



May 9, 1984

William E. Gilbertson, Pharm. D.
Director
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Center for Drugs and Biologics
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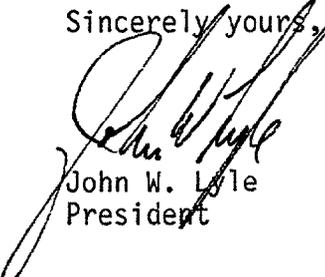
Dear Dr. Gilbertson:

During our meeting of April 24 we committed to provide you with a protocol for a phenylpropanolamine dose response study to determine the effect of phenylpropanolamine on blood pressure. Enclosed are three copies of a draft protocol of a blood pressure dose response study. Would you please assure that Dr. Raymond Lipicky receives one of the copies and has an opportunity to review and comment on it.

As soon as you and Dr. Lipicky have reviewed the protocol we would welcome an opportunity to meet with you to discuss your suggestions and comments. As soon as we have obtained FDA's concurrence in its design we will implement the study promptly.

I am requesting that Bob Pinco contact your office during the week of May 21 to arrange a mutually convenient date for a meeting to discuss the protocol.

Sincerely yours,



John W. Lyle
President

JWL:ls

PPA Dose-Blood Pressure Response Study

1. Brief Description of Study and Statement of Objectives:

The study will be conducted in 3 phases:

Phase I: This will be a placebo-controlled, rising oral dose titration with phenylpropanolmine (PPA), administered orally, conducted in 20 healthy, clearly normotensive (according to the criteria described under Baseline BP Screening below) normobaric (within -5 to +15% of the lower and upper weight limits, respectively, for height defined in the 1983 Metropolitan Life Insurance Company Tables) subjects (10 male and 10 female) between the ages of 20 and 45. The titration will proceed using single oral PPA doses of 12.5, 25, 50, 75, 100, 150 and 200 mg. Each titration step will involve 2 treatment days (separated by at least 1 non-drug day). On the first of these days, each of which will require about 10 inpatient hours, subjects will be randomized in a double-blind manner to either placebo or PPA, and on the second treatment day, after a 1-day washout, will receive the alternate regimen. BP and pulse rate will be measured in supine and standing positions at 0, 1/2, 1, 2, 3, 4, 5, 6, 7 and 8 hours post-dosing and blood will be drawn at 0, 1, 2, 3 and 4 hours post-dosing for estimation of blood PPA levels (venipuncture must follow BP determinations). The titration endpoint will be either that

PPA dose which produces a peak increase in SDBP from baseline of 25% (PPA⁺²⁵), or 200 mg.

The studies in this phase are designed to generate a PPA dose-blood pressure response curve.

Phase II: This phase will consist of 3 weeks of t.i.d. out-patient administration of the dose of PPA which, during Phase I, caused a peak increase in SDBP of 10% over baseline (PPA⁺¹⁰). The drug will be given as an immediate release capsule. Patients will be seen weekly during this phase and at these weekly visits BP and pulse rate will be monitored at 0, 3, 4, and 5 hours after the PPA dose and blood will be drawn for estimation of PPA concentrations at these points.

The studies in this phase are designed to determine whether BP response to a vasoactive dose of PPA changes with repeated dosing and whether the drug accumulates

Phase III: In this phase patients who have completed Phase II will undergo a single dose rechallenge with the maximal dose of PPA used in Phase I. In this phase BP will be measured at 0, 1/2, 1, 2, 3, 4, 5, 6, 7, and 8 hours post-dosing and blood will be drawn for PPA levels at 0, 1, 2, 3, 4 hours post-dosing. Again, blood-lettings must follow BP determinations.

The study in this phase is designed to determine whether chronic treatment with a vasoactive dose of PPA results in development of tolerance to the effects of a dose of the drug which produced significant BP elevations in Phase I.

2. Selection of Study Population:

A. Inclusion Criteria:

1. Age 20-45.
2. Weight within -5% and +15% of the lower and upper limits, respectively, for height as defined in the 1983 Metropolitan Life Insurance Company Tables.
3. Ability to read, comprehend and willingness to sign the informed consent form.
4. Availability for the duration of the study.
5. Ability to understand and adhere to the requirements of the protocol.
6. Willingness to abstain from coffee, tea, and all other methylxanthine-containing beverages or food--e.g., Coca Cola and chocolate), tobacco, alcohol and all drugs and dietary or vitamin supplements for the duration of the study.

B. Exclusion Criteria:

1. Fixed need for any drug therapy.
2. Current cardiovascular, pulmonary, gastrointestinal, genito-urinary, hematological, musculoskeletal, neurological or endocrine disease.

3. Prior history of significant cardiovascular, pulmonary, gastrointestinal, genito-urinary, hematological, musculoskeletal or neurological disease.
4. Family history of significant hypertension, cardiovascular disease, cerebrovascular accident, subarachnoid hemorrhage, intracranial aneurysm, arterio-venous malformation or brain tumor.
5. Significant abnormality on physical examination.
6. Significant abnormality on laboratory screen (as described in Appendix A), or chest x-ray.
7. Known allergy or adverse reaction to PPA or similar drug (or any decongestant or diet pill).

3. Baseline BP Screening:

The screening procedure will be carried out over 1 week. Subjects who qualify for the entry into the study on the basis of the inclusion and exclusion criteria defined above will, after a 10 min. rest, have BP and pulse rate measurements in supine and standing positions made 3 times (with the readings separated by 5 min) at 8 AM and 4 PM on Monday, Wednesday and Friday of 1 week. Korotkoff Phase 5 will be used as the measure of DBP. BP's and pulse rates at each time (8AM and 4PM) for each day are defined as the means of the 3 measurements for SBP and DBP.

In order to qualify for entry into the dose-titration phase of the study, the mean BP's (as defined above) for both times for each of the 3 days on which measurements are made must be between 95 and 127 mmHg for SBP and between 60 and 81 mmHg for DBP in both standing and supine positions.

Timing of observations for the BP screening period is summarized diagrammatically in Fig. 1.

4. Phase I:

A. Study Procedure:

Subjects qualifying for entrance into the study on the basis of results of the screening examinations outlined above will begin a titration procedure. As described previously, each step of the titration consists of 2 "treatment" days separated by at least one intervening "washout" day. For each of the steps (Step 1 = 12.5 mg PPA, Step 2 = 25 mg PPA, Step 3 = 50 mg PPA, Step 4 = 75 mg PPA, Step 5 = 100 mg PPA, Step 6 = 150 mg PPA and Step 7 = 200 mg PPA) subjects will be randomized in a double-blind manner to a first in-hospital treatment day of either PPA or placebo. After an out-patient washout period of at least 24 hours the alternate regimen will be administered on a second in-hospital treatment day. On both treatment days, supine and standing blood pressures and pulse rate will be measured 3 times with 5 min. periods intervening between measurements, prior to dosing and at 1/2, 1, 2, 3, 4, 5, 6, 7 and 8 hours post-dosing. Seven ml samples of venous blood will be obtained for estimates of PPA concentrations at baseline, 1, 2, 3, and 4 hours post-dosing. Blood-lettings must follow BP measurements. Blood pressures and pulse rates at each timepoint will be defined as the means of the 3 measurements made at each timepoint.

Subjects will proceed through the sequence of steps, receiving a higher dose of PPA at each succeeding step, unless a 25% increase in supine DBP from baseline is encountered at any post-dosing point, in association with a 10% increase in supine DBP from baseline in either the preceding or subsequent hourly BP measurement (PPA⁺²⁵). The interval separating titration steps must be at least 24 hours.

After the subject's last titration step, blood will be drawn for the laboratory screen detailed in Appendix A.

B. Withdrawal Criteria and Procedures for Handling Adverse Reactions during Phase I:

1. Withdrawal Criteria

- i. DBP at any position 110 mm Hg or higher or SBP in any position exceeding 170 mm Hg.
- ii. Pulse rate >130/min or <50/min.
- iii. Irregular pulse.
- iv. Sustained chest discomfort.
- v. Headache
- vi. Visual disturbance.
- vii. Seizure.
- viii. Paraesthesia or weakness, either generalized or localized.

ix. Any other neurological disturbance considered by the monitoring investigator to be of severity sufficient to prompt withdrawal of subject from the study.

x. Nausea and/or vomiting.

xi. Feelings of depersonalization.

2. Procedures for Handling Adverse Reactions during Phase I:

Any subject who is withdrawn from the study for an adverse reaction will be hospitalized immediately, cardiac monitoring begun, a 12-lead ECG obtained, q.1/2 h. monitoring of supine blood pressure instituted, a complete physical examination carried out and blood for the screen detailed in Appendix A obtained. Cardiac monitoring and monitoring of blood pressure will continue until the patient's vital signs have returned to within the normal range and the reaction prompting withdrawal from the study has subsided completely. Subjects withdrawn from the study for an adverse reaction will remain in-hospital for at least 24 hours after complete resolution of the reaction and will be seen and re-examined within 1 week of hospital discharge. At the discretion of the investigator, with permission from CIBA-GEIGY medical staff and after obtaining informed consent, a carefully monitored, in-hospital PPA rechallenge with the dose of the drug temporally associated with the adverse reaction may be considered.

5. Phase II:

Phase II will involve 3 weeks of open, t.i.d. outpatient dosing with an immediate release capsule formulation of PPA in either the dose found in Phase I to produce a 10% increase in supine DBP over baseline (PPA⁺¹⁰) or 50 mg, whichever is greater. Commencement of dosing with PPA in this phase must be separated from the last step in Phase I by at least 2 days.

During Phase II subjects will be seen weekly. At each visit pill counts will be made, new medication bottles supplied, supine and standing BP's and pulse rate measured (as previously described) 0, 1, 2, 3 and 4 hours after the preceding dose of PPA, and 7 ml samples of venous blood withdrawn at these timepoints for estimations of PPA concentrations. Venipunctures must follow BP determinations.

Data from subjects found to have used less than 80% or more than 120%, of prescribed PPA for any weekly period will not be included in the primary effectiveness analysis for this phase, but such subjects will be eligible for participation in Phase III if compliance has been in the 60-80% range.

Criteria for withdrawal of subjects from this phase of the study, and procedures for attention to withdrawn patients will be those outlined in Section 4 (Phase I) above.

Timing of observations and interventions for a typical titration step are summarized diagrammatically in Fig. 2.

6. Phase III:

This phase of the study consists of a rechallenge of subjects with a single administration of the PPA⁺²⁵ dose. Because this phase is designed to assess the possibility that tolerance to the hypertensive effects of PPA may develop, the rechallenge must be carried out on the day following the last day of Phase II.

Standing and supine BP's and pulse rate will be measured as previously described prior to and 1/2, 1, 2, 3, 4, 5, 6 and 8 hours after oral administration of the PPA⁺²⁵ dose in solution. Seven ml samples of venous blood will be obtained at the 0, 1, 2, 3 and 4 hour post-dosing timepoints. Venipunctures must follow BP measurements.

Criteria for withdrawal of the subject during this phase and procedures for attention to withdrawn subjects are as described for Phase I in Section 4B above.

7. Follow-up Visit:

All subjects must be seen within 1 week of departure from the study, regardless of whether the departure was prompted by adverse reaction or merely followed completion of the protocol-prescribed interventions and observations. At this visit a review of systems will be obtained and physical examination carried out. In addition, blood and urine will be collected for the laboratory screen described in Appendix A.

Appendix A

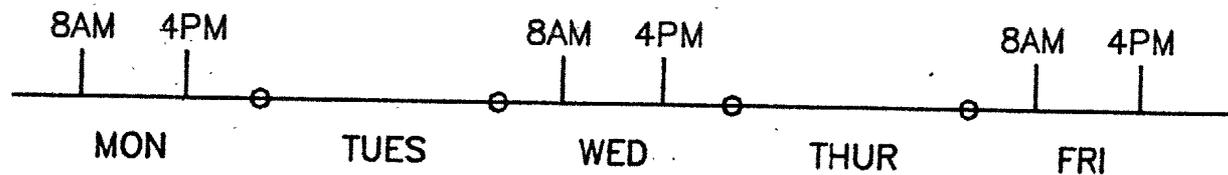
Laboratory Screen:

CBC, electrolytes, BUN, creatinine, FBS, Alb, Glob, PO₄,
CPK, Ca⁺⁺, AST, ALT, total bilirubin, alkaline
phosphatase, GGT, T3, T4, 12-lead ECG, urinalysis.

FIG. 1

B.P. SCREENING:

B.P. MEASUREMENTS
(3 X SPACED 5 MIN.
APART, SUPINE
AND STANDING)



PRESSURES DEFINED AS THE MEANS OF THE 3 MEASUREMENTS FOR EACH TIMEPOINT.

ENTRANCE CRITERION FOR PHASE I:

$95 < \text{SBP} < 127 \text{mm Hg}$ and $60 < \text{DBP} < 81 \text{mm Hg}$
IN BOTH POSITIONS AT BOTH TIMEPOINTS ON
ALL 3 DAYS.

FIG. 2

PHASE I: DOSING, AND, OBSERVATION SCHEDULE FOR A TITRATION STEP

