MEMORANDUM OF A MEETING

December 2, 1983
2:30 pm

ATTENDEES: See attached list

SUBJECT: Phenylpropanolamine Dose-Response Data

This meeting was called by FDA in order to discuss human responses to doses of phenylpropanolamine higher than those currently on the OTC market. Two companies made presentations: Thompson Medical Company and A. H. Robins Company.

Thompson addressed the subject by making presentations in three different areas.

William Waggoner, Ph. D., Vice President and Director, Thompson Research and Development, discussed preclinical toxicity data on rodent and canine species given massive overdoses of phenylpropanolamine and stated that the LD_{50} of phenylpropanolamine hydrochloride in mice is 1,252.8 mg/kg and that 619.6 mg/kg is the dose at which no deaths occurred (the latter 1,735 times the human clinical dose). In dogs, he reported that the minimum oral lethal dose of 1,000 mg/kg translates into a human dose of more than one-quarter pound of phenylpropanolamine.

Brent R. Ekins, Pharm. D., Intermountain Regional Poison Control Center presented the results of a 5-month prospective study of individuals who had ingested phenylpropanolamine and required treatment at a treatment facility. He gave examples of the ingestion of 1,500 mg (30-year-old patient) and 1,875 mg (14-year-old patient) of phenylpropanolamine in an immediate release dosage form resulting in adverse reaction requiring hospitalization but not resulting in death. He concluded that deliberate or accidental overdosing of phenylpropanolamine was not associated with serious, life-threatening problems in this study. The basis for this presentation is a paper by Ekins and Spoerke, entitled "An Estimation of the Toxicity of Non-Prescription Diet Aids From Seventy Exposure Cases" (Veterinary and Human Toxicology, 25:81-85, 1983) (CP0004).

Robert Marlin, Ph. D., Director, Thompson Clinical Testing, made a presentation summarizing available pulse and blood pressure data resulting from doses of up to 75 mg phenylpropanolamine as a bolus dose. He concluded that phenylpropanolamine produced no clinically significant differences in blood pressure and pulse based on the information contained in these single and multiple dose studies.

The presentation for A. H. Robins Company was made by Robert Keenan, M.D., Medical Director. He expressed concern about the continued marketing of phenylpropanolamine in currently recommended dosages as a nasal decongestant (25 mg every 4 hours) because of the adverse reactions which have been reported in the literature. He presented results of preliminary studies that in his opinion support effectiveness of phenylpropanolamine as a nasal decongestant in doses of as little as 5 mg. A. H. Robins intends to submit supporting data at a future time.

Drs. Waggoner and Marlin presented the agency with data submissions to be included in the administrative records for weight control and nasal decongestant drug products rulemaking (copies attached).

Thompson expressed concern that more stringent controls were being placed on phenylpropanolamine as compared to other ingredients in the OTC review. FDA's response was that we are concerned due to the serious adverse reactions which have been reported in the medical literature. FDA is concerned that an adequate margin of safety be determined for this drug.

Most of the discussion time was taken up with what FDA would consider to be adequate dose-response studies. It was agreed that FDA would work with industry in developing protocols.

Thompson made the point that almost all of the adverse reactions reported have been with higher than the marketed doses of phenylpropanolamine for weight control usage. They argued that if this is the case, there would be no need to determine the margin of safety. Thompson will generate a table containing all the anecdotal adverse reactions they are aware of and submit such to the FDA.

John R. Short

John R. Short

Attachments (2)

ATTENDEES

FDA Personnel

Robert Temple, M.D. (HFN-100)
Raymond Lipicky, M.D. (HFN-110)
Philip Dern, M.D. (HFN-110)
Patricia Russell, M.D. (HFN-160)
Peter Rheinstein, M.D., J.D., M.S. (HFN-200)
Jim Morrison (HFN-201)
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)
Ed Nevius, Ph. D. (HFN-713)

Industry and Press

Daniel Abraham, Thompson Medical
Matthew Bradley, M.D., Miami Heart Institute
P. E. Ciccone, Menley and James
Jerold Dorfman, Esq., Friend, Dorfman and Marks
Albert Eckian, M.D., Consultant
Brent Ekins, Pharm. D., Intermountain Regional Poison Control Center
Donald Flaster, M.D., LL.B., Scientific and Regulatory Consultants
Frank Funderburk, M.D., Antech, Inc./Johns Hopkins University
Edward Hanus, Richardson-Vick, Inc.
George Hoffnagle, Consultant
Robert Keenan, M.D., A. H. Robins
Lon Lowrey, Dorsey Laboratories
Robert Marlin, Ph. D., Thompson Medical
Raymond Ragland, Ph. D., Menley and James
M. B. Saltzman, Menley and James
Brenda Sandburg, FD&C Reports
Nelson Schimmel, Schering
Harold Silverman, D.Sc., Massachusetts College of Pharmacy
Edward Steinberg, O.D., Thompson Medical
William Waggoner, Ph. D., Thompson Medical

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PRECLINICAL TOXICITY

OF

PHENYLPROPANOLAMINE HYDROCHLORIDE

(PPA HCl)

December 2, 1983

Values in the appended tables are calculated from data of studies performed under the auspices of Smith, Kline and French and obtained from the Food and Drug Administration by way of Freedom of Information.

All values are expressed in terms of the phenylpropanolamine hydrochloride salt.

The multiple of the clinical dose is calculated on the basis of a 70 kilogram individual ingesting a 25 mg dose.

DOSE RESPONSE OF PPA HCl

♂ White Mice, CF, 18-21 g, n=3

Vehicle: water, gavage

Dose (mg/kg)	X Human Clinical Dose of 25mg (70 kg)	Effects	Comments
44.5	125	piloerection spontaneous motor activity lacrimation	Onset: 10 min. Duration: 35-50 min. No Deaths
89	249	Same	Onset: 10 min. Duration: 45-75 min. No Deaths
178	499	Same	Onset: 10 min. Duration: 50-110 min. No Deaths
356.4	997.8	Same	Onset: 10 min. Duration: 50-110 min. No Deaths

DOSE RESPONSE OF PPA HCl

♀ Rats, CR, 170-210 g, n=3

Vehicle: water, gavage

Dose (mg/kg)	X Human Clinical Dose of 25mg (70 kg)	Effects	Comments
42.7	119.7	piloerection tachypnea	Onset: 15 min. Duration: 105 min. No Deaths
85.5	239.4	piloerection tachypnea salivation 1/3	Onset: 15 min. Duration: 225 min. No Deaths
171.0	478.9	piloerection tachypnea salivation	Onset: 15 min. Duration: 225 min.
342.0	957.6	piloerection tachypnea ↓SMA or ↑SMA salivation	Onset: 15 min Duration: >5 hours 1/3 dead

DOSE RESPONSE OF PPA HCl

2♂, 2♀ Mongrel Dogs, 7.7-18.5 kg

Drug in Gelatin Capsules, PO

Dose (mg/kg)	X Human Clinical Dose 25mg (70 kg)	Effects	Comments
28.5	80	salivation tachypnea peripheral vaso-dilation mydriasis	Onset: 30 min. Duration: 7300 min.
28.5	80	peripheral vaso-dilation mydriasis salivation anorectic	Onset: 90 min. Duration: > 300 min.
57.0	160	salivation peripheral vaso-dilation	Onset: 30 min. Duration: 225 min.
57.0	160	emesis peripheral vaso-dilation salivation	Onset: 15 min. Duration: 225 min.

ACUTE ORAL TOXICITY OF PPA HCl

in ♂ CF Mice, 17-35g

in 0.5% tragacanth at 20 mg/kg

LD_{50} = 1252.8 mg/kg

Also, at 619.6 mg/kg (or 1735 times human clinical dose) no deaths occurred.

4 levels, 10/level

ACUTE ORAL TOXICITY OF PPA HCl

in CR Rats, 125-160 g

in 0.5% tragacanth at 20 ml/kg

LD_{50} = 1175.2 mg/kg

Also, at 619.6 mg/kg (or 1735 times human clinical dose) no deaths occurred.

4 levels, 10/level

MINIMUM ORAL LETHAL DOSE OF PPA HCl

Dogs, 8.2 - 14.2 kg, P.O.

Dog #	Dose (mg/kg)	X Human Clinical Dose of 25mg (70 kg)	Comments
1	100	280	Emesis
2	100	280	Emesis
3	500	1400	
4	500	1400	Emesis
5	1000	2800	Emesis, Dead
6	1000	2800	Emesis