

Nixon, Hargrave, Devans & Doyle

Attorneys and Counselors at Law

A PARTNERSHIP INCLUDING PROFESSIONAL CORPORATIONS

SUITE 1200, 1090 VERMONT AVENUE, N.W.

WASHINGTON, D. C. 20005

(202) 842-3600

BY HAND

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

ONE ROCKEFELLER PLAZA
NEW YORK, NEW YORK 10020
(212) 586-4100
CABLE: NIXONHARG NEW YORK
TELEX: 60521

247 ROYAL PALM WAY
POST OFFICE BOX 1027
PALM BEACH, FLORIDA 33460
(305) 659-6255

SUITE 510
1001 U.S. HIGHWAY ONE
JUPITER, FLORIDA 33458
(305) 746-1002

January 6, 1983

Dockets Management Branch [HFA-305]
Food and Drug Administration
Room 4-62
5600 Fishers Lane
Rockville, Maryland 20857

Re: Weight Control Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; Advance Notice of Proposed Rulemaking, 47 Fed. Reg. 8466 et seq. (February 25, 1982), Docket NO. 81N-0022

Dear Sir:

Pursuant to the request of the agency in the preamble to the above-referenced Advance Notice of Proposed Rulemaking for further studies regarding the safety of phenylpropanolamine hydrochloride for use in weight control products, enclosed please find a recently-completed study conducted at Johns Hopkins University Medical School, as well as a transmittal letter from Dr. Edward L. Steinberg, Vice Chairman of the Board of Thompson Medical Company, Inc.

Sincerely,

 Stephen Kurzman, P.C.

Stephen Kurzman, P.C.

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encs.

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
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: 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
(301) 997-0880

Date: December 6, 1982

TABLE OF CONTENTS

ABSTRACT	
INTRODUCTION	1
INVESTIGATIVE METHODS	1
Subjects	1
Design and Procedure	2
1. Addiction Research Center Inventory (ARCI)	2
2. Profile of Mood States (POMS)	3
Statistical Analysis	4
RESULTS	4
Parallel Groups Design	4
Crossover Design	6
DISCUSSION	9
REFERENCES	12

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 treatment 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 or 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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