	2	1	97.86207	101.06667	99.49152
STBPS52	2	2	96.82759	97.80000	97.32203
STBPSX2	2	3	97.72414	97.86667	97.79661
STBPS22	2	4	96.68965	99.76667	98.25424
STBPS42	2	5	93.10345	103.20000	99.22034
STBPD62	2	6	101.03448	104.40000	102.74576
STBPS82	2	7	98.89655	100.33333	99.62712
STBPSC2	2	8	101.24138	104.53333	102.91525
STBPS12	2	9	100.13793	106.26667	103.25424
MARGINAL			99.11877	101.80185	100.48305
COUNT			29	30	59

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

	ORDER =		A	B
	DOSE	TIME		
STBPS0	1	1	13.08291	19.45596
STBPS5	1	2	13.49621	18.36739
STBPS10	1	3	12.61401	18.58681
STBPS20	1	4	13.33612	19.25462
STBPS40	1	5	14.89371	19.90968
STBPS60	1	6	14.85098	14.13384
STBPS80	1	7	14.15641	21.53650
STBPSC	1	8	14.35785	16.75736
STBPS12	1	9	18.45965	16.21749
STBPS02	2	1	11.61195	17.16237
STBPS52	2	2	12.20676	17.32728
STBPSX2	2	3	13.02442	16.23052
STBPS22	2	4	14.46450	21.74727
STBPS42	2	5	12.45089	16.82035
STBPD62	2	6	13.65515	17.57271
STBPS82	2	7	12.46236	16.53488
STBPSC2	2	8	13.82972	16.72441
STBPS12	2	9	13.78333	15.93723

VARIABLE 2: STANDING SYSTOLIC BLOOD PRESSURE

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - STBPS0 STBPS5 STBPS10 STBPS20 STBPS40 STBPS60
STBPS12 STBPS02 STBPS52 STBPSX2 STBPS22 STBPS42
STBPSC2 STBPS12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	10714912.12500	1	10714912.12500	3391.79160	.000
D	1910.75977	1	1910.75977	.60485	.440
ERROR	180067.07422	57	3159.07147		
D	186.04907	1	186.04907	.63842	.428
DO	101.60474	1	101.60474	.34865	.557
ERROR	16611.08716	57	291.42258		
T	1714.53223	8	214.31653	2.87581	.004
TO	809.54590	8	101.19324	1.35786	.213
ERROR	33982.88379	456	74.52387		
DT	1572.67187	8	196.58398	2.77558	.00[illegible]
DTO	669.11621	8	83.63953	1.18091	.309
ERROR	32296.80640	456	70.82633		

VARIABLE 3: STANDING DIASTOLIC BLOOD PRESSURE

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

ORDER =	DOSE	TIME	A	B	MARGINAL
STBPD0	1	1	68.34483	65.60000	66.94915
STBPD5	1	2	67.17241	65.26667	66.20339
STBPD10	1	3	67.10345	62.23333	64.62712
STBPD20	1	4	67.24138	63.00000	65.08475
STBPD40	1	5	67.10345	67.13333	67.11864
STBPD60	1	6	63.03448	62.86667	62.94915
STBPD80	1	7	58.68965	64.00000	61.38983
STBPDC	1	8	62.06897	62.26667	62.16949
STBPD12	1	9	65.03448	67.60000	66.33898
STBPD02	2	1	62.34483	63.60000	62.98305
STBPD52	2	2	61.58621	64.13333	62.88136
STBPDX2	2	3	61.48276	64.60000	63.06780
STBPD22	2	4	60.68965	64.26667	62.50847
STBPD42	2	5	61.10345	63.66667	62.40678
STBPD62	2	6	62.75862	61.13333	61.93220
STBPD82	2	7	61.17241	59.20000	60.16949
STBPDC2	2	8	62.48276	61.00000	61.72881
STBPD12	2	9	65.17241	64.53333	64.84746
MARGINAL			63.58812	63.67222	63.63088
COUNT			29	30	59

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

ORDER =	DOSE	TIME	A	B
STBPD0	1	1	12.60464	10.29764
STBPD5	1	2	11.83840	11.57266
STBPD10	1	3	9.90795	12.77304
STBPD20	1	4	11.55624	11.67077
STBPD40	1	5	11.10452	12.06515
STBPD60	1	6	10.88407	13.06412
STBPD80	1	7	11.57924	13.84645
STBPDC	1	8	10.30233	11.71775
STBPD12	1	9	12.06673	10.75623
STBPD02	2	1	6.63473	12.19836
STBPD52	2	2	7.15900	13.26581
STBPDX2	2	3	8.10917	13.56618
STBPD22	2	4	7.86086	12.68975
STBPD42	2	5	9.06463	*12.83404
STBPD62	2	6	9.81855	14.39045
STBPD82	2	7	9.89753	13.57076
STBPDC2	2	8	11.35977	13.37780
STBPD12	2	9	[illegible]	14.32285

VARIABLE 3: STANDING DIASTOLIC BLOOD PRESSURE

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - STBPD0 STBPD5 STBPD10 STBPD20 STBPD40 STBPD60
STBPD12 STBPD02 STBPD52 STBPDX2 STBPD22 STBPD42
STBPDC2 STBPD12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	4298587.56250	1	4298587.56250	2863.06299	.000
D	1.87695	1	1.87695	.00125	.972
ERROR	85579.49707	57	1501.39468		
D	1365.91699	1	1365.91699	7.47812	.008
DD	142.01892	1	142.01892	.77753	.382
ERROR	10411.33936	57	182.65508		
T	2382.68311	8	297.83539	6.81190	.000
TD	238.39038	8	29.79880	.68154	.708
ERROR	19937.59351	456	43.72279		
DT	521.55347	8	65.19418	1.45187	.173
DTD	1593.75684	8	199.21960	4.43661	.000
ERROR	20476.01172	456	44.90353		

VARIABLE 4: SITTING SYSTOLIC BLOOD PRESSURE

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

	ORDER DOSE	= TIME	A	B	MARGINAL
SIBPS0	1	1	106.82759	109.06667	107.96610
SIBPS5	1	2	106.89655	107.33333	107.11864
SIBPS10	1	3	107.82759	108.03333	107.93220
SIBPS20	1	4	107.51724	107.86667	107.69491
SIBPS40	1	5	111.58621	110.46667	111.01695
SIBPS60	1	6	110.62069	110.13333	110.37288
SIBPS80	1	7	107.17241	110.53333	108.88136
SIBPSC	1	8	105.44828	109.26667	107.38983
SIBPS12	1	9	105.51724	111.46667	108.54237
SIBPS02	2	1	105.58621	109.86667	107.76271
SIBPS52	2	2	102.34483	105.80000	104.10169
SIBPSX2	2	3	105.96552	105.33333	105.64407
SIBPS22	2	4	101.86207	105.93333	103.93220
SIBPS42	2	5	101.10345	106.13333	103.66102
SIBPS62	2	6	107.51724	110.66667	109.11864
SIBPS82	2	7	106.27586	108.33333	107.32203
SIBPSC2	2	8	106.00000	107.53333	106.77966
SIBPS12	2	9	108.00000	111.60000	109.83051
	MARGINAL		106.33716	108.63148	107.50377
	COUNT		29	30	59

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

	ORDER DOSE	= TIME	A	B
SIBPS0	1	1	11.98233	19.48108
SIBPS5	1	2	12.54234	15.78592
SIBPS10	1	3	12.93961	14.69807
SIBPS20	1	4	11.54686	15.25809
SIBPS40	1	5	15.77864	12.51408
SIBPS60	1	6	14.91982	12.74615
SIBPS80	1	7	16.54878	12.46162
SIBPSC	1	8	14.33175	13.67084
SIBPS12	1	9	17.42457	13.55381
SIBPS02	2	1	12.75460	15.77369
SIBPS52	2	2	13.33169	13.92938
SIBPSX2	2	3	12.80759	14.11610
SIBPS22	2	4	10.47352	15.83086
SIBPS42	2	5	11.01410	15.89564
SIBPS62	2	6	15.90737	15.27977
SIBPS82	2	7	13.28503	17.41251
SIBPSC2	2	8	12.30563	15.81517
SIBPS12	2	9	14.44300	15.41517

DATA DOCUMENTS/INC.

VARIABLE 4: SITTING SYSTOLIC BLOOD PRESSURE

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - SIBPS0 SIBPS5 SIBPS10 SIBPS20 SIBPS40 SIBPS
SIBPS12 SIBPS02 SIBPS52 SIBPSX2 SIBPS22 SIBPS
SIBPSC2 SIBPS12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	12265629.37500	1	12265629.37500	5207.72302	.000
O	1397.16016	1	1397.16016	.59320	.444
ERROR	134250.77930	57	2355.27682		
D	1165.89600	1	1165.89600	4.46456	.039
DO	113.91113	1	113.91113	.43620	.512
ERROR	14885.23425	57	261.14446		
T	1818.73779	8	227.34222	2.99980	.003
TO	439.27881	8	54.78485	.72289	.671
ERROR	34558.37256	456	75.78590		
DT	1485.18066	8	185.64758	2.85488	.004
DTO	559.33496	8	69.91687	1.07518	.379
ERROR	29652.86499	456	65.02821		

VARIABLE 5: SITTING DIASTOLIC BLOOD PRESSURE

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

	ORDER DOSE	= TIME	A	B	MARGINAL
SIBPD0	1	1	66.75862	68.60000	67.69491
SIBPD5	1	2	68.06896	68.13333	68.10169
SIBPD10	1	3	69.17241	69.50000	69.33898
SIBPD20	1	4	70.68965	69.20000	69.93220
SIBPD40	1	5	71.65517	71.33333	71.49152
SIBPD60	1	6	63.86207	66.66667	65.28814
SIBPD80	1	7	64.13793	66.93333	65.55932
SIBPDC	1	8	64.48276	65.40000	64.94915
SIBPD120	1	9	66.55172	69.00000	67.79661
SIBPD02	2	1	63.93103	68.06667	66.03390
SIBPD52	2	2	64.75862	66.20000	65.49152
SIBPDX2	2	3	66.41379	65.93333	66.16949
SIBPD22	2	4	63.58621	66.63333	65.13559
SIBPD42	2	5	65.44828	64.46667	64.94915
SIBPD62	2	6	64.48276	63.00000	63.72881
SIBPD82	2	7	63.86207	63.20000	63.52542
SIBPDC2	2	8	63.72414	63.20000	63.45763
SIBPD122	2	9	67.10345	66.80000	66.94915
	MARGINAL		66.03831	66.79259	66.42185
	COUNT		29	30	59

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

	ORDER DOSE	= TIME	A	B
SIBPD0	1	1	7.73515	10.29429
SIBPD5	1	2	10.61647	11.28848
SIBPD10	1	3	8.28970	9.78651
SIBPD20	1	4	11.01007	11.89146
SIBPD40	1	5	11.84506	9.94236
SIBPD60	1	6	10.55504	10.69106
SIBPD80	1	7	13.58498	11.45586
SIBPDC	1	8	11.00201	8.32363
SIBPD120	1	9	11.73391	9.52311
SIBPD02	2	1	8.90398	9.69156
SIBPD52	2	2	8.33947	11.00909
SIBPDX2	2	3	7.33639	9.98597
SIBPD22	2	4	7.23838	12.45816
SIBPD42	2	5	9.03796	10.95046
SIBPD62	2	6	10.94995	12.96946
SIBPD82	2	7	9.88406	9.87648
SIBPDC2	2	8	9.42222	9.43362
SIBPD122	2	9	9.22088	11.16151

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VARIABLE 5: SITTING DIASTOLIC BLOOD PRESSURE

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - SIBPD0 SIBPD5 SIBPD10 SIBPD20 SIBPD40 SIBPD
SIBPD12 SIBPD02 SIBPD52 SIBPDX2 SIBPD22 SIBPD4
SIBPDC2 SIBPD12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	4683147.75000	1	4683147.75000	5005.32391	.000
O	151.00928	1	151.00928	.16140	.689
ERROR	53331.09814	57	935.63330		
D	1993.95837	1	1993.95837	11.28782	.001
DO	22.13171	1	22.13171	.12529	.725
ERROR	10068.87134	57	176.64686		
T	2315.44312	8	289.43039	5.26077	.000
TO	241.17725	8	30.14716	.54796	.820
ERROR	25087.64160	456	55.01676		
DT	808.12109	8	101.01514	2.21541	.025
DTO	485.23584	8	60.65448	1.33024	.226
ERROR	20792.05859	456	45.59662		

VARIABLE 6: SUSPINE SYSTOLIC BLOOD PRESSURE

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

	ORDER DOSE	= TIME	A	B	MARGINAL
SUBPS0	1	1	107.58621	114.80000	111.25424
SUBPS5	1	2	110.89655	113.13333	112.03390
SUBPS10	1	3	111.58621	114.96667	113.30508
SUBPS20	1	4	112.20690	115.26667	113.76271
SUBPS40	1	5	119.51724	119.60000	119.55932
SUBPS60	1	6	115.37931	119.13333	117.28814
SUBPS80	1	7	108.68965	117.33333	113.08475
SUBPSC	1	8	111.03448	117.33333	114.23729
SUBPS120	1	9	111.51724	119.33333	115.49152
SUBPS02	2	1	109.31034	111.86667	110.61017
SUBPS52	2	2	108.27586	110.23333	109.27119
SUBPSX2	2	3	107.72414	110.06667	108.91525
SUBPS22	2	4	108.06896	111.96667	110.05085
SUBPS42	2	5	107.79310	112.86667	110.37288
SUBPS62	2	6	111.65517	118.46667	115.11864
SUBPS82	2	7	111.51724	116.40000	114.00000
SUBPSC2	2	8	111.31034	112.80000	112.06780
SUBPS1202	2	9	114.96552	119.00000	117.01695
MARGINAL			111.05747	115.25370	113.19115
COUNT			29	30	59

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

	ORDER DOSE	= TIME	A	B
SUBPS0	1	1	11.17880	18.79545
SUBPS5	1	2	11.73013	15.10134
SUBPS10	1	3	12.50576	14.53292
SUBPS20	1	4	13.39877	15.76975
SUBPS40	1	5	17.57153	20.24948
SUBPS60	1	6	14.13308	14.75953
SUBPS80	1	7	13.97217	18.43784
SUBPSC	1	8	12.97933	20.18079
SUBPS120	1	9	14.64489	14.38209
SUBPS02	2	1	13.78691	14.35446
SUBPS52	2	2	9.80851	14.96590
SUBPSX2	2	3	13.95630	11.24625
SUBPS22	2	4	12.42673	16.70945
SUBPS42	2	5	15.97628	13.57161
SUBPS62	2	6	12.32963	13.71315
SUBPS82	2	7	12.00780	13.50760
SUBPSC2	2	8	12.35517	14.55169
SUBPS1202	2	9	11.98357	19.07336

VARIABLE 6: SUPINE SYSTOLIC BLOOD PRESSURE

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - SUBPS0 SUBPS5 SUBPS10 SUBPS20 SUBPS40 SUBPS60
SUBPS12 SUBPS02 SUBPS52 SUBPSX2 SUBPS22 SUBPS42
SUBPSC2 SUBPS12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	13594134.50000	1	13594134.50000	5564.55609	.000
D	4673.67969	1	4673.67969	1.91310	.172
ERROR	139250.22070	57	2442.98633		
D	1660.84766	1	1660.84766	7.35186	.009
DO	73.00623	1	73.00623	.32317	.572
ERROR	12876.78149	57	225.90845		
T	4603.22559	8	575.40320	7.32561	.000
TO	608.88037	8	76.11005	.96898	.460
ERROR	35817.34424	456	78.54681		
DT	2434.13330	8	304.26666	4.09794	.000
DTO	733.43262	8	91.67908	1.23476	.277
ERROR	33857.36230	456	74.24060		

VARIABLE 7: SUPINE DIASTOLIC BLOOD PRESSURE

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

	ORDER = DOSE	TIME	A	B	MARGINAL
SUBPD0	1	1	64.48276	69.53333	67.05085
SUBPD5	1	2	69.75862	67.93333	68.83051
SUBPD10	1	3	70.82759	68.46667	69.62712
SUBPD20	1	4	72.48276	70.20000	71.32203
SUBPD40	1	5	72.20690	76.13333	74.20339
SUBPD60	1	6	63.86207	72.20000	68.10169
SUBPD80	1	7	63.31034	70.33333	66.88136
SUBPDC	1	8	66.06896	69.46667	67.79661
SUBPD120	1	9	68.82759	73.40000	71.15254
SUBPD02	2	1	66.75862	67.80000	67.28814
SUBPD52	2	2	64.34483	67.80000	66.10169
SUBPDX2	2	3	66.13793	69.26667	67.72881
SUBPD22	2	4	67.44828	68.60000	68.03390
SIBPD42	2	5	65.58621	65.93333	65.76271
SUBPD62	2	6	64.00000	62.46667	63.22034
SUBPD82	2	7	63.86207	62.60000	63.22034
SUBPDC2	2	8	65.17241	62.86667	64.00000
SUBPD1202	2	9	69.24138	69.26667	69.25424
	MARGINAL		66.90996	68.57037	67.75424
	COUNT		29	30	59

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

	ORDER = DOSE	TIME	A	B
SUBPD0	1	1	11.71879	9.69441
SUBPD5	1	2	9.62012	10.32551
SUBPD10	1	3	10.02165	10.44768
SUBPD20	1	4	10.77902	11.29357
SUBPD40	1	5	16.79579	14.12196
SUBPD60	1	6	12.14121	12.84765
SUBPD80	1	7	10.90578	11.86224
SUBPDC	1	8	12.51836	13.26581
SUBPD120	1	9	13.37927	9.32405
SUBPD02	2	1	9.32606	10.05296
SUBPD52	2	2	9.00903	11.65421
SUBPDX2	2	3	12.51206	9.49022
SUBPD22	2	4	8.76513	11.18065
SIBPD42	2	5	10.34241	9.64877
SUBPD62	2	6	11.91637	11.26096
SUBPD82	2	7	10.70288	9.35359
SUBPDC2	2	8	10.39941	9.33194
SUBPD1202	2	9	10.09121	15.38009

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VARIABLE 7: SUPINE DIASTOLIC BLOOD PRESSURE

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - SUBPD0 SUBPD5 SUBPD10 SUBPD20 SUBPD40 SUBPD6
SUBPD120 SUBPD02 SUBPD52 SUBPDX2 SUBPD22 SUBPD42
SUBPD02 SUBPD1202

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	4871829.68750	1	4871829.68750	4952.87860	.000
D	731.76172	1	731.76172	.74394	.392
ERROR	56067.25195	57	983.63599		
D	2982.92041	1	2982.92041	11.91405	.001
DO	388.99243	1	388.99243	1.55367	.218
ERROR	14271.08862	57	250.36997		
T	3682.98389	8	460.37299	6.22211	.000
TO	460.59863	8	57.57483	.77814	.622
ERROR	33739.37158	456	73.98985		
DT	1343.68311	8	167.96039	2.85307	.004
DTO	1955.50977	8	244.43872	4.15217	.000
ERROR	26844.75488	456	58.87008		

VARIABLE 8: SUBJECTIVE RATING OF DRUG EFFECT

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

	ORDER DOSE	TIME	A	B	MARGINAL
DRUGEF0	1	1	.20690	.56667	.38983
DRUGEF5	1	2	3.62069	1.16667	2.37288
DRUGE10	1	3	6.06897	2.23333	4.11864
DRUGE20	1	4	3.75862	3.96667	3.86441
DRUGE40	1	5	2.68966	5.20000	3.96610
DRUGE60	1	6	4.34483	7.63333	6.01695
DRUGE80	1	7	4.37931	4.73333	4.55932
DRUGEC	1	8	1.58621	4.33333	2.98305
DRUGE12	1	9	1.31034	3.23333	2.28814
DRUGE02	2	1	-.24138	.60000	.42373
DRUG52	2	2	2.34483	2.23333	2.28814
DRUGX2	2	3	3.03448	3.66667	3.35593
DRUG202	2	4	4.03448	4.83333	4.44068
DRUG402	2	5	3.58621	3.93333	3.76271
DRUG602	2	6	4.44828	6.16667	5.32203
DRUG802	2	7	2.34483	5.03333	3.71186
DRUGC2	2	8	1.34483	5.46667	3.44068
DRUG122	2	9	1.41379	2.66667	2.05085
	MARGINAL		2.81992	3.75926	3.29755
	COUNT		29	30	59

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

	ORDER DOSE	TIME	A	B
DRUGEF0	1	1	.77364	1.61210
DRUGEF5	1	2	9.08851	2.24505
DRUGE10	1	3	10.28845	3.47090
DRUGE20	1	4	7.45297	7.89798
DRUGE40	1	5	6.99542	11.28441
DRUGE60	1	6	8.35069	12.97606
DRUGE80	1	7	8.44061	10.85939
DRUGEC	1	8	2.86004	10.75217
DRUGE12	1	9	2.60636	9.84950
DRUGE02	2	1	.83045	1.67332
DRUG52	2	2	6.13698	3.49071
DRUGX2	2	3	7.40407	6.39145
DRUG202	2	4	12.39090	7.41426
DRUG402	2	5	12.37947	7.82980
DRUG602	2	6	12.91894	9.54511
DRUG802	2	7	6.66695	7.92849
DRUGC2	2	8	5.02434	12.20439
DRUG122	2	9	5.03216	6.14948

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VARIABLE 8: SUBJECTIVE RATING OF DRUG EFFECT

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - DRUGEF0 DRUGEF5 DRUGE10 DRUGE20 DRUGE40 DRUGE60
DRUGE12 DRUGE02 DRUG52 DRUGX2 DRUG202 DRUG402
DRUGC2 DRUG122

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	11489.03369	1	11489.03369	23.68283	.000
D	234.19702	1	234.19702	.48276	.490
ERROR	27651.88306	57	485.12075		
D	10.84869	1	10.84869	.09810	.755
DD	36.83740	1	36.83740	.33312	.566
ERROR	6303.31018	57	110.58439		
T	2129.03296	8	266.12912	5.80509	.000
TD	636.78882	8	79.59860	1.73629	.088
ERROR	20904.90186	456	45.84408		
DT	62.37329	8	7.79666	.30461	.964
DTD	263.46973	8	32.93372	1.28668	.248
ERROR	11671.68394	456	25.59580		

VARIABLE 9: SUBJECTIVE RATING OF "GOOD" EFFECTS

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

ORDER = DOSE	TIME	A	B	MARGINAL
GOOD0	1	1	1.10345	3.10000	2.11864
GOOD5	1	2	5.00000	3.63333	4.30508
GOOD10	1	3	6.37931	4.50000	5.42373
GOOD20	1	4	5.27586	5.50000	5.38983
GOOD40	1	5	4.58621	4.73333	4.66102
GOOD60	1	6	3.65517	5.06667	4.37288
GOOD80	1	7	3.31034	4.03333	3.67797
GOODC	1	8	1.34483	3.66667	2.52542
GOOD120	1	9	1.13793	3.40000	2.28814
GOOD02	2	1	1.27586	2.00000	1.64407
GOOD52	2	2	3.13793	3.86667	3.50847
GOODX2	2	3	3.13793	4.30000	3.72881
GOOD202	2	4	2.48276	4.30000	3.40678
GOOD402	2	5	2.37931	4.16667	3.28814
GOOD602	2	6	3.24138	3.06667	3.15254
GOOD802	2	7	2.93103	2.13333	2.52542
GOODC2	2	8	5.17241	3.30000	4.22034
GOOD122	2	9	2.41379	1.50000	1.94915
MARGINAL			3.22031	3.68148	3.45480
COUNT			29	30	59

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

ORDER = DOSE	TIME	A	B
GOOD0	1	1	5.19165	11.57092
GOOD5	1	2	10.92180	11.38506
GOOD10	1	3	11.80319	11.67594
GOOD20	1	4	10.10267	13.26585
GOOD40	1	5	10.12605	12.93467
GOOD60	1	6	7.31572	12.93467
GOOD80	1	7	7.33438	11.61593
GOODC	1	8	3.75382	11.59171
GOOD120	1	9	3.19290	11.46389
GOOD02	2	1	5.42413	8.96353
GOOD52	2	2	7.75852	9.49313
GOODX2	2	3	7.39075	11.04583
GOOD202	2	4	5.81022	10.32957
GOOD402	2	5	6.29293	9.44707
GOOD602	2	6	7.97162	6.17522
GOOD802	2	7	7.85098	4.16664
GOODC2	2	8	13.98231	6.52396
GOOD122	2	9	7.15900	2.68778

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VARIABLE 9: SUBJECTIVE RATING OF "GOOD" EFFECTS

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - GOOD0 GOOD5 GOOD10 GOOD20 GOOD40 GOOD6
GOOD120 GOOD02 GOOD52 GOODX2 GOOD202 GOOD402
GOODC2 GOOD122

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	12643.36963	1	12643.36963	21.47020	.000
O	56.45068	1	56.45068	.09586	.758
ERROR	33566.15137	57	588.87984		
D	175.11768	1	175.11768	.33650	.564
DO	9.35498	1	9.35498	.01798	.894
ERROR	29663.04053	57	520.40421		
T	842.58838	8	105.32355	3.61195	.000
TO	89.44348	8	11.18044	.38342	.929
ERROR	13296.84363	456	29.15974		
DT	284.82397	8	35.60300	1.28535	.249
DTO	381.36621	8	47.67078	1.72103	.091
ERROR	12630.75549	456	27.69903		

VARIABLE 10: SUBJECTIVE RATING OF "BAD" EFFECTS

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

	ORDER =		A	B	MARGINAL
	DOSE	TIME			
BAD0	1	1	.17241	.46667	.32203
*TB*1180 RE-BOOT AT 10:50.....10 MIN.....					
BAD5	1	2	2.44828	1.23333	1.83051
BAD10	1	3	2.51724	1.23333	1.86441
BAD20	1	4	1.75862	2.70000	2.23729
BAD40	1	5	.55172	3.00000	1.79661
BAD60	1	6	1.00000	4.30000	2.67797
BAD80	1	7	1.48276	4.86667	3.20339
BADC	1	8	.93103	2.06667	1.50847
BAD120	1	9	.68966	2.93333	1.83051
BAD02	2	1	1.34483	.56667	.94915
BAD52	2	2	1.65517	2.50000	2.08475
BADX2	2	3	1.89655	5.86667	3.91525
BAD202	2	4	1.44828	6.63333	4.08475
BAD402	2	5	1.58621	4.10000	2.86441
BAD602	2	6	1.55172	6.80000	4.22034
BAD802	2	7	1.51724	4.90000	3.23729
BADC2	2	8	2.44828	6.43333	4.47458
BAD1202	2	9	2.44828	2.93333	2.69492
	MARGINAL		1.52490	3.52963	2.54426
	COUNT		29	30	59

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

	ORDER =		A	B
	DOSE	TIME		
BAD0	1	1	.60172	2.02967
BAD5	1	2	7.69780	2.71247
BAD10	1	3	7.44322	2.78770
BAD20	1	4	5.60392	6.87399
BAD40	1	5	1.18280	8.55812
BAD60	1	6	1.88982	10.00396
BAD80	1	7	4.16294	11.05701
BADC	1	8	1.48639	4.04230
BAD120	1	9	1.19832	8.42383
BAD02	2	1	5.78962	1.81342
BAD52	2	2	5.40685	5.82947
BADX2	2	3	5.35420	12.08228
BAD202	2	4	4.88866	12.16689
BAD402	2	5	5.27472	9.56773
BAD602	2	6	4.95398	10.43998
BAD802	2	7	4.92530	9.33422
BADC2	2	8	7.36103	12.82692
BAD1202	2	9	7.22884	7.89121

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VARIABLE 10: SUBJECTIVE RATING OF "BAD" EFFECTS

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - BAD0 BAD5 BAD10 BAD20 BAD40 BAD.
BAD120 BAD02 BAD52 BADX2 BAD202 BAD402
BADC2 BAD1202

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	6781.12646	1	6781.12646	18.06776	.000
O	1066.71753	1	1066.71753	2.84218	.097
ERROR	21393.03198	57	375.31635		
D	406.58685	1	406.58685	3.30967	.074
DO	151.26483	1	151.26483	1.23131	.272
ERROR	7002.35510	57	122.84833		
T	699.71265	8	87.46408	3.20061	.002
TO	572.05566	8	71.50696	2.61669	.008
ERROR	12461.23889	456	27.32728		
DT	202.83606	8	25.35451	1.16983	.316
DTO	335.47986	8	41.93498	1.93483	.053
ERROR	9883.20129	456	21.67369		

VARIABLE 11: SUBJECTIVE RATING OF "DRUG LIKING"

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

	ORDER DOSE	TIME	A	B	MARGINAL
LIKE0	1	1	28.93103	31.00000	29.98305
LIKE5	1	2	29.58621	31.10000	30.35593
LIKE10	1	3	29.72414	31.56667	30.66102
LIKE20	1	4	29.20690	31.60000	30.42373
LIKE40	1	5	30.34483	29.96667	30.15254
LIKE60	1	6	31.00000	28.50000	29.72881
LIKE80	1	7	30.62069	28.76667	29.67797
LIKEC	1	8	28.96552	29.56667	29.27119
LIKE120	1	9	30.96552	28.16667	29.54237
LIKE02	2	1	29.93103	32.20000	31.08475
LIKE52	2	2	29.93103	29.93333	29.93220
LIKEX2	2	3	29.93103	28.40000	29.15254
LIKE202	2	4	29.96552	27.26667	28.59322
LIKE402	2	5	31.03448	29.93333	30.47458
LIKE602	2	6	32.31034	30.40000	31.33898
LIKE802	2	7	31.06897	30.43333	30.74576
LIKEC2	2	8	32.17241	30.60000	31.37288
LIKE122	2	9	31.93103	29.96667	30.93220
	MARGINAL		30.42337	29.96481	30.19021
	COUNT		29	30	59

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

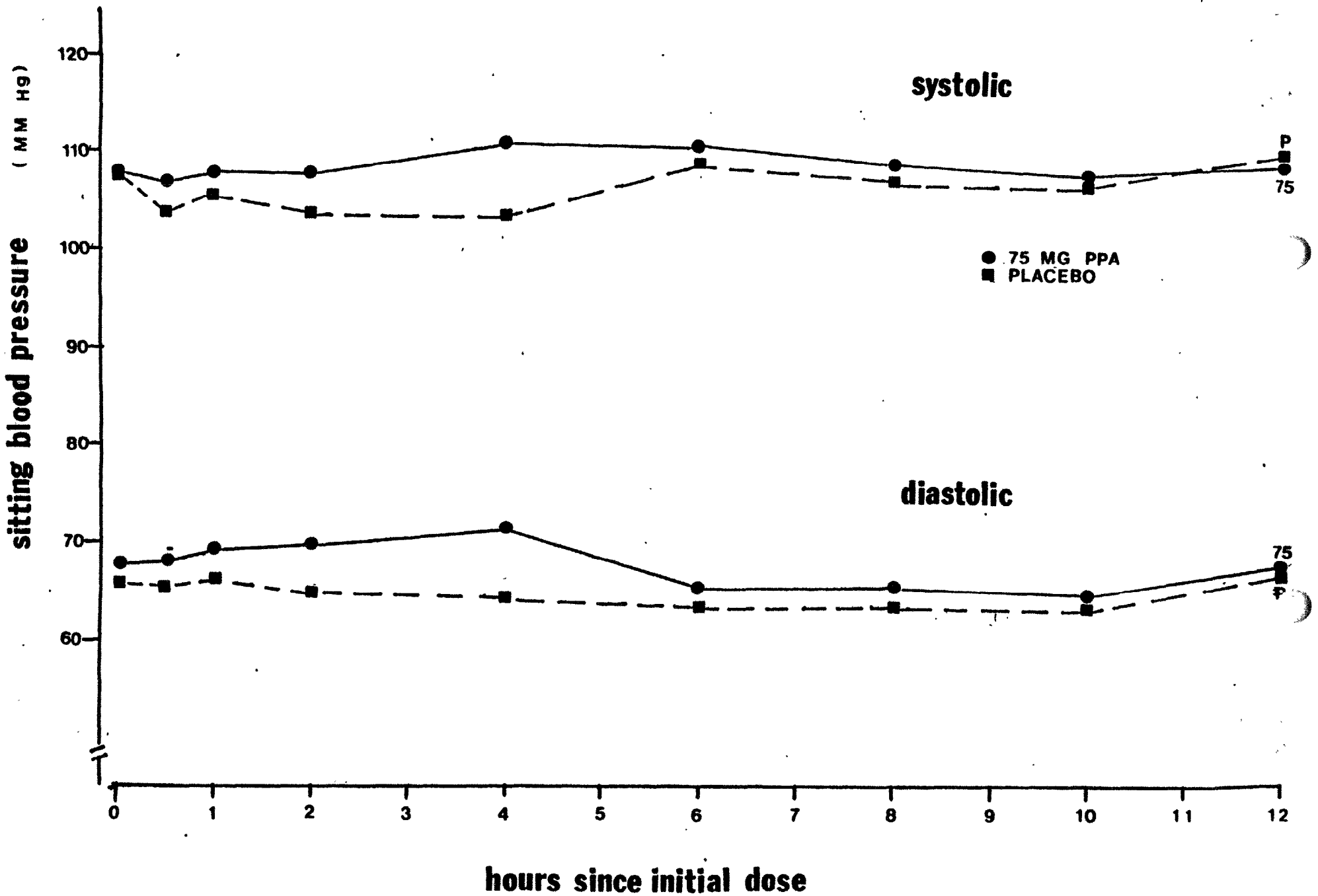
	ORDER DOSE	TIME	A	B
LIKE0	1	1	7.74104	.26261
LIKE5	1	2	8.59617	.40258
LIKE10	1	3	8.58527	2.32947
LIKE20	1	4	7.61755	2.94314
LIKE40	1	5	10.08987	6.07132
LIKE60	1	6	7.82852	7.56922
LIKE80	1	7	6.51599	5.80537
LIKEC	1	8	8.07325	4.38401
LIKE120	1	9	8.31729	7.64327
LIKE02	2	1	5.75656	5.67146
LIKE52	2	2	5.76276	6.26943
LIKEX2	2	3	6.19292	7.38405
LIKE202	2	4	5.77855	8.31257
LIKE402	2	5	8.28718	8.83540
LIKE602	2	6	9.83472	12.85892
LIKE802	2	7	8.30633	10.74688
LIKEC2	2	8	10.08559	13.61186
LIKE122	2	9	9.40718	11.69876

ATA DOCUMENTS/INC.

VARIABLE 11: SUBJECTIVE RATING OF "DRUG LIKING"

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - LIKE0 LIKE5 LIKE10 LIKE20 LIKE40 LIKE60
LIKE120 LIKE02 LIKE52 LIKEX2 LIKE202 LIKE40
LIKEC2 LIKE122

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	967929.20312	1	967929.20312	2007.51176	.000
O	55.81177	1	55.81177	.11576	.735
ERROR	27482.76025	57	482.15369		
D	50.23804	1	50.23804	.44295	.508
DO	82.43018	1	82.43018	.72680	.397
ERROR	6464.69690	57	113.41573		
T	97.28516	8	12.16064	.31094	.962
TO	480.75757	8	60.09470	1.53660	.142
ERROR	17833.62622	456	39.10883		
DT	450.32056	8	56.29007	2.01950	.043
DTO	267.11157	8	33.38895	1.19788	.298
ERROR	12710.21533	456	27.87328		


systolic
diastolic
75 MG PPA
PLACEBO
sitting blood pressure (MM Hg)
120
110
100
90
80
70
60
P
75
75
P
0
1
2
3
4
5
6
7
8
9
10
11
12
hours since initial dose

● 75mg SUSTAINED RELEASE
■ PLACEBO

SUMMARY OF MOOD EFFECTS OF PPA CROSSOVER

I.D._____ DATE_____ NAME_____

MARK THE LINES TO INDICATE HOW YOU FEEL:

HOUR/TIME	ARE THERE ANY DRUG EFFECTS? (NONE – A LOT)	ARE THERE GOOD EFFECTS? (NONE – A LOT)	ARE THERE ANY BAD EFFECTS? (NONE – A LOT)	DO YOU LIKE OR DISLIKE THE EFFECTS? (DISLIKE – NEUTRAL – LIKE)
0 ____				
½ ____				
1 ____				
2 ____				
4 ____				
6 ____				
8 ____				
10 ____				
12 ____				

FINAL REPORT OF

CLINICAL PROTOCOL NO. 82-8(A)

An Evaluation of the Acute Effects of Phenylpropanolamine in Normal Volunteers: Parallel Groups Design

Sponsor: Thompson Medical Company, Inc.
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Protocol developed by: The Clinical Consulting Group
ANTECH, Inc. and the
Behavioral Pharmacology Research Unit

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Project start date: 25 June 82

Project completion date: 31 August 82

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ABSTRACT

One hundred fifty (150) healthy normotensive volunteers (mean age = 25.9) participated in a double-blind, placebo controlled comparison of the effects of phenylpropanolamine HCL on blood pressure, pulse, and mood. Two dosage forms of phenylpropanolamine were studied (75 mg sustained release and 25 mg t.i.d.) in comparison with placebo. Subjects were randomly assigned to one of the three drug treatment conditions. Subjects in one group (Group A) received the 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 capsules 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 (sitting, standing, and supine), pulse, and subjective drug effect ("mood") were obtained 9 times during the session at baseline (prior to drug administration) and at 1/2 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr, and 12 hr post initial dosing.

Mixed design analysis of variance revealed no main effects for drug treatment on any of the measures. As expected, all measures showed main effects for time of day (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.

Final Report:
An Evaluation of the Acute Effects of Phenylpropanolamine in Normal Volunteers: Parallel Groups Design

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. The present project was designed to provide such information.

OBJECTIVE

The proposed research aimed to provide an objective characterization of the effects of PPA on various behavioral and physiological parameters over a 12 hour testing session.

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).

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.

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

INVESTIGATIVE METHODS

Subjects

Subjects were 150 healthy normal volunteers (mean age = 25.9) (both male and female). The study population consisted of 83 caucasians, 63 blacks, 3 orientals, and 1 American Indian. Approximately 58% of the subjects were men. All had given informed consent and had been screened to meet the following criteria:

a. between 18 and 55 years of age

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

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

d. no history of severe emotional disturbance, chronic alcoholism, or drug abuse

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

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

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

Design and Procedure

Subjects were randomly assigned to one of three treatment groups upon entry into the study. The basic investigative procedures followed for each subject are detailed below.

1. General Procedures

a. Subject control. Subjects were instructed to be free of all medications for the week prior to the first administration of a test product. Subjects who had ingested substances which could have 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 (approximately 13 hours) on the test day.

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 days.

c. Drug administration. In this investigation two currently marketed doses of test products containing PPA (PPA, 25 mg, t.i.d. and 75 mg sustained release PPA) were being compared with placebo. On each test day subjects received three administrations of a test product. Study medications were identical in appearance and were labeled in code so that neither the investigator nor the subject could know which medication was being administered. Doses were given at 4 hour intervals (e.g., approximately 8:00 am, 12 noon, and 4:00 pm).

Subjects were randomly assigned to one of three treatment conditions. One group of subjects (Condition A) received the 75 mg sustained release product at their first dosing and matching placebo capsules on subsequent dosings. Another group of subjects (Condition B) received 25 mg PPA at each of the three dosings. Finally, one group (Condition C) received placebo at all three dosings. This dosing schedule is illustrated in Table 1.

Table 1

Dosing Schedule on a Test Day

	Dose 1 (approx. 8:00 am)	Dose 2 (approx. 12 noon)	Dose 3 (approx. 4:00 pm)
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 9 times during each experimental session: Once prior to initial drug administration (0 hr) and at 1/2 hr, 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr, and 12 hr following initial drug administration. Blood pressure (sitting, standing, supine) was measured using procedures recommended by the American Heart Association (Kirkendall et al., 1980). Clinical measures of subjective state were obtained using visual analogue mood-scales on which subjects indicated the extent to which they felt a drug effect and their subjective impression of that drug effect. These measures were supplemented by subjective reports of subjects and the observations of research staff.

2. Design

This study may be viewed as a 3 (drug treatment conditions) x 9 (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) and measurement occasion (0 hr, 1/2 hr, etc.). Treatment assignment was a between-groups factor 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 increase slightly over the course of the session (F = 16.67, p < .01) for subjects in all treatment conditions. No main effect for drug treatment was identified.

Standing systolic blood pressure was generally higher later in the session (F = 4.34, p < .05) for subjects in all treatment groups. This trend was more marked for subjects in the placebo group (F = 3.39, p < .05). No main effect for drug treatment condition was identified. Standing diastolic blood pressure was generally lowest at 8-10 hours post initial medication for subjects in all treatment groups (F = 13.80, p < .01). No main effects for drug treatment was identified.

Sitting systolic blood pressure was generally lowest at 1-4 hours post medication (F = 4.01, p < .05). Subjects in the 75 mg sustained release treatment group tended to show decreased sitting systolic blood pressure later in the session as compared with subjects in the 25 mg t.i.d. or placebo groups (F = 3.65, p < .05). Sitting diastolic blood pressure was generally lower at 4-8 hours post dosing for subjects in all treatment groups (F = 11.22, p < .01). No main effect for drug treatment was identified. These results are shown in Figure 1 (attached).

Supine systolic blood pressure was generally higher later in the session (F = 11.09, p < .01). This increase tended to be largest in the placebo treatment group (F = 4.44, p < .05). No main effect for drug condition was identified. Supine diastolic blood pressure tended to be lowest at 6-10 hours post initial dosing (F = 17.70, p < .01). No main effect for drug condition was identified.

Subjective measures of drug effect and mood revealed no significant differences between the three drug conditions. There were, however, significant changes in mood over the course of the session. These included measures of "drug effect" ($F = 8.53$, $p < .01$), ratings of feeling "good" ($F = 6.35$, $p < .01$), ratings of feeling "bad" ($F = 5.30$, $p < .01$), and ratings of drug liking (F 5.30, $p < .01$) over the course of the session. In general, subjects in all treatment groups (including placebo) reported feeling better (more pleasurable) early in the session and more dysphoric later in the session. These variations in subjective state, although statistically reliable, were very small and were not considered clinically relevant. Figure 2 illustrates these effects.

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 (sitting, standing, and supine) and subjective state ("mood") 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. No consistent pattern of differences between drug treatments was observed. On some measurement occasions, subjects receiving active drug

treatments showed 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.

As expected, statistically significant differences in blood pressure were found over the course of the daily session. Circadian variation of blood pressure is well documented (see, e.g., Millar-Craig, Bishop, & Raftey, 1978). Our results are consistent with this literature.

The present results also suggest that PPA, in the dosage forms studied, had no systematic effect on subjective ratings of drug effect or drug liking. No statistically reliable differences between drug treatments were observed on measures of drug effect or drug liking. The effects of the two PPA treatments were not rated as any better or any worse than that of the placebo. 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. As was the case with blood pressure, subjective state ("mood") showed circadian changes over the course of the session. In general, subjects in all treatment groups reported feeling "better" 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 mood.

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APPENDIX

KEY:

C = DRUG CONDITION (HI=75MG SUSTAINED RELEASE: LO=25MG T.I.D.: P=PLACEBO)

R = REPEATED MEASUREMENT OCCASIONS (1=BASELINE; 2=30 MINUTES; 3=1 HOUR; 4=2 HOUR; 5=4 HOUR; 6=6 HOUR; 7=8 HOUR; 8=10 HOUR; 9=12 HOUR).

FOR EACH VARIABLE STUDIED, MEANS AND STANDARD DEVIATIONS AT EACH MEASUREMENT OCCASION ARE PRESENTED IN ONE TABLE, WHILE ANALYSIS OF VARIANCE RESULTS ARE PRESENTED IN ANOTHER. A CONSERVATIVE E-TEST WAS USED TO EVALUATE THE RESULTS OF ALL FACTORS INVOLVING REPEATED MEASURES.

EFFECTS OF PHENYLPROPANOLAMINE ON BLOOD PRESSURE, PULSE, AND MOOD: PARALLEL GROUPS DESIGN

Study Site: Behavioral Pharmacology Research Unit
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Contact: Frank R. Funderburk
Director, Clinical Consulting
ANTECH, Inc.
(301) 997-0880

Date: October 8, 1982

VARIABLE 1: PULSE

CELL MEANS FOR 1-ST DEPENDENT VARIABLE

COND	R	HI	LO	P	MARGINAL
PUL0	1	76.20000	77.92000	76.08000	76.73333
PUL5	2	75.52000	77.40000	76.16000	76.36000
PUL10	3	74.76000	77.08000	76.44000	76.09333
PUL20	4	76.36000	77.12000	75.88000	76.45333
PUL40	5	74.28000	77.08000	74.84000	75.40000
PUL60	6	81.48000	83.64000	84.20000	83.10667
PUL80	7	77.60000	80.08000	80.72000	79.46667
PULC	8	74.76000	77.32000	78.04000	76.70667
PUL120	9	73.72000	79.56000	77.84000	77.04000
MARGINAL		76.07555	78.57778	77.80000	77.48444
COUNT		50	50	50	150

STANDARD DEVIATIONS FOR 1-ST DEPENDENT VARIABLE

COND	R	HI	LO	P
PUL0	1	10.23200	10.02906	10.11735
PUL5	2	11.76338	10.03870	10.49657
PUL10	3	10.64369	8.41000	11.78924
PUL20	4	11.04861	9.42563	11.69273
PUL40	5	10.31749	9.39135	11.78785
PUL60	6	11.53387	11.06338	13.59622
PUL80	7	11.05829	10.93924	11.97112
PULC	8	10.06014	10.59542	12.54861
PUL120	9	9.84790	9.80037	12.21468

VARIABLE 1: PULSE

ANALYSIS OF VARIANCE FOR 1-ST DEPENDENT VARIABLE - PUL0 PUL5 PUL10 PUL20 PUL40 PUL60 PUL120

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	8105174.37500	1	8105174.37500	12334.66577	.000
C	1475.98340	2	737.99170	1.12310	.328
ERROR	96594.48047	147	657.10531		
R	6826.92969	8	853.36621	16.67249	.000
RC	799.23340	16	49.95209	.97593	.481
ERROR	60192.47119	1176	51.18407		

VARIABLE 2: STANDING SYSTOLIC BLOOD PRESSURE

CELL MEANS FOR 2-ND DEPENDENT VARIABLE

COND	= R	HI	LO	P	MARGINAL
STBPS0	1	99.44000	97.80000	99.52000	98.92000
STBPS5	2	99.72000	97.20000	97.72000	98.28000
STBPS10	3	100.08000	97.84000	98.36000	98.76000
STBPS20	4	100.20000	97.00000	98.54000	98.58000
STBPS40	5	100.76000	95.24000	101.04000	99.01333
STBPS60	6	101.08000	97.92000	103.00000	100.66667
STBPS80	7	96.12000	96.80000	100.48000	97.82333
STBPSC	8	96.64000	99.60000	104.52000	100.25333
STBPS12	9	99.32000	100.56000	106.56000	102.14667
MARGINAL		99.26222	97.78444	101.10444	99.38370
COUNT		50	50	50	150

STANDARD DEVIATIONS FOR 2-ND DEPENDENT VARIABLE

COND	= R	HI	LO	P
STBPS0	1	12.50659	12.32674	16.32106
STBPS5	2	13.46202	12.10161	16.84484
STBPS10	3	12.11482	12.30125	15.73085
STBPS20	4	12.31723	11.92665	19.24197
STBPS40	5	13.95556	12.01964	15.35559
STBPS60	6	13.87530	12.91074	16.70024
STBPS80	7	13.25055	12.26285	14.47057
STBPSC	8	13.18899	13.03060	15.06346
STBPS12	9	17.10763	14.60243	15.88756

VARIABLE 2: STANDING SYSTOLIC BLOOD PRESSURE

ANALYSIS OF VARIANCE FOR 2-NO DEPENDENT VARIABLE - STBPS0 STBPS5 STBPS10 STBPS20 STBPS40 STBPS
STBPS12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	13334097.00000	1	13334097.00000	10210.83582	.000
C	2489.95898	2	1244.97949	.95337	.388
ERROR	191963.93750	147	1305.87712		
R	2256.77148	8	282.09644	4.34381	.000
RC	3518.25977	16	219.89124	3.38595	.000
ERROR	76372.04004	1176	64.94221		

VARIABLE 3: STANDING DIASTOLIC BLOOD PRESSURE

CELL MEANS FOR 3-RD DEPENDENT VARIABLE

COND	R	HI	LO	P	MARGINAL
STBPD0	1	66.96000	62.80000	63.36000	64.37333
STBPD5	2	65.96000	63.90000	64.40000	64.75333
STBPD10	3	65.76000	63.08000	65.24000	64.69333
STBPD20	4	66.00000	63.20000	63.96000	64.38667
STBPD40	5	65.24000	61.52000	63.56000	63.44000
STBPD60	6	61.64000	60.08000	60.72000	60.81333
STBPD80	7	58.92000	60.12000	59.84000	59.62667
STBPDC	8	61.12000	61.76000	61.52000	61.53333
STBPD12	9	64.68000	64.56000	64.40000	64.54667
MARGINAL		64.03111	62.35778	63.00000	63.12963
COUNT		50	50	50	150

STANDARD DEVIATIONS FOR 3-RD DEPENDENT VARIABLE

COND	R	HI	LO	P
STBPD0	1	11.58634	8.12153	11.84554
STBPD5	2	11.40347	10.21054	12.80943
STBPD10	3	10.13895	8.94619	12.38755
STBPD20	4	11.32092	8.70374	11.69329
STBPD40	5	10.65902	8.56724	12.19093
STBPD60	6	10.60373	9.95467	13.15378
STBPD80	7	10.25559	7.93247	12.87199
STBPDC	8	10.72217	11.29558	12.45767
STBPD12	9	11.69413	10.23033	14.12481

VARIABLE 3: STANDING DIASTOLIC BLOOD PRESSURE

ANALYSIS OF VARIANCE FOR 3-RU DEPENDENT VARIABLE -- STBPD0 STBPD5 STBPD10 STBPD20 STBPD40 STBPD
STBPD12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	5380216.62500	1	5380216.62500	6976.24384	.000
C	641.33887	2	320.66943	.41580	.661
ERROR	113369.29492	147	771.21969		
R	4574.54639	8	571.81830	13.79514	.000
RC	862.95117	16	53.93445	1.30117	.188
ERROR	48746.03076	1176	41.45071		

VARIABLE 4: SITTING SYSTOLIC BLOOD PRESSURE

CELL MEANS FOR 4-TH DEPENDENT VARIABLE

COND	R	HI ○	LO △	P □	MARGINAL
SIBPS0	1	107.72000	107.80000	109.00000	108.17333
SIBPS5	2	107.58000	107.58000	105.84000	107.00000
SIBPS10	3	107.22000	106.96000	106.96000	107.04667
SIBPS20	4	106.52000	105.44000	106.16000	106.04000
SIBPS40	5	108.84000	104.04000	105.16000	106.01333
SIBPS60	6	110.96000	106.28000	110.12000	109.12000
SIBPS80	7	106.56000	104.12000	108.24000	106.70667
SIBPSC	8	105.16000	109.96000	108.48000	107.86667
SIBPS12	9	105.40000	110.44000	111.92000	109.25333
MARGINAL		107.32889	106.95778	107.98667	107.42444
COUNT		50	50	50	150

STANDARD DEVIATIONS FOR 4-TH DEPENDENT VARIABLE

COND	R	HI	LO	P
SIBPS0	1	12.02725	11.34433	14.90788
SIBPS5	2	11.93654	10.95089	14.45522
SIBPS10	3	12.45283	10.89647	14.93518
SIBPS20	4	11.21085	11.79443	15.34815
SIBPS40	5	14.83564	11.74206	14.92342
SIBPS60	6	13.01327	11.11726	16.20990
SIBPS80	7	13.78576	11.43864	16.07452
SIBPSC	8	12.41520	13.13347	15.02412
SIBPS12	9	14.74823	12.68320	14.88437

VARIABLE 4: SITTING SYSTOLIC BLOOD PRESSURE

ANALYSIS OF VARIANCE FOR 4-TH DEPENDENT VARIABLE - SIBPS0 SIBPS5 SIBPS10 SIBPS20 SIBPS40 SIBPS
SIBPS12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	15578997.25000	1	15578997.25000	13602.24463	.000
C	244.33594	2	122.16797	.10667	.899
ERROR	168362.84570	147	1145.32547		
R	1868.45312	8	233.55664	4.01151	.000
RC	3395.40430	16	212.21277	3.64492	.00
ERROR	68468.55176	1176	58.22156		

VARIABLE 5: SITTING DIASTOLIC BLOOD PRESSURE

CELL MEANS FOR 5-TH DEPENDENT VARIABLE

COND	R	HI	LO	P	MARGINAL
SIBPD0	1	68.00000	69.96000	68.36000	68.77333
SIBPD5	2	68.04000	63.96000	67.28000	68.09333
SIBPD10	3	68.60000	68.56000	67.16000	68.10667
SIBPD20	4	69.68000	69.16000	67.70000	68.84667
SIBPD40	5	70.28000	65.64000	64.76000	66.89333
SIBPD60	6	65.12000	65.44000	63.32000	64.62667
SIBPD80	7	64.24000	64.24000	63.64000	64.04000
SIBPDC	8	66.24000	68.72000	63.40000	66.12000
SIBPD12	9	67.32000	70.76000	67.44000	68.50667
MARGINAL		67.50222	67.93778	65.89556	67.11185
COUNT		50	50	50	150

STANDARD DEVIATIONS FOR 5-TH DEPENDENT VARIABLE

COND	R	HI	LO	P
SIBPD0	1	8.04071	8.42242	10.66514
SIBPD5	2	11.46772	9.66576	12.63465
SIBPD10	3	8.92829	8.79740	10.18274
SIBPD20	4	10.73890	10.15062	12.35239
SIBPD40	5	10.64461	8.73828	10.79599
SIBPD60	6	9.77096	8.99015	12.16626
SIBPD80	7	12.09918	7.34725	9.73686
SIBPDC	8	10.34617	9.02387	10.14386
SIBPD12	9	10.92916	8.55131	11.62713

Variable 5: Sitting Diastolic Blood Pressure

ANALYSIS OF VARIANCE FOR 5-TH DEPENDENT VARIABLE - SIBPD0 SIBPD5 SIBPD10 SIBPD20 SIBPD40 SIBP
SIBPD12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	6080394.56250	1	6080394.56250	10388.65442	.000
SYSTEM WARNING - MAX PAGES					
C	1041.27734	2	520.63867	.88954	.413
ERROR	86037.07844	147	585.29182		
R	3946.87451	8	493.35931	11.22334	.000
RC	1422.28682	16	88.93668	2.02320	.010
ERROR	51694.99854	1176	43.95833		

VARIABLE 6: SUPINE SYSTOLIC BLOOD PRESSURE

CELL MEANS FOR 6-TH DEPENDENT VARIABLE

COND	= R	HI	LO	P	MARGINAL
SUBPS0	1	108.54000	111.12000	110.52000	110.06000
SUBPS5	2	110.68000	111.34000	109.66000	110.56000
SUBPS10	3	111.96000	111.52000	109.96000	111.14667
SUBPS20	4	112.64000	112.74000	110.74000	112.04000
SUBPS40	5	116.84000	110.24000	111.24000	112.77333
SUBPS60	6	115.22000	113.92000	116.56000	115.23333
SUBPS80	7	111.12000	112.96000	115.00000	113.02667
SUBPSC	8	111.76000	118.04000	114.96000	114.92000
SUBPS12	9	112.40000	116.24000	120.08000	116.24000
MARGINAL		112.35111	113.12444	113.19111	112.88889
COUNT		50	50	50	150

STANDARD DEVIATIONS FOR 6-TH DEPENDENT VARIABLE

COND	= R	HI	LO	P
SUBPS0	1	11.27252	13.22434	13.07941
SUBPS5	2	12.35931	12.34142	14.98518
SUBPS10	3	11.14278	11.73559	11.24488
SUBPS20	4	11.64397	12.37643	15.05203
SUBPS40	5	14.80259	12.34629	13.73742
SUBPS60	6	12.12063	10.52856	13.57092
SUBPS80	7	14.09681	10.64637	12.82377
SUBPSC	8	11.84002	11.74206	13.56008
SUBPS12	9	12.44088	12.70475	17.88380

VARIABLE 6: SUPINE SYSTOLIC BLOOD PRESSURE

ANALYSIS OF VARIANCE FOR 6-TH DEPENDENT VARIABLE - SUBPS0 SUBPS5 SUBPS10 SUBPS20 SUBPS40 SUBP
SUBPS12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	17204248.00000	1	17204248.00000	17563.70898	.000
C	196.21875	2	98.10937	.10016	.905
ERROR	143991.48047	147	979.53387		
R	5709.95410	8	713.74426	11.09191	.000
RC	4572.07422	16	285.75464	4.44076	.000
ERROR	75673.48242	1176	64.34820		

VARIABLE 7: SUPINE DIASTOLIC BLOOD PRESSURE

CELL MEANS FOR 7-TH DEPENDENT VARIABLE

COND	R	HI	LO	P	MARGINAL
SUBPD0	1	66.52000	69.36000	67.96000	67.94667
SUBPD5	2	69.66000	71.08000	69.16000	69.96667
SUBPD10	3	70.32000	72.04000	69.64000	70.66667
SUBPD20	4	72.08000	72.44000	69.00000	71.17333
SUBPD40	5	72.12000	69.60000	67.28000	69.66667
SUBPD60	6	66.32000	68.44000	63.88000	66.21333
SUBPD80	7	64.20000	67.88000	64.52000	65.53333
SUBPDC	8	68.44000	72.76000	66.36000	69.18667
SUBPD12	9	69.92000	73.76000	72.04000	71.90667
MARGINAL		68.84222	70.81778	67.76000	69.14000
COUNT		50	50	50	150

STANDARD DEVIATIONS FOR 7-TH DEPENDENT VARIABLE

COND	R	HI	LO	P
SUBPD0	1	11.31234	9.49707	10.32129
SUBPD5	2	10.15715	10.80597	12.22971
SUBPD10	3	9.50497	9.90147	9.62726
SUBPD20	4	10.38020	10.22434	10.91152
SUBPD40	5	13.85882	10.05292	9.86240
SUBPD60	6	11.90685	8.86442	11.10550
SUBPD80	7	11.22133	9.47960	10.70426
SUBPDC	8	11.50184	9.58647	11.55424
SUBPD12	9	11.74532	10.64177	14.10451

VARIABLE 7: SUPINE DIASTOLIC BLOOD PRESSURE

ANALYSIS OF VARIANCE FOR 7-TH DEPENDENT VARIABLE - SUBPD0 SUBPD5 SUBPD10 SUBPD20 SUBPD40 SUBP
SUBPD12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	6453451.75000	1	6453451.75000	10579.21545	.000
C	2163.63477	2	1081.81738	1.77344	.173
ERROR	89671.81055	147	610.01231		
R	5711.99512	8	713.99939	12.70422	.000
RC	1605.79297	16	100.36206	1.78575	.028
ERROR	66093.28320	1176	56.20177		

VARIABLE 8: SUBJECTIVE RATING OF DRUG EFFECT

CELL MEANS FOR 8-TH DEPENDENT VARIABLE

COND	R	HI	LO	P	MARGINAL
DRUGEF0	1	.48000	.64000	1.18000	.76667
DRUGEF5	2	4.16000	4.92000	3.28000	4.12000
DRUGE10	3	5.52000	6.46000	4.76000	5.58000
DRUGE20	4	3.88000	7.16000	5.84000	5.62667
DRUGE40	5	2.96000	6.04000	3.38000	4.12667
DRUGE60	6	5.46000	8.70000	4.50000	6.22000
DRUGE80	7	3.94000	8.74000	5.06000	5.91333
DRUGEC	8	2.50000	6.34000	4.78000	4.54000
DRUGE12	9	2.48000	4.84000	2.50000	3.27333
MARGINAL		3.48667	5.98222	3.92000	4.46296
COUNT		50	50	50	150

STANDARD DEVIATIONS FOR 8-TH DEPENDENT VARIABLE

COND	R	HI	LO	P
DRUGEF0	1	1.11098	2.45581	4.19275
DRUGEF5	2	9.24134	8.23343	6.54042
DRUGE10	3	11.57802	10.11406	9.88414
DRUGE20	4	10.23328	12.23137	11.35756
DRUGE40	5	8.14902	12.45721	7.35372
DRUGE60	6	11.29423	14.77484	8.46180
DRUGE80	7	8.11250	15.12102	10.19686
DRUGEC	8	4.77902	13.37620	10.33972
DRUGE12	9	5.36519	12.64808	6.29626

VARIABLE 8: SUBJECTIVE RATING OF DRUG EFFECT

ANALYSIS OF VARIANCE FOR 8-TH DEPENDENT VARIABLE - DRUGEF0 DRUGEF5 DRUGE10 DRUGE20 DRUGE40 DRUGE
DRUGE12

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	26889.33398	1	26889.33398	59.87049	.000
C	1600.25098	2	800.12549	1.78152	.172
ERROR	66021.37695	147	449.12301		
R	3466.07812	8	433.25977	8.52578	.000
RC	776.41309	16	48.52582	.95490	.505
ERROR	59761.48047	1176	50.81258		

VARIABLE 9: SUBJECTIVE RATING OF "GOOD" EFFECTS

CELL MEANS FOR 9-TH DEPENDENT VARIABLE

COND	R	HI	LO	P	MARGINAL
GOOD0	1	2.02000	1.06000	2.38000	1.82000
GOOD5	2	5.16000	4.36000	6.00000	5.17333
GOOD10	3	5.74000	6.14000	6.84000	6.24000
GOOD20	4	4.44000	5.70000	7.38000	6.03333
GOOD40	5	4.20000	4.98000	5.16000	4.78000
GOOD60	6	4.16000	5.10000	4.70000	4.65333
GOOD80	7	4.66000	6.06000	3.92000	4.88000
GOODC	8	3.08000	4.68000	5.10000	4.28667
GOOD120	9	4.12000	3.90000	3.92000	3.98000
MARGINAL		4.17556	4.67333	5.10000	4.64963
COUNT		50	50	50	150

STANDARD DEVIATIONS FOR 9-TH DEPENDENT VARIABLE

COND	R	HI	LO	P
GOOD0	1	8.02926	3.38309	8.80141
GOOD5	2	11.82588	11.27895	12.93469
GOOD10	3	11.71047	12.74716	14.79156
GOOD20	4	9.87712	12.96981	15.33123
GOOD40	5	10.11566	11.83128	12.15270
GOOD60	6	8.91767	10.82938	10.98282
GOOD80	7	12.10938	13.85701	10.39199
GOODC	8	8.63746	11.84498	10.90076
GOOD120	9	10.80370	12.64951	10.49556

Variable 9: Subjective Rating of "Good" Effects

ANALYSIS OF VARIANCE FOR 9-TH DEPENDENT VARIABLE - GOOD0 GOOD5 GOOD10 GOOD20 GOOD40 GOOD.
GOOD120

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	29185.70898	1	29185.70898	34.55958	.000
C	192.66309	2	96.33154	.11407	.892
ERROR	124142.12500	147	844.50425		
R	2006.28027	8	250.78503	6.34792	.000
RC	534.30615	16	33.39413	.84528	.634
ERROR	46452.83496	1176	39.50666		

VARIABLE 10: SUBJECTIVE RATING OF "BAD" EFFECTS

CELL MEANS FOR 10-TH DEPENDENT VARIABLE

COND	R	HI	LO	P	MARGINAL
BAD0	1	.52000	.92000	1.18000	.87333
BAD5	2	2.26000	2.68000	2.80000	2.58000
BAD10	3	2.10000	3.32000	5.46000	3.62667
BAD20	4	2.28000	3.68000	5.90000	3.95333
BAD40	5	1.02000	3.54000	3.68000	2.74667
BAD60	6	2.38000	5.58000	4.96000	4.30667
BAD80	7	1.58000	7.32000	4.94000	4.61333
BADC	8	1.98000	4.34000	5.00000	3.77333
BAD120	9	1.88000	3.48000	2.68000	2.68000
MARGINAL		1.77778	3.87333	4.06667	3.23926
COUNT		50	50	50	150

STANDARD DEVIATIONS FOR 10-TH DEPENDENT VARIABLE

COND	R	HI	LO	P
BAD0	1	1.29741	2.97500	4.41098
BAD5	2	6.44541	6.62845	6.47444
BAD10	3	5.87714	7.88809	11.07158
BAD20	4	6.03067	9.83214	11.45221
BAD40	5	1.88971	7.15488	8.91786
BAD60	6	8.57831	10.68298	9.40030
BAD80	7	3.70928	14.15575	10.90106
BADC	8	6.06256	10.29684	10.88530
BAD120	9	6.66590	10.36918	7.18967

VARIABLE 10: SUBJECTIVE RATING OF "BAD" EFFECTS

ANALYSIS OF VARIANCE FOR 10-TH DEPENDENT VARIABLE -- BAD0 BAD5 BAD10 BAD20 BAD40 BAD60 BAD120

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	14165.22002	1	14165.22002	44.64634	.000
C	1450.16113	2	725.08057	2.28532	.105
ERROR	46639.75781	147	317.27726		
R	1584.04395	8	198.00549	5.29571	.000
RC	851.32910	16	53.20807	1.42306	.122
ERROR	43970.38037	1176	37.38278		

VARIABLE 11: SUBJECTIVE RATING OF "DRUG LIKING"

CELL MEANS FOR 11-TH DEPENDENT VARIABLE

COND	R	HI	LO	P	MARGINAL
LIKE0	1	29.28000	30.74000	30.78000	30.26667
LIKE5	2	29.36000	31.22000	29.74000	30.27333
LIKE10	3	29.68000	31.46000	28.76000	29.96667
LIKE20	4	29.36000	30.80000	27.74000	29.30000
LIKE40	5	30.08000	31.26000	29.20000	30.18000
LIKE60	6	29.48000	28.76000	29.96000	29.40000
LIKE80	7	30.78000	28.68000	28.84000	29.43333
LIKEC	8	29.08000	31.50000	28.52000	29.70000
LIKE120	9	30.22000	31.40000	29.06000	30.22667
MARGINAL		29.75778	30.64667	29.17778	29.86074
COUNT		50	50	50	150

STANDARD DEVIATIONS FOR 11-TH DEPENDENT VARIABLE

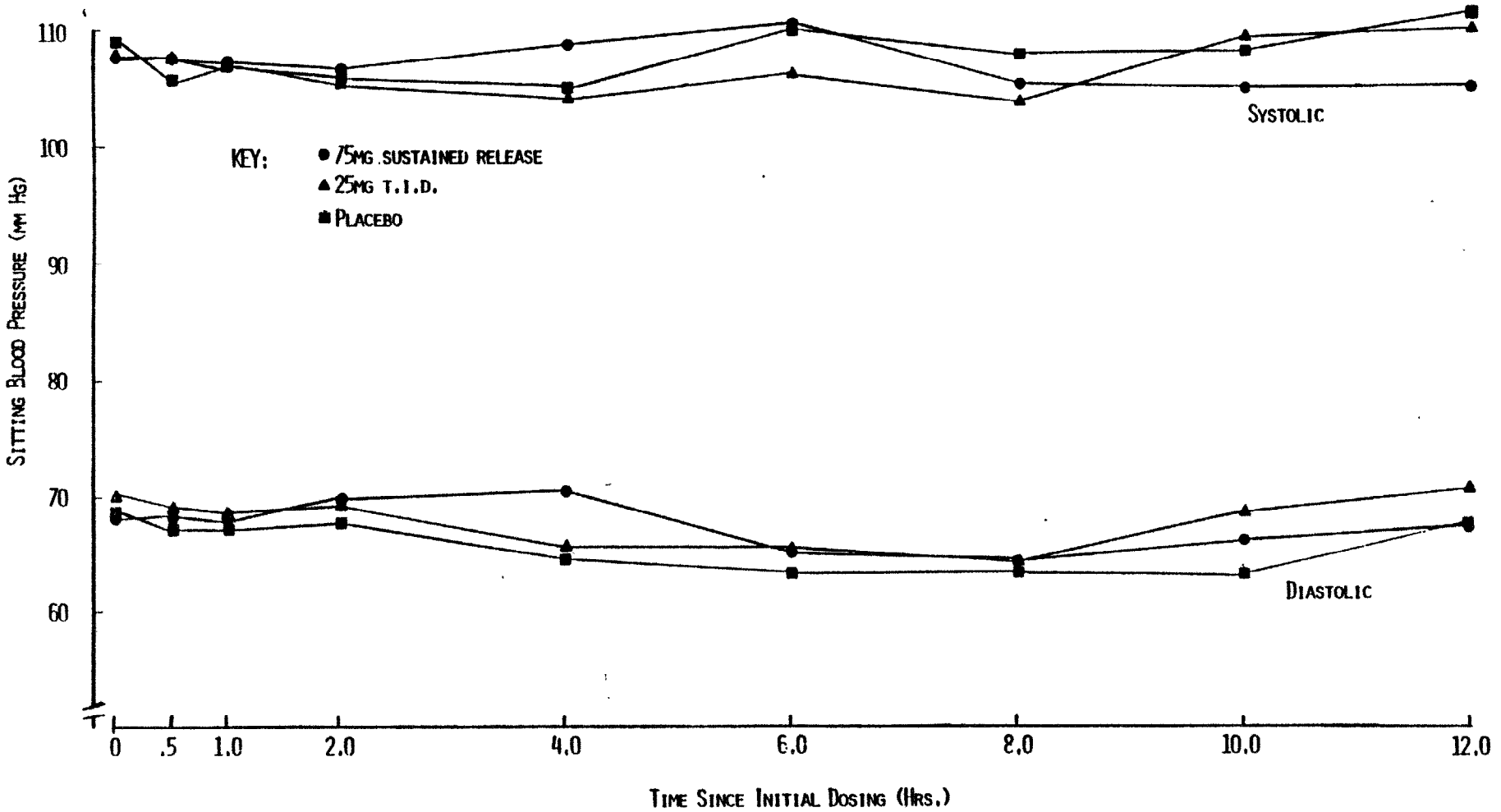
COND	R	HI	LO	P
LIKE0	1	6.89584	4.74152	7.98031
LIKE5	2	7.68250	8.26670	7.23881
LIKE10	3	7.50901	7.66974	7.88064
LIKE20	4	6.73934	6.78834	7.29696
LIKE40	5	8.29024	10.53625	9.06440
LIKE60	6	8.38424	9.72596	12.50463
LIKE80	7	7.75200	9.94154	10.69114
LIKEC	8	7.27263	11.02548	12.79866
LIKE120	9	7.46499	11.39817	12.39554

VARIABLE 11: SUBJECTIVE RATING OF "DRUG LIKING"

ANALYSIS OF VARIANCE FOR 11-TH DEPENDENT VARIABLE - LIKE0 LIKE5 LIKE10 LIKE20 LIKE40 LIKE/
LIKE120

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	MEAN SQUARE	F	PROB. F EXCEEDED
MEAN	1203744.60937	1	1203744.60937	3092.57547	.000
C	492.63037	2	246.31519	.63282	.533
ERROR	57217.83008	147	389.23694		
R	197.59082	8	24.69885	.58547	.791
RC	738.48047	16	46.15503	1.09407	.355
ERROR	49411.23584	1176	42.18642		

FIGURE 1: SITTING BLOOD PRESSURE OVER THE COURSE OF A DAILY SESSION



Study

Key:

- ● 25 mg sustained release
- ▲ 25 mg T.I.D.
- ■ Placebo

SUMMARY OF MOOD EFFECTS OF PPA

I.D. DATE NAME

Mark the Line to Indicate How You Feel:

Hour/Time	Are there any drug effects? (None – A lot)	Are there good effects? (None – A lot)	Are there any bad effects? (None – A lot)	Do you like or dislike the effects? (Dislike – Neutral – Like)
0				
5				
1				
2				
4				
6				
8				
10				
12				