MEMORANDUM OF A MEETING

December 2, 1983
1:30 pm

BETWEEN: FDA PERSONNEL
Robert Temple, M.D. (HFN-100)
Raymond Lipicky, M.D. (HFN-110)
Philip Dern, M.D. (HFN-110)
William E. Gilbertson, Pharm. D. (HFN-510)
Saul Bader, Ph. D. (HFN-513)
Helen Cothran (HFN-513)
Dennis Myers, R.Ph. (HFN-514)
John Short, R.Ph. (HFN-514)

and

THOMPSON MEDICAL COMPANY REPRESENTATIVES
Daniel Abraham
Chairman of the Board
Edward Steinberg, O.D.
Vice Chairman of the Board
William Waggoner, Ph. D.
Vice President & Director, Research & Development
Robert Marlin, Ph. D.
Director, Clinical Testing
Matthew Bradley, M.D.
Miami Heart Institute
Brent R. Ekins, Pharm. D.
Intermountain Regional Poison Control Center
Frank Funderburk, M.D.
Antech, Inc./Johns Hopkins University
Harold Silverman, D.Sc.
Massachusetts College of Pharmacy

SUBJECT: Discontinued Phenylpropanolamine Safety Study

Thompson Medical Company had been requested (see memorandum of telephone conversation between Mr. John R. Short and Mr. Daniel Abraham dated November 7, 1983) to make available to FDA data from a high-dose phenylpropanolamine safety study that had been performed at Johns Hopkins University and prematurely discontinued. Subsequently, Thompson agreed to present the data at this meeting and leave a submission with us.

Dr. Frank Funderburk presented the results of the study in which 24 normotensive subjects (3 groups of 8 each) received either 150 mg (2-75 mg capsules) of sustained-release phenylpropanolamine in one dose; 50 mg (2-25 mg capsules) of immediate-release phenylpropanolamine three times daily; or a placebo capsule three times daily. Blood pressure, pulse, and mood were observed over a 12-hour period. The study was designed to include many more patients but when patient #19 developed higher-than-expected blood pressure readings, the study was prematurely discontinued. All data developed to that point in time is included in the attached submission. In addition, blood pressure was monitored in patient #19 subsequent to the above episode but no medication was given; these results are also included in the submission.

Time was also allocated for presentation of another study by Thompson performed subsequent to the one described above. Dr. Harold Silverman reported the results of a safety study conducted on 17 healthy subjects who ingested two 75 mg sustained-release capsules of phenylpropanolamine in one dose. Blood pressure, pulse, and mood were observed over a 12-hour period. The results of this study are also attached.

Dr. Matthew Bradley, a cardiologist, briefly mentioned his ongoing study with patients who are obese and hypertensive. They are receiving a sustained-release 75 mg phenylpropanolamine capsule once a day. Dr. Bradley noted that he has not seen any adverse reactions, but he has noticed a lowering of blood pressure in patients because of the weight loss.

It was mutually agreed that the minutes of the meeting could be made public as part of the OTC Drug Review feedback policy.

John R. Short

John R. Short, R.Ph.

Attachments (2)

Effects of High Doses of Phenylpropanolamine on Blood Pressure, Pulse, and Mood

Testimony of

Frank R. Funderburk
Director, Clinical Consulting
Antech, Inc.

To

Food and Drug Administration

December 2, 1983

Effects of High Doses of Phenylpropanolamine on Blood Pressure, Pulse, and Mood

Frank R. Funderburk
Director, Clinical Consulting
Antech, Inc.

Introduction

Thank you. For the past two years, in response to the FDA's request for information, our firm - in collaboration with the Behavioral Pharmacology Research Unit at the Johns Hopkins University - has been studying the effects of phenylpropanolamine HCL (PPA) on a variety of physiological and psychological parameters. Our first study - which was reported to the Agency in October, 1982 - investigated the effects of a 75 mg sustained release product and a 25 mg T.I.D. dosing regimen in comparison with placebo. One hundred fifty subjects were studied. No significant effects on blood pressure, pulse, or mood were observed. No evidence of euporogenic or amphetamine-like effects were noted on standardized measures of subjective drug effect. This result was replicated in a crossover study (using 59 subjects) which compared 75 mg sustained release product with placebo. This study was also submitted to the Agency early in 1983. Subsequent studies at the University of California and the University of Washington, using a total of 441 subjects, also found no clinically significant effects associated with PPA at the 75 mg dose.

THE STUDY I WILL DESCRIBE TODAY WAS UNDERTAKEN TO EXTEND OUR UNDERSTANDING OF THE EFFECTS OF PPA AT DOSES HIGHER THAN THOSE RECOMMENDED FOR OVER-THE-COUNTER USE IN THIS COUNTRY.

SUMMARY

TWENTY-FOUR (24) HEALTHY NORMOTENSIVE VOLUNTEERS (MEAN AGE = 25.8) 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 - 150 MG SUSTAINED RELEASE (ADMINISTERED AS TWO 75 MG SUSTAINED RELEASE CAPSULES) AND 50 MG T.I.D. (ADMINISTERED AS TWO 25 MG CAPSULES) IN COMPARISON WITH PLACEBO. SUBJECTS WERE RANDOMLY ASSIGNED TO ONE OF THE THREE DRUG TREATMENT CONDITIONS. SUBJECTS IN ONE GROUP (GROUP A) RECEIVED TWO 75 MG SUSTAINED RELEASE DOSES ON THEIR FIRST MEDICATION OCCASION AND TWO PLACEBO CAPSULES AT EACH OF THE OTHER TWO DOSING OCCASIONS. SUBJECTS IN ANOTHER GROUP RECEIVED TWO 25 MG CAPSULES AT EACH MEDICATION OCCASION (GROUP B). SUBJECTS IN THE OTHER GROUP (GROUP C) RECEIVED TWO PLACEBO CAPSULES AT EACH MEDICATION OCCASION. SUBJECTS WERE STUDIED FOR A 12 HOUR TESTING SESSION.

MEASUREMENTS OF BLOOD PRESSURE (STANDING AND SUPINE), PULSE AND SUBJECTIVE DRUG EFFECTS ("MOOD") WERE OBTAINED 11 TIMES DURING THE SESSION AT BASELINE (PRIOR TO DRUG ADMINISTRATION) AND AT 1/2 HR, 1 HR, 2 HR, 4 HR, 4 1/2 HR, 6 HR, 8 HR, 8 1/2 HR, 10 HR, AND 12 HR POST INITIAL DOSING.

MIXED DESIGN ANALYSIS OF VARIANCE REVEALED NO MAIN EFFECTS FOR DRUG TREATMENTS ON MEASURES OF EITHER STANDING OR SUPINE SYSTOLIC BLOOD PRESSURE.

STANDING AND SUPINE DIASTOLIC MEASURES DID, HOWEVER, INDICATE A RELIABLE DRUG EFFECT. PULSE WAS NOT AFFECTED BY DRUG CONDITION BUT DID SHOW NORMAL CIRCADIAN VARIATIONS IN BOTH STANDING AND SUPINE BODY POSITIONS. FURTHER EXAMINATION OF THE DATA SUGGESTED THAT THE OVERALL ANALYSIS OF DIASTOLIC BLOOD PRESSURE MAY HAVE OVERSTATED THE DIFFERENCES BETWEEN GROUPS DUE TO DIFFERENCES IN BASELINE DIASTOLIC BLOOD PRESSURE PRIOR TO DRUG ADMINISTRATION. ANALYSIS OF PEAK CHANGE VALUES (CHANGE FROM BASELINE) REVEALED THAT ONLY THE MEASURE OF SUPINE DIASTOLIC BLOOD PRESSURE WAS RELIABLY DIFFERENT FROM PLACEBO (PEAK DIFFERENCE = 12.0 FOR 150 MG SR; 8.88 FOR 50 T.I.D.). EVEN IN THESE ANALYSES THE EFFECT MAY HAVE BEEN EXAGGERATED BY ATYPICAL RESPONSES OF A FEW INDIVIDUALS IN SUCH A SMALL SAMPLE STUDY. ANALYSIS OF MOOD EFFECTS INDICATED NO EUPHOROGENIC OR AMPHETAMINE-LIKE EFFECTS.

ALTHOUGH THE BLOOD PRESSURE CHANGES OBSERVED IN THIS STUDY ARE LARGER THAN THOSE SEEN WITH APPROVED DOSES OF PPA, THEIR MAGNITUDE IS WITHIN THE RANGE OBSERVED IN SIMILAR PATIENT POPULATIONS UNDER PLACEBO TREATMENT CONDITIONS. FURTHER, THESE INCREASES ARE SMALLER THAN THOSE ASSOCIATED WITH A NUMBER OF COMMON LIFE EXPERIENCES, SUCH AS DRINKING COFFEE. THE RESULTS OF THE PRESENT STUDY, IN COMBINATION WITH PREVIOUS FINDINGS AND DR. SILVERMAN'S RECENTLY COMPLETED STUDY, DO NOT SUGGEST ANY UNIQUE HYPERTENSIVE RISK DUE TO PPA, EVEN IN DOSES DOUBLE THOSE CURRENTLY AVAILABLE FOR OVER-THE-COUNTER SALE.

RESULTS

SPECIFIC RESULTS FOR THE VARIOUS MEASURES TAKEN FOLLOW:

STANDING PULSE TENDED TO BE MORE RAPID DURING THE MIDDLE PORTION OF THE SESSION FOR SUBJECTS IN ALL TREATMENT GROUPS (MEAN DIFFERENCE = 7 BPM, $F = 3.53$, $p < .05$).

SUPINE PULSE TENDED TO BE HIGHEST AT THE BEGINNING AND END OF THE SESSION FOR MOST SUBJECTS (MEAN DIFFERENCE - 12.5 BPM, $F = 7.26$, $p < .01$). NO MAIN EFFECTS FOR OR INTERACTIONS WITH DRUG TREATMENT GROUP WERE IDENTIFIED.

STANDING SYSTOLIC BLOOD PRESSURE DID NOT SHOW ANY STATISTICALLY RELIABLE EFFECTS FOR DRUG TREATMENT OR MEASUREMENT OCCASION.

STANDING DIASTOLIC BLOOD PRESSURE WAS HIGHER FOR SUBJECTS WHO RECEIVED THE ACTIVE DRUG TREATMENTS AS COMPATED WITH THOSE WHO RECEIVED THE PLACEBO ($\bar{x} = 81.83, 77.74, 70.00$ FOR 150 MG SR, 50 MG T.I.D., AND PLACEBO GROUPS RESPECTIVELY; $F = 4.88$, $p < .05$). OVERALL, NO STATISTICALLY RELIABLE CHANGES OVER THE COURSE OF THE TIME WERE OBSERVED. THE OVERALL MAIN EFFECT OF DRUG TREATMENT WAS PRESENT HOWEVER EVEN AT BASELINE (PRIOR TO DRUG ADMINISTRATION) SUGGESTING THAT THIS EFFECT IS AT LEAST PARTLY DUE TO BASELINE DIFFERENCES BETWEEN SUBJECTS. THIS INTERPRETATION IS SUPPORTED BY THE ANALYSIS OF CHANGE FROM BASELINE (TABLE 4, APPENDIX 3), IN WHICH NO STATISTICALLY RELIABLE DRUG EFFECTS ARE OBSERVED.

SUPINE SYSTOLIC BLOOD PRESSURE DID NOT SHOW ANY STATISTICALLY RELIABLE EFFECTS FOR DRUG TREATMENT OR MEASUREMENT OCCASION.

SUPINE DIASTOLIC BLOOD PRESSURE WAS HIGHER FOR SUBJECTS WHO HAS RECEIVED THE ACTIVE DRUG TREATMENTS AS COMPARED WITH THOSE WHO RECEIVED THE PLACEBO ($\bar{x} = 78.59, 74.61$, AND 65.85 FOR 150 MG SR, 50 MG T.I.D., AND PLACEBO GROUPS RESPECTIVELY; $F = 4.88$, $p < .05$). OVERALL, NO STATISTICALLY RELIABLE CHANGES OVER THE COURSE OF THE SESSION WERE OBSERVED. DIFFERENCES BETWEEN DRUG TREATMENTS WERE ALSO OBSERVED IN THE ANALYSIS OF CHANGE FROM BASELINE, ALTHOUGH THE RESULT WAS ONLY BARELY RELIABLE ($F = 3.49$. $p < .05$), AS SHOWN IN APPENDIX 3, TABLE 4.

APPENDIX 1 PRESENTS OVERALL MEANS AND STANDARD DEVIATIONS FOR EACH CONDITION AT EACH MEASUREMENT OCCASION. APPENDIX 2 PRESENTS THE OVERALL ANALYSIS OF VARIANCE RESULTS FOR EACH VARIABLE. APPENDIX 3 PRESENTS SUPPLEMENTAL ANALYSES WHICH FOCUS ON PEAK BLOOD PRESSURE EFFECTS. APPENDIX 4 PRESENTS THE RAW DATA FOR EACH SUBJECT STUDIED.

SUBJECTIVE EFFECTS WERE MEASURED USING THE ADDICTION RESEARCH CENTER INVENTORY (ARCI). THIS INVENTORY MEASURED THE SIMILARITY OF PPA EFFECTS TO THOSE OF AMPHETAMINE (AMP) AND OTHER STIMULANTS (BEN) AS WELL AS INDEXING THE DRUGS EUPHORIC (MBG), SEDATIVE (PCAG) AND DYSPHORIC (LSD) EFFECTS. PPA IN EITHER DOSE FORM, DID NOT PRODUCE STIMULANT OR AMPHETAMINE-LIKE EFFECTS. NO EUPHORIC NOR DYSPHORIC EFFECTS FOUND. A RELIABLE OVERALL DIFFERENCE WAS FOUND FOR THE PCAG (SEDATION) SCALE IN WHICH THE 50 MG T.I.D. DOSAGE FORM WAS SLIGHTLY, BUT RELIABLY, LOWER THAN EITHER THE 150 MG SUSTAINED RELEASE DOSE OR PLACEBO ($F = 3.98$, $p < .05$).

Discussion

The results of this study must be interpreted with caution. First, our sample size was very small - with only eight cases per treatment group. Baseline differences in blood pressure, reflecting substantially lower initial values for placebo subjects, further complicate the interpretation. These baseline difference ranged from 5.5 mm Hg for supine diastolic measures (71.9 vs 66.4 mm Hg) to 9.6 mm Hg (117.9 vs 108.3 mm Hg) for standing systolic measures.

Before one can legitimately attribute differences between treatment groups to a drug effect, one must rule out alternative causes of the differences. Case 19 is a good example. When his blood pressure was observed to be higher than expected he was moved from the normal testing area to a more restricted research ward area for more intensive medical monitoring. This change in environmental circumstances could well have resulted in psychological stress accompanied by an increase in blood pressure. Further, it should be noted that when this patient returned for another session - this time with no medication and no change in environmental circumstances - his blood pressure was still quite variable, reaching a peak of 153/98. Even at baseline during the second session this individual showed considerable variability in response to situations such as changes in body position (diastolic standing, 78 mm Hg; diastolic supine 92 mm Hg). In a large sample study such differences may be adequately controlled through random assignment. In a small sample study such as this one, however, one can only speculate as to whether changes observed are an idiosyncratic response to medication or a result of some other unknown patient characteristic such as labile hypertension.

IT IS ALSO USEFUL TO EXAMINE THE PRESENT FINDINGS IN LIGHT OF OUR PREVIOUS EXPERIENCE WITH NORMAL VOLUNTEERS STUDIED IN EXTENDED SESSIONS UNDER PLACEBO. AS I TESTIFIED BEFORE CONGRESS IN JULY AND AUGUST OF THIS YEAR, OUR INITIAL HOPKINS STUDIES NOTED A NUMBER OF CASES OF TRANSIENT BLOOD PRESSURE ELEVATIONS IN SUBJECTS WHO RECEIVED PLACEBO. IN THE 150 SUBJECT STUDY, FOR EXAMPLE, 5 OF 50 CASES ON PLACEBO SHOWED PEAK DIASTOLIC BLOOD PRESSURE READINGS GREATER THAN 94 MM HG, THE HIGHEST BEING 176/116. SLIGHTLY FEWER SUBJECTS IN THE PPA GROUPS (3 AND 4 OF 50 FOR 75 MG SUSTAINED RELEASE AND 25 MG T.I.D. GROUPS) SHOWED THIS RESPONSE, BUT OCCASIONAL HIGH VALUES WERE OBSERVED IN THESE SUBJECTS ALSO.

A RECENTLY COMPLETED ANALYSIS OF CIRCADIAN BLOOD PRESSURE VARIATION IN NORMAL VOLUNTEERS OVER A 12 HOUR PERIOD - USING 73 CASES TREATED ONLY WITH PLACEBO INDICATED AN AVERAGE DIASTOLIC PEAK DIFFERENCE OF 16 MM HG OVER THE COURSE OF THE SESSION, WITH A STANDARD DEVIATION OF 5.9 MM HG. THIS MEANS THAT A PEAK CHANGE FROM, SAY, A MINIMUM OF 80 MM HG TO 96 MM HG WOULD NOT BE UNEXPECTED. I SHOULD NOTE THAT EVEN THE HIGHEST BLOOD PRESSURE READINGS IN THE PRESENT STUDY WERE WITHIN THIS RANGE OF VARIABILITY. THIS STUDY WAS CONDUCTED AT THE UNIVERSITY OF WASHINGTON, BUT ITS RESULTS ARE QUITE CONSISTENT WITH OUR CLINICAL EXPERIENCE AT THE HOPKINS SITE. EVEN SEEMINGLY INNOCUOUS NORMAL LIFE EVENTS SUCH AS DRINKING COFFEE CAN HAVE SUPRISINGLY LARGE EFFECTS ON BLOOD PRESSURE. A RECENT REPORT IN THE HARVARD MEDICAL SCHOOL HEALTH LETTER (AUGUST, 1983), FOR EXAMPLE, NOTED THAT "THE EQUIVALENT OF 2-3 CUPS OF COFFEE RAISES BLOOD PRESSURE OF NORMAL PEOPLE AN AVERAGE OF 14/10 (SYSTOLIC/DIASTOLIC) POINTS-ENOUGH TO BRING MANY OF THEM INTO THE RANGE OF 'MILD' HYPERTENSION - AND THIS INCREASE CAN LAST AS LONG AS THREE HOURS." THAT SAME REPORT NOTED THAT SMOKING TWO CIGARETTES CAN PRODUCE BLOOD PRESSURE INCREASES OF 10/8 MM HG, AND THAT COMBING CIGARETTES AND COFFEE CAN HAVE ADDITIVE EFFECTS.

WHILE SUBJECTS IN THE PRESENT STUDY WERE NOT PERMITTED CAFFEINATED FOODS AND REFRAINED FROM SMOKING FOR AT LEAST 15 MINUTES PRIOR TO EACH MEASUREMENT OCCASION, THESE RESULTS, AS REPORTED IN THE HARVARD REPORT, HELP TO PUT THE INDIVIDUAL FLUCTUATIONS WE OBSERVED INTO A "REAL LIFE" PERSPECTIVE.

IN A LARGE SAMPLE STUDY SUCH WITHIN-SUBJECT VARIATION IS LESS OF A PROBLEM, BUT IN A SMALL SAMPLE STUDY IT CAN PRODUCE EXTREMELY UNSTABLE RESULTS. WHILE PARAMATRIC STATISTICS ARE RELATIVELY ROBUST WITH RESPECT TO SUCH PROBLEMS IN LARGE SAMPLE STUDIES, THIS IS NOT THE CASE WITH SMALL SAMPLES.

GIVEN THE INHERENT VARIABILITY OF BLOOD PRESSURE, THE SUBSTANTIAL BETWEEN-GROUP BASELINE DIFFERENCES, AND THE LIMITATIONS IMPOSED BY THE SMALL SAMPLE SIZE, IT IS DIFFICULT TO DRAW STRONG CONCLUSIONS FROM THE RESULTS OF THIS STUDY. OVERALL, HOWEVER, PPA, EVEN AT THE 150 MG DOSE, DOES NOT APPEAR TO POSE A DANGEROUS OR UNIQUE HYPERTENSIVE RISK TO HEALTHY INDIVIDUALS.

PPA, LIKE ALL MEDICATIONS, MUST BE TAKEN WITH APPROPRIATE CAUTION. CONSUMERS SHOULD BE INFORMED ABOUT POSSIBLE EFFECTS OF THEIR MEDICATION AND GIVEN CLEAR AND EASY TO UNDERSTAND DIRECTIONS REGARDING APPROPRIATE USE. AT THE SAME TIME, THE MEDICAL RESEARCH COMMUNITY HAS AN OBLIGATION TO CAREFULLY EVALUATE THE RESULTS OF CLINICAL STUDIES, SUCH AS THOSE REPORTED ON TODAY, IN AN APPROPRIATE SCIENTIFIC FORUM. THANK YOU FOR GIVING ME THAT OPPORTUNITY TODAY.