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

May 11, 1984

Dr. William Gilbertson
Bureau of Drug Standards
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Gilbertson:

Pursuant to my letter of April 25, 1984, enclosed please find two(2) independent analyses of phenylpropanolamine drug reports from 1965 to the present, in which approximately two-thirds of the subjects took cough and cold products containing PPA and one-third of the subjects took appetite suppressants containing PPA.

1. Report from Walter J. Decker, Ph.D., Adjunct Associate Professor of Pharmacology, Toxicology, and Pediatrics, University of Texas-Medical Branch, Galveston, Texas:

Dr. Decker analyzed 101 reports of which approximately 50 were original citations associated with adverse reactions in which PPA was a component of the preparation used. He stated, "In general there appears to be very weak links between normal use of the drug and side effects. Also, abuse was connected with frank overdose through naiveness or intent to do harm, not because of a desired euphoric effect. In consideration of the widespread use of phenylpropanolamine in the cough/cold market and appetite suppressant market, it is remarkable that only a few mostly anecdotal (and/or coincidental) reports of adverse effect have emerged over the past 40 years."

2. Harold I. Silverman, D.Sc., Professor, Massachusetts College of Pharmacy and Robert L. Marlin, Ph.D., independently analyzed the same reports.

They surveyed approximately 50 adverse reaction reports and the data, presented in a succinct tabulated form and also in a separate narrative summary, demonstrated that:

a. The subjects were predominantly users of cough/cold preparations.
b. Adverse reactions that are reported, cleared without sequelae in the vast majority of instances.
c. Blood assays to verify the presence of phenylpropanolamine were generally missing.

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d. Prior medical history was generally missing.
e. Most of the reactions were due either to drug interaction or frank overdose.

I will phone you in order to arrange for a mutually convenient appointment for you, Dr. Lipicky, and members of your department in conjunction with our medical researchers to meet and discuss the literature reports.

John P. Morgan, M.D., Professor, City University of New York, is currently preparing for publication an in-depth evaluation of the PPA adverse reactions reported in the literature relative to the history of phenylpropanolamine, its pharmacology, toxicity and clinical effectiveness. Dr. Morgan will also be available to participate in the conference with members of your department.

We are also enclosing a draft protocol for a dose escalation clinical study of PPA, for discussion purposes at our next meeting.

separate communication dated 5/10/84

Sincerely yours,

THOMPSON MEDICAL COMPANY, INC.

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

ELS:fm
Encl.

Rec'd OTC 5/14/84

REVIEW OF ADVERSE EFFECTS ATTRIBUTED TO THE USE OF PRODUCTS CONTAINING PHENYLPROPANOLAMINE

As analyzed by

Walter J. Decker, Ph.D.
Adjunct Associate Professor of Pharmacology,
Toxicology, and Pediatrics
University of Texas-Medical Branch
Galveston, Texas

REVIEW OF ADVERSE EFFECTS ATTRIBUTED TO THE USE OF PHENYLPROPANOLAMINE AND PHENYLPROPANOLAMINE-CONTAINING PRODUCTS

One hundred one documents were presented for critical review. Most of them were journal articles or letters to the editor publis in journals. A few were portions of the Federal Register, informa typed on letterhead or plain paper, and articles published in non-scientific media (magazines and newspapers).

With few exceptions, a cause-and-effect relationship of pheny propanolamine to disease states did not appear to be firmly establ ed. In a number of cases, phenylpropanolamine was only one compor of the drug combination ingested. In others, lack of information patients' drug-taking histories and past medical histories preclud an adequate evaluation of the contribution of phenylpropanolamine to the particular patient's condition.

Many of the documents involved incidents where the patient did not appear to follow instructions for use; an excess of med-ication was taken. In other cases, the medication was deliberatel taken for the wrong purpose (e.g., use of a diet aid or oral nasal decongestant to induce sleep or keep awake). In yet others, "stre preparations were taken, usually in large quantities (the drug for ulations commonly referred to as "look-alikes") - - frank drug ab The contents of "street" preparations are often not known, and ascribing any observed side effects to phenylpropanolamine alone i ludicrous, although done by some authors.

Of the 101 documents, 37 were review in nature. Also, 34 wer related to overdose, ingestion of combinations of drugs, or drug misuse. Thus, of the 101 reports, 71 contributed no new information concerning adverse effects of phenylpropanolamine.

Although 7 documents reported hypertension, 6 others divulge a lack of significant cardiovascular effects. In general, there appears to be very weak links between normal use of the drug and side effects. Also, abuse was connected with frank overdose throu naiveness or intent to do harm, not because of a desired euphoric effect. In consideration of the widespread use of phenylpropanola in the cough/cold market and appetite suppressant market it is remarkable that only a few mostly anecdotal (and/or coincidental) reports of adverse effects have emerged over the last 40 years.

REPORTS OF EFFECTS ATTRIBUTED TO PHENYLPROPANOLAMINE

Category	Reference Number	Comments
Review (includes editorials and letters) (37)	13, 14, 18, 26a, 29, 29a, 30, 31, 32, 33, 34, 36a, 37, 37a, 41, 42, 44, 46, 48, 50, 50a, 54a, 54b, 55a, 56, 57, 58, 61, 62, 63, 63a, 64, 66a, 66b, 67, 71, 71a	No additional information is provided.
Overdoses, combinations of drugs, drug misuse. (34)	1, 2, 3, 5a, 7, 9, 10, 15, 17, 19, 21, 22, 26, 26b, 26c, 30b, 32a, 38, 43, 45a, 49, 51, 53, 55, 56a, 59, 60, 60a, 62a, 65, 65a, 66, 69, 70a	17 addresses a possible interaction with ind methacin; the others provide pertinent information.
Hypertension (7)	5, 8, 11, 16, 24, 27a, 47	Association is questionable in 5, 11, and 27a; supersensitivit is possible in 16, and 47; 24 deals with high doses.
Lack of significant cardiovascular effects (6)	4a, 25, 30a, 36, 45, 70	4a, 25, 30a, an 36 appear to be valid, 45 is possibly valid, and 70 is proba valid.
Psychiatric disturbances (4)	4, 23, 27, 28	Association is questionable in all four report
Interaction with monoamine oxidase inhibitors (3)	6, 49a, 54	6 and 49a appea to be valid; 54 is probably val
Lack of abuse potential (1)	12	Appears to be valid.
Dystonia (1)	27b	Association is questionable.
Phenylpropanolamine analog (1)	68	Irrelevant.
Raynaud's phenomena (1)	64	Association is questionable.

Renal disease (1)	17a	Association is questionable.
Seizures (1)	20	Association is questionable.
Animal pharmacological study (2)	31a, 40	No obvious relevance to adverse effect in humans.

1. Salmon, P.R. Hypertensive crisis with Eskornade. Brit. Med. J. 1, 193 (1965).

A 16-year-old male was admitted in a confused state to a hospital after reportedly ingesting 8 Eskornade capsules (total of 400 mg phenylpropanolamine, 20 mg isopropamide iodide, and 40 mg diphenylpyraline hydrochloride in sustained release form). Tachycardia (104 bpm) and hypertension (190/150 mm Hg) were evident upon admission. Recovery was uneventful. He had apparentl taken the capsules to help him sleep. It is clear that the patient did not follow instructions on the bottle label (one capsule to be taken). Further, this is a case involving polydrug ingestion; it is not possible at the state of current knowledge of drug interactions to ascertain with any degree of certainty precisely what caused the patient's signs and symptoms. The extreme agitatio manifested by the patient, combined with repeated episodes of vomiting, may have contributed markedly to the patient's tachycardi and hypertension.

Category:

Overdoses, combinations of drugs, drug misuse.

2. Ostern, S., and Dodson, W.H. Hypertension following Ornade ingestion. J. Amer. Med. Assoc. 194, 240 (1965).

A 20-year-old male was hospitalized after presenting with a severe headache of 20 minutes duration. He said he took 4 Ornade Spansules (total of 200 mg phenylpropanolamine hydrochloride, 10 mg isopropamide iodide, and 32 mg chlorpheniramine maleate, sustained release) "for sleep" 20 minutes prior to the onset of headache. Initial blood pressure was 220/120 mm Hg. He was moderately disoriented and agitated. He was given 1 mg reserpine IM; in 45 minutes, blood pressure had fallen to 180/110 mm Hg and the patient "became rational." The patient denied taking other medication. Without further therapy, he became normotensive and essentially asymptomatic at 18 hours post-ingestion. Blood pressure was 140/80 mm Hg 6 weeks after discharg from the hospital.

The authors attributed this patient's hypertension to phenylpropanolamine ingestion. However, the time frame of presumably 40 minutes from ingestion to initial blood pressure screening seems much too short for a significant amount of phenylpropanolamine to be released from the sustained-release preparation. The agitated state of the patient(perhaps a result of his severe headache) could have contributed markedly to the hypertensive episode. Although the patient denied taking any other drugs, the possibility cannot be discounted.

Category:

Overdoses, combinations of drugs, drug misuse.

3. Livingston, P.H. Transient hypertension and phenylpropanolamine. J. Amer. Med. Assoc. 196, 143 (1966).

This short (4 sentences) anecdotal report stated that 2 young men examined for insurance purposes had blood pressures in the "range of 180/110 mm Hg". They apparently stated that they had ingested (an unknown amount) of Contac capsules (50 mg phenylpropanolamine hydrochloride, 4 mg chlorpheniramine maleate, and 0.2 mg belladonna alkaloids per capsule, sustained release) for acute rhinitis. Blood pressures "returned to normal the following day, after discontinuance of the medication."

Too little information was presented to evaluate these episodes.

Category:

Overdoses, combinations of drugs, drug misuse.

4. Kane, F.J., and Green, B.Q. Psychotic episodes associated with the use of common proprietary decongestants. Amer. J. Psychiat. 123, 484-487 (1966).

Three cases were described wherein psychiatric patients apparently developed acute psychotic episodes after taking Ornade (2 patients) and Propadrine (one patient). Two of these patients reportedly had not evidenced mental illness before taking the drugs.

The authors' statements, "That these drugs were the sole or sufficient cause for the psychoses cannot be proven. Likely additional factors of importance are the age and illness of the first patient and the personality defects of the other two." act as an adequate critique of this report.

Category:

Psychiatric disturbances.

4a. Mitchell, C.A. Possible cardiovascular effect of phenylpropanolamine and belladonna alkaloids. Current Therapeut. Research 10, 47-53 (1968).

In a blind crossover randomized study, 32 normotensive volunteers were given 5 times weekly for 3 weeks placebo, phenylpropanolamine hydrochloride (50 mg, sustained release), or belladonna alkaloids (.25 mg) plus phenylpropanolamine hydrochloride (50 mg, sustained release), all treatments one capsule twice daily. Blood pressure and pulse rate were measured daily by three observers. ECG measurements were performed weekly by the same physician. A substudy was performed on 6 volunteers to rule out missing the detection of transient blood pressure or pulse rate changes. Neither phenylpropanolamine nor belladonna alkaloids caused statistically significant rise in mean arterial pressure (MAP) and pulse rate. MAP increase was no more than 20 mm Hg in any subject receiving the drugs. ECG showed no changes except for slowing of heart rate when phenylpropanolamine and belladonna alkaloids were administered in combination.

This appears to be a well-designed, well-carried out study, demonstrating that a divided daily dose of 100 mg phenylpropanolamine hydrochloride in sustained-release formulation did not produce any pressor effects in normotensive individuals 19-53 years of age.

Category:

Lack of significant cardiovascular effects.

5. Hypertension due to anorectic agent.

Shapiro, S.R.
Sauls, L.J. N.E.J. Med. 280, 1363 (1969).

These are brief anecdotal reports (prompted by Duvernoy's report, 5a) of hypertensive episodes attributed to phenylpropanolamine. Insufficient detail is presented to permit any critical evaluation.

Category:

Hypertension.

5a. Duvernoy, W.F.C. Positive phentolamine test in hypertension induced by a nasal decongestant. N.E.J. Med 280, 877 (1969).

A 21 year old male confessed to the ingestion of "the contents of 3 Ornade Spansules on the afternoon of admission." The patient had abdominal pain, severe headache, and nausea. An initial blood pressure was 240/120 mm Hg; after 330 mg phenobarbital (I.M.) and 32 mg codeine were given, blood pressure dropped to 170/120. After some unspecified time, he was placed in a hospital, where blood pressure was 180/130. ECG was normal. Possibility of pheochromocytoma was considered, so 5 mg phentolamine was given I.V., which dropped the blood pressure to 120/60 in 30 seconds with later rebound. The patient was given chlorpromazine for sedation; 2 hours later the blood pressure was 120/85, remaining in the normal range thereafter.

If the term "the contents of 3 Ornade Spansules" is taken to mean that the subject opened the capsules and swallowed the sustained release microcapsules therein, then this is clearly a case of drug misuse if not drug abuse. No reference is made to any other medication which might have been taken by the patient. Elevated SGOT (GGT) activity in this patient may be pathomnemonic for moderate to heavy alcohol use, but this may be complicated by the fact that the patient was shown as a result of liver biopsy to have sarcoidosis affecting that organ.

Category:

Overdose, combination of drugs, drug misuse.

6. Cuthbert, M.F., Greenberg, M.P., and Morley, S.W. Cough and cold remedies: a potential danger to patients on monamine oxidase inhibitors. Brit. Med. J. 1, 404-406 (1969).

In 3 healthy normotensive adult subjects, 50 mg phenylpropanolamine hydrochloride in gelatin capsules produced a small rise in only systolic blood pressure (18-26 mm Hg). When 100 mg was given, a more extensive rise in systolic and some rise in diastolic blood pressure ensued (a maximum rise of about 60 mm Hg systolic was recorded). Fifty mg phenylpropanolamine in a proprietary sustained release capsule had no significant effect on the blood pressure. When 50 mg phenylpropanolamine was given after administration of the monoamine oxidase inhibitor, tranylcypromine, a rapid and dramatic rise in blood pressure occurred (210/140 in one subject). This effect was also observed, but less so, in subjects taking a sustained release preparation. Indeed, it was felt necessary to reduce markedly elevated blood pressures by the use of phentolamine.

The authors present strong evidence that taking phenylpropanolamine-containing preparations concurrently with monoamine oxidase inhibitors constitutes a severe risk of hypertensive crisis. Although the sustained release formulations of phenylpropanolamine-containing pharmaceuticals would presumably evoke less of a pressor response in the presence of monamine oxidase inhibitors, implicit in the authors' conclusions are that these products also should be avoided. The authors make a plea that both physicians and laity be warned of the danger; some recent product labelling practices (e.g. Thompson Medical Company, Inc., and Verex Laboratories, Inc.) do indeed stress this warning.

Category:

Interaction with monoamine oxidase inhibitors.

7. Wharton, B.K. Nasal decongestants and paranoid psychosis. Brit. J. Psychiat. 117, 439-440 (1970).

A 37-year-old male had reportedly ingested 30 tablets of Anahist (12.5 mg phenylpropanolamine hydrochloride, 97.2 mg phenacetin, 6.25 mg thorsylamine hydrochloride, 6.25 mg phenyltoxolamine citrate, and caffeine, aspirin, and ascorbic acid in unspecified amounts) for nasal stuffiness, over an 8-day period. He manifested behavior akin to paranoia over approximately a two-day period, and was treated with chlorpromazine. A day afterwards, he was pronounced to be recovered. Eight weeks later, a second "less florid paranoid outburst occurred", he was treated further (presumably also with chlorpromazine), and "in a few days his paranoid episode had once more remitted."

The author compared the similarity in structural formula of phenylpropanolamine to amphetamine, and went on to state that the quantity of phenylpropanolamine taken by the patient over the eight day period is "well in accord with the amounts of amphetamine known to induce psychosis." No evidence was submitted in support of this analogy except to say that an "invariable absence of thought disorder" was common to both amphetamine-induced psychosis and the patient described in the article. No one has reported any evidence that the two drugs have equipotency in any physiological system studied.

Category:

Overdoses, combination of drugs, drug misuse.

8.. Gibson, G.J., and Warrell, D.A. Hypertensive crises and phenylpropanolamine. Lancet 2, 492 (1972).

A 28-year-old male apparently took 2 Mucron tablets (32 mg phenylpropanolamine each tablet) for nasal congestion. Ten minutes later he developed a severe headache, a sensation of colored lights, tightness in his chest, and pounding heart. Blood pressure 20 minutes later was 180/110 mm Hg, one hour later 160/90, and 12 hours later 140/80. No other data are presented except that he stated he had eaten a meal which contained cheese.

The authors ventured that tyramine present in the cheese may have acted synergistically with the phenylpropanolamine, but it was their opinion that this latter drug precipitated the hypertensive episode. No mention of the patient's use of other drugs was made. It is possible that the patient was supersensitive to the drug, perhaps in combination with tyramine from the cheese.

Category:

Hypertension.

9. Peterson, R.B., and Vasquez, L.A. Phenylpropanolamine-induced arrythmias. J.Amer. Med. Assoc. 223, 324-325 (1973).

An obese 15 year old female was admitted to the hospital with a sudden and severe headache. She was very restless and vomited frequently. Admission blood pressure was 188/112 mm Hg; 20 minutes later, it was 210/130. ECG revealed frequent premature atrial contractions with paroxysms of ventral and atrial tachycardia. She was treated with atropine, lidocaine, and reserpine, resulting in a blood pressure fall to 110/56 mm Hg. The patient soon experienced a seizure lasting 2 minutes. She then remained normotensive, no further therapy (except lidocaine drip) was given, and her headache disappeared. The next morning, all ECG abnormalities were gone. A history of "diet pill" ingestion was obtained.

Presumably, the patient had taken 3 "anorectic tablets" containing 25 mg phenylpropanolamine, 25 mg caffeine, and 25 mg methylcellulose per day. It seems most likely that the patient had taken far in excess of this amount of tablets on the day of admission, based on clinical studies of phenylpropanolamine and caffeine administration. The authors pinpoint the phenylpropanolamine component of the tablet as responsible for the arrythmias, but caffeine, even in small doses, can produce tachycardia and premature vertricular contractions in sensitive individuals (Goodman & Gilman, 6th edition, p. 594).

Category:

Overdoses, combination of drugs, drug misuse.

10. Rumack, B.H., Anderson, R.J., Wolfe, R., Fletcher, E.C., and Vestal, B.K. Ornade and anticholinergic toxicity: hypertension, hallucinations, and arrythmias. Clin. Toxicol. 7, 573-581 (1974).

This is a review of 3 cases in which Ornade Spansules were involved. In two of the cases, massive ingestion was reported (15-30 capsules). The main contribution of the article was to show that I.V. administration of physostigmine can reduce significantly both systolic and diastolic blood pressures in such overdoses.

The third case appears to be an idiosyncratic reaction to imipramine, perhaps as a result of interaction with chlorpheniramine.

Category:

Overdoses, combinations of drugs, drug misuse.

11. McLaren, E.H. Severe hypertension produced by interaction of phenylpropanolamine with methyldopa and oxprenolol. Brit. Med. J. 2. 283-284 (1976).

A 31-year-old male was found to have severe hypertension (blood pressure 200/120 mm Hg). The hypertension was apparently controlled with methyldopa and oxprenolol. He was prescribed Triogesic tablets (12.5 mg phenylpropanolamine and 500 mg acetaminophen) 3 times per day for a cold. Two days later, he presented with headache and hypertension (200/160 mm Hg). After stopping the Triogesic regimen, his blood pressure dropped to 140/110 in (presumably) one day. Peritoneal dialysis was instituted. His blood pressure stabilized at 140/90 on oxprenolol 80 mg 3 times a day.

The patient's BUN of 133 mg/dl at the time of diagnosis of hypertension indicates that he was already in a state of renal failure. After the patient had taken the antihypertensive drugs, the latter disease progressed (BUN 183 mg/dl) and progressed further after taking Triogesic (BUN 253 mg/dl). The author pointed out the possible potentiation of the pressor effects of symathomimetic drugs with methyldopa and beta adrenergic receptor blockers, but did not mention the fact that acetaminophen can in itself cause renal tubular necrosis. This can set up a vicious cycle; with decreasing renal function, plasma acetaminophen concentrations will rise and cause further renal damage. This damage will lead to further hypertension, etc. Thus, it appears that the patient's hypertension results from the interaction of many factors, and cannot be solely attributed to phenylpropanolamine.

Category:

Hypertension.

12. Griffiths, R.R., Brady, J.V., and Snell, J.D. Relationship between anorectic and reinforcing properties of appetite suppressant drugs: implications for assessment of abuse liability. Biol. Psychiat. 13, 283-290 (1978).

Using a method developed by the authors (published in 1976), the ability of a number of drugs to induce self-administration (an indicator of potential abuse) was evaluated in 11 chair-restrained baboons. Phenylpropanolamine administration (0.1 to 30 mg/Kg/ infusion) did not result in any higher self-infusion rate than did saline. This fact clearly indicated that phenylpropanolamine has very little (if any) potential for abuse for stimulant effects.

Category:

Lack of abuse potential.

13. This is a typewritten paragraph on a plain sheet of paper (author, source, etc. not stated). It appears to summarize a 1976 review by the Food and Drug Administration (USA) of reports to the Bureau of Drugs on adverse effects of phenylpropanolamine-containing products.

The material presented appears to be consistent with reports published in the literature.

Category:

Review.

14. Federal Register 41 (176), 38400-38402 (1976).

A panel convened by the U.S. Food and Drug Administration (FDA) reviewed phenylpropanolamine preparations. The panel's conclusion was that phenylpropanolamine and its salts, used orally, are safe and effective as oral nasal decongestants for OTC use as specified in a stated dosage regimen. Included in the reviews were reports of adverse side effects, the incidence of which the panel agreed was low in adults and children when therapeutic doses were taken.

Category:

Review.

15. Chouinard, G., Ghadirian, A.M., and Jones, B.D. Death attributed to ventricular arrythmia induced by thioridazine in combination with a single Contac·C capsuel. Canad. Med. Assoc. J. 119. 729-731 (1978).

A 27-year-old female, diagnosed as having schizophrenia, was apparently given by her husband a prescribed 100 mg dose of thioridazine 1 hour after dinner, and because she complained of nasal congestion, he gave her a single Contac·C capsule (4 mg chlorpheniramine and 50 mg phenylpropanolamine hydrochloride). She was found dead in bed approximately 2 hours after ingestion of these medications. Autopsy revealed thioridazine, 0.5 mg/dl in blood and 1.1 mg/100g in liver.

The authors stated that "it is likely that phenylpropanolamine, an ephedrine-like drug contained in Contac·C favoured the initiation by thioridazine of the ventricular arrythmia that lead to the woman's death," and cited a reference indicating that the liver concentration of thioridazine was too low for the possibility of overdose to have occurred. However, Osselton (Bull. Internat. Assoc. Forensic Tox. 17 16-33, 1983) reported that thiordazine concentrations in liver in fatal cases range form 0.7 to 30.5 mg/100g. Clearly, that of the subject of this report,, 1.1mg/100g, falls in this range. Furthermore, Baselt (Disposition of Toxic Drugs and Chemicals in Man, Vol. I, p.112) stated that after a single 100 mg dose of thioridazine, maximal serum concentration averaged 0.024 mg/dl at 1.7 hours (the patients was 0.5 at approximately 2 hours). The reference quoted re unreliability of postmortem thioridazine determinations in blood was published in 1962; by 1976, much more reliable techniques became available. Hence, it is quite possible to conclude that the patient died of thioridazine overdose. Since the authors stated that "the liquid in the trachea and bronchi were similar to the gastric fluid," pulmonary aspiration as at least a contribution to the cause of death is possible.

Category:

Overdoses, combinations of drugs, drug misuse.

16. Frewin, D.B. Leonello, P.P., and Frewi M.E. Hypertension after ingestion of Trimolets. Med. J. Austral. 2, 497-498 (1978).

A 21-year-old female was admitted to the hospital; she said she took one Trimolets tablet (85 mg phenylpropanolamine, nonsustained release) for its "pick-me-up" effect. She reported a severe headache of sudden onset approximately 1½ hours after taking the medication; she vomited 4-5 times soon thereafter. Review of her past medical records revealed blood pressure of about 90 to 110/60 mm Hg; at the time of admission (at an unspecified time after drug ingestion), her blood pressure was 190/120 mm Hg. Four and one half hours after the onset of her headache, her blood pressure was 140/100 mm Hg; it fell to 120/70 during the next hour, and remained in the 95-120/60 range during the next 3 days of hospitalization. No specific therapy was administered.

The dose of phenylpropanolamine purportedly taken was considerably higher than that recommended in the U.S. The patient clearly misused the drug for its stimulatory effect rather than its intended use as an anorexigenic agent. Individuals in such circumstances have been known in the past to underreport the amount of drug they took, so it is possible that the patient actually took 2 or more tablets. The anxiety of the patient about her severe headache, plus the 4 or 5 episodes of vomiting, plus the mental trauma of being hospitalized, could have contributed markedly to her hypertension. The authors point out the distinct possibility that the patient's exaggerated response to the drug could be an idiosyncratic reaction.

Category:

Hypertension.

17. Lee, K.Y., Vandongen, R., and Beilin, L.J.
Severe hypertension after ingestion of an appetite suppressant with indomethacin. Lancet 1, 1110-1111 (1979).

A 27-year-old female who reportedly had been taking one Trimolets capsule (85 mg phenylpropanolamine, nonsustained release) per day for several months to reduce her appetite developed a severe frontal headache approximately 15 minutes after taking 25 mg indomethacin (prescribed for her for tendonitis). When admitted to a hospital, her blood pressure rose to a maximum of 200/110 mm Hg. Challenge with Trimolets and indomethacin (alone and in combination) revealed that Trimolets alone did not increase blood pressure, that indomethacin alone resulted only in a small rise in diastolic pressure, and that the combination produced an increase in diastolic pressure up to 200 mm Hg.

This case report strongly indicates an interaction between phenylpropanolamine and indomethacin which resulted in a temporary hypertensive state. The authors, instead of urging product labelling to assist in precluding other such incidents, chose to argue for withdrawal of pharmaceutical preparations containing phenylpropanolamine. This in indicative of considerable bias on their part.

Category:

Overdoses, combinations of drugs, drug misuse. Addresses a possible interaction with indomethacin.

17 a. Bennett, W.M. Hazards of the appetite supressant phenylpropanolamine. Lancet 2, 42-43 (1979).

A 28-year-old female was admitted to a hospital with progressive renal failure. She was normotensive (100/60mm Hg). Renal biopsy revealed acute interstitial nephritis. It was reported that she had "for 3 weeks taken phenylpropanolamine in the appetite suppressant 'Fullstop.' Over this period she had also ingested two or three 325 mg aspirin tablets and 650 mg acetaminophen." Two days after admission, urine output increased, she improved symptomatically, and renal function recovered.

With the scanty information on her use of phenylpropanolamine (and other drugs), it is virtually impossible to link drug use with her renal failure.

Category:

Renal disease.

18. The Medical Letter, Vol. 21, No. 2, January 26, 1979, P. 12.

This is a listing on interactions of sympathomimetic amines (including phenylpropanolamine) with other drugs. It was clearly pointed in a footnote that the interaction of MAO inhibitors and phenylpropanolamine is one of the "most dangerous."

Category:

Review.

19. Horowitz, J.D., McNeil, J.J., Sweet, B., Mendelsohn, F.A.O., and Louis, W.J. Med. J. Austral. 1, 175-176 (1979).

A 17-year-old female was hospitalized after apparent ingestion of 6 Trimolets capsules (total of 510 mg phenylpropanolamine, 90 mg ferrous gluconate, and various vitamin additives in nonsustained release form). On admission, her tachycardia was evident (98 bpm standing and 62 supine), as was hypertension (150/95 mm Hg supine). She recovered without sequelae. Three weeks later, the patient was challenged with 85 mg phenylpropanolamine. It is stated in the report that a prolonged rise in blood pressure (measured in the supine position) occured (maximum of 175/120 mm Hg) ninety minutes after drug administration. It is surprising that this hypertensive response was greater than that observed upon admission after frank overdose of the drug (she had taken approximately 9 times the dose recommended in the U.S.) at a time somewhat in excess of 3 hours postingestion (the article is not clear on this time frame). It is possible that this patient was supersensitive to phenylpropanolamine, in view of the fact that the authors challenged six normotensive subjects with 85 mg of the drug. Here, there was no evidence presented that statistically significant hypertension occurred in these subjects 90 minutes after drug administration.

Category:
Overdose, combinations of drugs, drug misuse.

20. Decampo, P.D. Convulsive seizures due to phenylpropanolamine. J. Med. Soc. N.J. 76, 591-592 (1979).

A 44-year-old female was seen in an emergency room; she had a severe headache of sudden onset, blurred vision followed by a transient loss of vision, and "cold, clammy sweats" about one and a half hours after taking Diadax (75 mg phenylpropanolamine, sustained release). Soon after, she had a generalized seizure. She had 3 more in the next 4 hours; they responded to IV diazepam. Spinal fluid opening pressure was very high; the fluid was grossly bloody. Brain scan, computed tomography of the brain, and EEG were normal. No further seizures ensued. History revealed a seizure at age 5 after taking a "cold medication."

This report does not relate how many Diadax the patient ingested (nor does it reveal whether the drug was in capsule or tablet form). It is possible, therefore, that this might be a case of overdose. The author reports that the patient's mother died of a ruptured berry aneurism at age forty. With this family history, the possibility of a small intracranial hemorrhage, not evident in the brain scan, CT, or EEG, being responsible for the patient's seizure cannot be discounted. The very high spinal fluid opening pressure and the presence of blood in the fluid support this possibility. The report of the patient's seizure at age 5 after taking a "cold medication" cannot be taken as prima facia evidence that the patient was prone to seizures upon taking phenylpropanolamine, since the drugs present in this medication are not specified.

Category:

Seizures.

21. King, J. Hypertension and cerebral haemorrhage after Trimolets ingestion. Med. J. Austral. 2, 258 (1979).

Details on the first case presented are so lacking that a critical evaluation is impossible.

In the second case, there is no information on past use of Trimolets. Past medical and familial history is not provided, nor is maximum blood pressure soon after symptomatology developed. The dose the patient took was excessive (170 mg phenylpropanolamine). Thus, the association between the patient's use of the drug and her intracerebral hemorrhage is at best anecdotal.

Category:
Overdoses, combinations of drugs, drug misuse.

22. Teh, A.Y.F. Phenylpropanolamine and hypertension. Med. J. Austral. 2, 425-426 (1979).

A 23-year-old male complained of a faint feeling, generalized weakness, nausea, and a pounding sensation in his chest about 3 hours after he reportedly had taken 2 Contac 500 capsules (each containing 50 mg phenylpropanolamine hydrochloride and 0.2 mg belladonna alkaloids, sustained release). Blood pressure 7 hours after he had taken the medication was 160/110 mm Hg, and dropped to 130/80 approximately 3 hours later.

No information or prior blood pressure or blood pressure on discharge from the hospital was provided. The dose of Contac 500 taken was twice the dose recommended.

Category:

Overdoses, combinations of drugs, drug misuse.

23. Norvenius, ..., Widerlov, E, and Lonnerholm, G. Phenylpropanolamine and mental disturbances. Lancet 2, 1367-1368 (1979).

This is a very brief review of several reports submitted to the Swedish Adverse Drug Reaction Committee during 1979. Sixty-one cases involving (unspecified) preparations containing phenylpropanolamine reported restlessness, irritability, agressiveness, and sleep disturbances. Five cases classed as psychotic episodes are mentioned; there include manifestations such as confusion, inability to recognize parents, hallucinations, and seizure, exitation and lacking in concentration with sleep/wakefulness disturbances and paranoia, and a mania-like psychosis.

Lack of detail and the fact that many of these patients had taken combinations of drugs (particularly with antihistaminies) make this report difficult of evaluate. The patient developing the mania-like psychosis revealed apparent ingestion of large quantities of phenylpropanolamine and brompheniramine.

Category:

Psychiatric disturbances.

24. Horowitz, J.D. et al. Hypertensive responses induced by phenylpropanolamine in anorectic and decongestant preparations. Lancet 1, 60-61 (1980).

A study was carried out to determine the hypertensive effect of a single capsule of each of two phenylpropanolamine-containing preparations (Trimolets, 85 mg, apparently nonsustained release, and Contac 500, 50 mg, sustained release) compared to placebo, in healthy medical students.

The design of this study is flawed in that each subject did not act as his own control, hence individual response to the effect of the drug could not be accounted for. The dose of nonsustained release phenylpropanolamine was much higher than that currently recommended.

Category:
Hypertension.

25. Silverman, I. et al. Lack of side effects from orally administered phenylpropanolamine and phenylpropanolamine with caffeine: a controlled three-phase study. Current Therapeutic Research 28, 185-194 (1980).

Fifteen healthy young males were given a capsule containing 25 mg phenylpropanolamine hydrochloride (nonsustained release). Over a 3-hour period no significant rise in blood pressure or pulse rate was noted. A second group was given the same amount of phenylpropanolamine combined with 100 mg caffeine. Over a 4-hour period, again no significant differences in the parameters studied occurred. A third group received 25 mg phenylpropanolamine hydrochloride and placebo in a double-blinded randomized crossover design; again no differences were found.

The authors could be criticized for not setting up the first two groups in a crossover design to minimize differences in individual response, but since no significant effects of the drugs were seen, these studies can be considered valid. This report provides strong evidence that a relatively low oral dose of phenylpropanolamine does not cause significant myocardial or pressor responses in a healthy adult.

Category:
Lack of significant cardiovascular effects.

26. Schaffer, C.B., and Pauli, M.W. Psychotic reaction caused by proprietary oral diet agents. Amer. J. Psychiat. 137, 1256-1257 (1980).

A 23-year-old female was admitted to a hospital "because she had been taking too many 'diet pills'." Reportedly, about 3 days previously, she began taking "copious amounts" of these medications (her husband believed she was taking "3-5 pills per day" each from a bottle of Permathene and a bottle of Dexatrim). She was disoriented, agitated, disorganized, and displayed regressive intrusive, hyperactive behavior requiring restraints. After 3 days of hospitalization (without any medication), her signs and symptoms abated fully. There was no history of prior psychiatric problems or drug/alcohol abuse.

The authors attempted to equate phenylpropanolamine with amphetamine and ephedrine in drug-induced psychosis, presumably on the basis of their chemical similarity, but no evidence for this association is presented. The possibility of a dormant, preexisting mental disease was not discussed.

Category:
Overdoses, combinations of drugs, drug misuse.

26 a. Mashford, M.L. et al. Adverse Drug Reactions Advisory Committee: Report for 1979. Med. J. Austral. 2, 569-571 (1980).

This report documents this Committee's support of restricting the use of phenylpropanolamine in appetite suppression preparations, ostensibly because of reports of unanticipated hypertensive episodes associated with the use of the drug.

No new information is presented.

Category:

Review.

26 b. Patterson, F.K. Delayed fatal outcome after possible Ru-Tuss overdose. J. Forensic Sci. 25 349-352 (1980).

A 19-year-old female reportedly ingested, "in a fit of depression" 10-12 Ru-Tuss sustained release tablets. Seen in the emergency room about an hour later, she was drowsy, but had normal vital signs and ECG. She apparently was recovering (alert and ambulatory) until the third hospital day when she developed dyspnea, chest pain, wet rales, and labored respiration; in the next 4 hours cardiopulmonary arrest occurred. Diagnosis of "shock lung" (acute respiratory distress syndrome) was made. Ventricular tachycardia, asystole, and death occurred about 24 hours later. Autopsy confired the diagnosis of ARDS.

The author did not implicate any particular agent in Ru-Tuss as causing or contributing to the patient's syndrome.

Category:

Overdoses, combinations of drugs, drug misuse.

26 c. Lee, K.Y., eilin, L.J., and Vandonge R. Severe Hypertension following ingestion of an appetite suppressant (phenylpropanolamine) with indomethicin. Austral. and N. Zealand J. Med. 10, 122 (1980).

This appears to be an abstract of an article published in 1979 (Reference number 17). No additional information is provided in this report.

Category:

Overdoses, combinations of drugs, drug misuse.

27. Dietz, A.J., Jr. Amphetamine-like reactions to phenylpropanolamine. J. Amer. Med. Assoc. 245. 601-602 (1981).

This is a short report gleaned from emergency room records; presumably the author was not (at least actively) involved in the care of the 7 patients reported on. Reported symptoms included anxiety, agitation, dizziness and hallucinations.

All patients purportedly developed symptomatology "within one or two hours after ingesting a single tablet" (containing either 50 or 75 mg phenylpropanolamine, with or without caffeine). No documentation of dose, use of other medications, or past psychiatric history was provided. Tachypnea and tachycardia in the range reported (20-34 breaths per minute and 95-120 beats per minute, respectively) are not uncommon in subjects who manifest anxiety and agitation brought on by any circumstances. The author's statement that lack of a methyl group on the nitrogen atom of phenylpropanolamine's side chain enhances its propensity to exert CNS effects is completely unsubstantiated.

Category:

Psychiatric disturbances.

27 a. Elliott, C.F., and Whyte, J.C. Phenylpropanolamine and hypertension. Med. J. Austral. 1, 715 (1981).

A 54-year-old female with a history of adult onset diabetes was admitted to a hospital after sudden onset of headache, vomiting, and confusion; a short time afterward she became comatose. Blood pressure was 160/100 mm Hg; three days earlier it was 110/70. CT scan showed left occipital hemorrhage; this was confirmed on autopsy. Supposedly, she had taken one Dietgard capsule (75 mg phenylpropanolamine) on the day prior to and on the day of admission.

The author states that this report "does not prove any association between phenylpropanolamine and intracerebral hemorrhage." A systolic blood pressure of 160 mm Hg seems low to be the cause of rupture of brain vascularity. The author did not address the widely-held opinion that diabetics are predisposed to cerebral vascular accidents and brain hemorrhages.

Category:
Hypertension.

27 b. Lewith, G.T., and Davidson, F. Dystonic reactions to Dimotapp Elixir. J. RoyalColl. Gen. Practit. 31, 241 (1981).

An 8-year-old female was prescribed Dimotapp Elixir, 5 ml per night, for a cough. This dose was only partly effective in suppressing the cough, so the dose was increased to 10 ml. At an unspecified time after the dose was increased, she developed increasingly severe bouts of spasmodic torticollis, which culminated in an oculogyric crisis. The day before the latter appeared, she was given 1.5 mg haloperidol After discontinuance of both drugs, her dystonic reactions disappeared.

The authors pointed out that haloperidol is known to cause oculogyric crisis, and that this drug probably precipitated the more severe dystonic reaction. The authors did not implicate any particular component of the Dimotapp Elixir.

Category:

Dystonia.

28. Achor, M.B. and Extein, I. Diet aids, mania, and affective illness. Amer. J. Psychiat. 138, 392 (1981).

Three patients having histories of mental disorders were admitted to a hospital. Bipolar affective disorders were diagnosed in all 3 patients. All had apparently been taking phenylpropanolamine-containing diet aids for 2 weeks to 3 months prior to the behavioral crises precipitating their admission.

So little documentation is provided on amounts and frequencies of diet aids taken, use of other drugs, and progress of their behavioral problems, that it is impossible to evaluate the possible contribution of these diet aids in exacerbating symptoms of hypomania or mania or in precipitating affective illness.

Category:

29. Blum, A. Phenylpropanolamine: an over-the-counter amphetamine? (Editorial) J. Amer. Med. Assoc. 245, 1346-1347 (1981).

This is a polemic on phenylpropanolamine as an anorexiant drug. the author's position can be summed up by his statement, "there is no need for phenylpropanolamine."

Category:

29 a. O'Connor, T.W. Losing weight: the pharmacist's role in counseling obese people. NARD Journal 103, 49-53 (1981).

This educational presentation discusses the role of phenylpropanolamine preparations in weight reduction in a factual, dispassionate manner. It clearly addresses guidelines for the use of these medications, and points out succinctly their side effects and contraindications.

Category:

Review.

30. Personal communications: Letters of H.I. Silverman and R.S. Frank, March 2 and March 27, 1981.

These address the question of potential abuse of phenylpropanolamine in "look-alike" illicit dosage forms. No new information on adverse effects of this drug is presented.

Category:

Review.

30 a. Seppala, T., Nuotto, E., and Korttila, K. Single and repeated dose comparison of three antihistamines and phenylpropanolamine: psychomotor performance and subjective appraisals of sleep. Brit. J. C.in. Pharmacol. 12, 179-188 (1981).

In a double-blind randomized crossover study in 9 healthy young males, 50 mg phenylpropanolamine hydrochloride (compared to placebo) improved reaction times, decreased reaction mistakes, enhanced flicker recognition, and increased alertness. The authors concluded that phenylpropanolamine behaved as a mild psychomotor stimulant which can facilitate information retreival from the memory, that this drug did not produce significant mood elevation, did not adversely affect sleep, divided attention, speed anticipation, and tracking, and that the results of the study suggested that phenylpropanolamine is comparatively harmless to psychomotor performance and driving skills.

The design of the study (including the behavioral test employed and the statistical analyses used) appears to be highly appropriate. The conclusions of the authors seem to be backed up adequately by their findings. Interestingly, this is the first publication reviewed in which plasma or serum concentrations of phenylpropanolamine were measured.

Category:
Lack of significant cardiovascular effects.

30b. Duffy, W.B., Senekjian, H.O., Knight, T.F., Gyorkey, F. and Weinman, E.J. Acute renal failure due to phenylpropanolamine. Southern Med. J. 74, 1548-1549 (1981).

A 25-year-old male who stated he had ingested 34 "diet pills" (total dose of 1190 mg phenylpropanolamine and 4760 mg caffeine) in an attempt at suicide, presented at an emergency room 12 hours after the ingestion. Blood pressure was 120/76 mm Hg and BUN was 8 mg/dl. About 48 hours later, these increased to 160/100 and 52, respectively. Urinalysis showed 4 + proteinuria and " a trace of blood." Renal biopsy revealed interstitial edema, debris in the tubular lumen, and degeneration and regenerative changes in tubular epithelium. Initial 24-hour urine output was 100 ml, and endogenous creatinine clearance was 3 ml/min. The patient's condition apparently resolved 12 days post-ingestion.

The authors pointed out that their patient did not have severe hypertension or acute interstitial nephritis. This stands in contrast to other reports on phenylpropanolamine toxicity, and is especially surprising in view of the enormous overdose purportedly taken. In the last definitive statement in their article, the authors acknowledge this fact, and raise " the possibility that the nephrotoxic reaction to phenylpropanolamine was due to the co-ingestion of another drug with nephrotoxic potential." Although the authors were "not able to obtain such a history" (of such co-ingestion), the possibility more likely becomes a probability, particularly since the laboratory tests did not reveal an immunologic basis for the patient's condition.

Category:
Overdoses, combinations of drugs, drug misuse.

31. Griffiths, R.R., Brady, J.V., and Bigelow, G.E. Predicting the dependence liability of stimulant drugs. In: Thompson, T., and Johanson, C.E. (eds.) Behavioral Pharmacology of Human Drug Dependence, NIDA Research Monograph No. 37, pp. 182-196, DHHS Publication No. (ADM) 81-1137, U.S.G.O.P., Washington, DC, 1981.

This is a review article, in which the authors included results of their prior studies (Reference No. 12). No new information on phenylpropanolamine was provided, except for a statement that, in their extensive review of the literature, "There are no reports of human abuse of phenylpropanolamine in spite of its wide availability as a nonprescription anorectic sold on an over-the-counter basis."

Category:

Review.

31 a. Wellman, P.J., Malpas, P.B., and Wikler, K.C. Conditioned taste aversion and unconditioned suppression of water intake induced by phenylpropanolamine in rats. Physiol. Psychol. 9, 203-207 (1981).

In this study, phenylpropanolamine hydrochloride solutions (10, 20, and 40 mg/Kg) administered IP produced dose-dependent conditioned taste aversion to saccharin and dose-dependent unconditioned suppression of water intake.

The authors questioned the commonly-held assumption that the drug induces anorexia through the activation of a CNS satiety mechanism, and suggested that nonspecific malaise may mediate the drug's anoretic activity. Their arguments in this regard, however, appear to be based more on inference and speculation than on experimental data.

Category:

Animal pharmacological study.

32. The New Diet Pills. Consumer Reports, pp. 14-16, January 1982.

This is a report that lacks both completeness of coverage and easily-retrievable references. It contains many errors of fact. This article adds nothing to the literature which would be useful in assessing the safety of phenylpropanolamine used as an anorexiant.

Category:
Review.

32 a. Dougherty, R.J. Pseudo-speed: look-alikes or pea shooters. N.Y. State J. of Med., January 1982, pp 74-75.

The 3 case reports in this article clearly involve outright drug abuse -- the ingestion of enormous doses of capsules (up to 20 per day) containing (presumably) such drugs as phenylpropanolamine, caffeine, and ephedrine in varying amounts (prepared in "garage" laboratories), along with other drugs (notably alcohol and marijuana) in order to "get high." Hence, this article is of absolutely no use in assessing the safety of phenylpropanolamine used as an anorexiant.

Category:

Overdoses, combinations of drugs, drug misuse.

33. Gruson, L. A controversy over widely sold diet pills. New York Times, February 13, 1982.

This newspaper article is a polemic on phenylpropanolamine as used in appetite control medications. It contains many undocumented allegations. The article is therefore unscientific in nature, and cannot be used to evaluate the safety of such pharmaceuticals.

Category:
Review.

34. Phenylpropanolamine.

Silverman, H.I., and Lewis, B.P. J. Amer. Med Assoc. 247, 460 (1982)

Blum, A. J. Amer. Med. Assoc. 247, 460-461(1982).

This in an exchange of letters as a result of Dr. Blum's editorial (J. Amer Med. Assoc. 245, 1346-1347, 1981). They contribute no additional scientific information to the literature.

Category:
Review.

36. Altschuler, S., Conte, A., Sebok. M., Marlin, R.L., and Winick, C. Three controlled trials of weight loss with phenylpropanolamine. Internat. J. Obesity 6, 549-556 (1982).

This multisite double-blind study was designed primarily to determine the effectiveness of phenylpropanolamine/caffeine combination compared to placebo, mazindol, or diethylproprion in achieving weight loss by otherwise healthy subjects aged 18-65. Adverse side effects were reported by subjects in the study. With doses of phenylpropanolamine administered (37.5 mg b.i.d., 50 mg once per day, and 25 mg t.i.d.). 4/72 subjects reported dry mouth, diuresis, diarrhea, or constipation, 0/67 subjects reported any adverse effects, and 5/62 patients reported dry mouth, headache, nervousness, or cramps on the three regimens respectively. No hypertensive or other pressor effects were reported by physicians who examined these subjects weekly.

These data appear to confirm the commonly-observed adverse side effects seen in earlier clinical studies.

Category:

Lack of significant cardiovascular effects.

36 a. Federal Register 47 (101), Book 2, pp 22711-22930, May 25, 1982.

This is a review by a FDA panel on over-the-counter oral health care and discomfort drugs, and is mainly concerned with topical use of phenylpropanolamine in the form of a swab, spray, or lozenge. It presents little information on systemic uptake of the drug from these preparations, but the recommended warnings for topical use are very similar to those for oral use.

Category:

Review.

37. Federal Register 47 (39), pp. 8466-8484, February 24, 1982.

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products reviewed a number of reports on adverse effects of phenylpropanolamine, and recommended further studies to resolve safety questions raised by these reports, particularly as to hypertensive effects in normotensive patients, aggravation of preexisting hypertension, and interaction with aspirin and other prostaglandin systhesis inhibitors.

Category:

Review.

37 a. Gardner, E.R., and Hall, R.C.W. Psychiatric symptoms produced by over-the counter drugs. Psychosomat. 23, 186-190 (1982).

This is a literature review; no new information on phenylpropanolamine was presented.

Category:

Review.

38. Pentel, P., Mikell, F.L., and Zavoral, J. H. Myocardial injury after phenylpropanolamine ingestion. Brit. Heart J. 47, 51-54 (1982).

Three patients who had ingested phenylpropanolamine-containing medications developed hypertension, elevated serum creatinine kinase (MB isoenzyme) concentrations and ECG abnormalities. The latter 2 indicated myocardial injury.

Two of the cases were deliberate overdoses (ingestion of some 8 capsules and 40 talbets), but one of the patients admitted taking only one capsule (50 mg phenylpropanolamine, 4 mg chlorpheniramine, and 0.2 mg belladonna alkaloids). The presence of phenylpropanolamine and other components in the patients' urine was disclosed by thin layer chromatography and confirmed by GC/MS.

It is unfortunate that quantitative analysis of phenylpropanolamine in a 24-hour urine specimen was not performed in the patient who said she had taken only one capsule; this would have confirmed or denied this allegation. The authors concluded that myocardial injury may result from overdose of phenylpropanolamine-containing medications, and that an effort should be made to document the incidence and relation of this effect to drug dose. These points appear to be well taken.

Category:

Overdoses, combinations of drugs, drug misuse.

39. Escobar, J. I., and Karno, M. Chronic hallucinosis from nasal drops. J. Amer. Med. Assoc. 247, 1859-1860 (1982)

The use of phenylpropanolamine is not even implied in this article.

40. Mc Phail, R.C. Comparison of the effects of phenylpropanolamine and caffeine on schedule-controlled performance. Fed. Proc. 41, 1074 (1982).

This is an abstract of a paper (presumably presented at a FASEB meeting) on certain behavioral effects influenced by the 2 drugs. Doses of phenylpropanolamine administered (I.P. to rats, 3.125 to 25 mg/Kg) are much higher than those taken for therapeutic purposes by humans, so considerable doubt can be cast on attempting to transfer the results of this study (dose-related decrease in response) to man.

Category:

41. Editorial. Phenylpropanolamine over the counter. Lancet 1, 839 (1982).

This editorial presents no new information on adverse effects attributed to phenylpropanolamine. Its thrust appears to be towards regulating this drug in the United Kingdom.

Category:

Review.

42. Salzman, M.B. Phenylpropanolamine over the counter. Lancet 1, 1242 (1982).

This letter to the editor is in refutation to the editorial of the same title (Lancet 1, 839, 1982, Reference No. 41). It mentions a clinical study on the safety of phenylpropanolamine in over 400 obese patients to be presented to the U.S. FDA later in the year. (See Reference no. 70).

Category:
Review.

43. Bernstein, E., and Diskant, B.M. Phenylpropanolamine: a potentially hazardous drug. Ann. Emerg. Med 11, 311/43-44/312 (1982).

The first case presented was an 18-year-old obese female who apparently had no prior history of illness developed severe headache, nausea, epigastric pain, blurred vision, and shakiness after she admitted to taking 2 Comtrex tablets 2½ hours prior for "congestion." Hypertension (210/130 mm Hg) and tachycardia (120 beats/min) were apparent. A seizure enroute to the hospital, and another seizure soon after arrival occured. She became normotensive (118/80 mm Hg) within 4 hours after admission. Recovery was unremarkable.

Comtrex tablets contain a relatively small amount of phenylpropanolamine (12½ mg as the hydrochloride). If this drug is to be implicated in the patient's disease state, than it seems reasonable to assume she ingested many more than 2 tablets.

The other two cases involve ingestion of "look-alikes." In one case, history of possible hypoxia due to upper airway obstruction , arterial pO_2 was 52 mm Hg, and Kussmaul type of respiration was evident upon admission. At autopsy, extensive subarachnoid and intraventricular hemorrhages were found. In the other case, a CT scan revealed intracerebral hemorrhage, and evidence of bilateral brainstem disfunction was apparent. Intracerebral hemorrhage and intraventricular hemorrhage were confirmed upon autopsy. Even though no cerebral/vascular abnormalities were found in these patients, it is possible that their CVA's were not drug related.

Category:

Overdoses, combinations of drugs, drug misuse.

44. Rumack, B.H. Phenylpropanolamine: a potentially hazardous drug (Editorial). Ann. Emerg. Med. 11, 332/81 (1982).

This editorial is in response to Bernstein and Diskant's article (Ann. Emerg. Med. 11, 311/43 -44/312, 1982, see Reference No. 43). The author's impression was that the first patient had consumed "an excessive number of the tablets." He expressed the opinion that, when taken in prescribed amounts, the use of licit preparations containing phenylpropanolamine appears to be safe. His statement, "The 'look-alike' drugs have no reason to exist," is well taken. Indeed, the FDA believes that the triple combination of caffeine, phenylpropanolamine, and ephedrine found in the "look-alikes" presents a potential health hazard (Federal Register 47 (157) p. 35345, August 13, 1983.

Category:
Review.

45. Noble, R.E. Phenylpropanolamine and blood pressure. Lancet 1, 1419 (1982).

The author presents data from a clinical study involving more than 400 patients which indicates that 50 mg phenylpropanolamine taken three times per day ("twice the recommended dose for weight loss") over a 12-week period did not cause a significant increase in blood pressure. His data shows a reduction in blood pressure within the first 2 weeks after the drug regimen was instituted. The figure presented in his letter shows only pooled mean systolic and diastolic pressures; no statistical analyses are presented. He stated that the full report will be published elsewhere.

Category:

Lack of significant cardiovascular effects.

45 a. Knapp, M., and Avioli, L.V. Analgesic nephropathy. Arch. Internal Med. 142, 1197-1199 (1982).

The possible role of phenylpropanolamine in the patient discussed was not addressed.

Category:

Overdoses, combinations of drugs, drug misuse.

46. Cohen, B.I. Safety of phenylpropanolamine. Lancet 2, 96 (1982).

This short letter addresses dosage and phenylpropanolamine contents of 3 products containing this drug used for decongestant purposes, and provides no new information for safety evaluation.

Category:
Review.

47. Pentel, P., and Mikel, F. Reaction to phenylpropanolamine/chlorpheniramine/belladonna compound in a woman with unrecognized autonomic disfunction. Lancet 2, 274 (1982).

In a patient hypersensitive to the pressor effect of exogous epinephrine, a possible alpha-adrenergic hypersensitivity due to autonomic insufficiency was proposed to explain her supersensitivity to pressor effects of phenylpropanolamine. The argument appears logical, but a challenge with a "pure" alpha agonist which is not rapidly inactivated in the body, such as methoxamine, would strengthen it.

Category:

Hypertension.

48. Tornatore, F.L., and Gilderman, A.M. Substance-induced organic mental disorders. Amer. Pharmacy NS22, 43-46 (1982).

This review article presents no new information which could be used for assessment of adverse effects of phenylpropanolamine.

Category:

Review.

49. Swenson, R.[illegible], Golper, T.A., and Bennet[illegible], W.M.
Acute renal failure and rhabdomyolysis after ingestion of phenylpropanolamine-containing diet pills.
J. Amer. Med. Assoc. 248, 1216 (1982)

A 28-year-old female, after 3 weeks of supposedly taking (an unspecified amount of) an appetite suppressant containing phenylpropanolamine, was diagnosed as having rhabdomyolysis. Renal biopsy revealed interstitial nephritis.

A 21-year-old male, who had reportedly consumed " 9½ quarts of malted beverages and 30 to 50 appetite suppressant tablets, each containing 50 mg of phenylpropanolamine hydrochloride and 200 mg of caffeine (Dexatrim)", presented with signs and symptoms of myopathy, proteinuria and hemoglobinuria.

The authors attempted to link phenylpropanolamine ingestion to the development of rhabdomyolysis. Such a link in the first case described is very weak for a number of reasons. First, the amount of phenylpropanolamine consumed over the 3 week period (and the frequency of such drug use) is not documented in the article. Second, the use of other drugs or chemicals which could induce the disease is also not addressed. Third, the acute interstitial nephritis (perhaps more precisely called acute tubulointerstitial nephritis) could have been caused by the drug used to treat her bacteruria, ampicillin (Kempson, R.L., table in Dictionary and Encyclopedia of Laboratory Medicine and Technology, W. B. Saunders Co., Philadelphia, 1984, p.1537). In the second case, the authors themselves quote a reference that clearly showed that alcohol ingestion can cause rhabdomyolysis even in the absence of trauma (evidence to the lack of which is absent in the article). Again, documentation (except for the patient's say-so) of the use of drugs which can induce rhabdomyolysis is absent.

The argument by the authors for possible mechanisms by which phenylpropanolamine could cause rhabdomyolysis are by undeveloped analogy (to intravenous use of amphetamine) and by sheer speculation (exerting a direct toxic effect on the muscle cells or causing a sympathomimetically-induced depletion of nutrients in the muscle cells leading to injury or death of these cells).

Category:

Overdoses, combinations of drugs, drug misuse.

49 a. Smookler, S. and Bermudez, A. J. Hypertensive crisis resulting from a MAO inhibitor and an over-the-counter appetite suppressant. Ann. Emerg. Med. 11, 482/51-484/53 (1982).

This case report further documents the adverse (hypertensive) interaction between MAO inhibitors and phenylpropanolamine.

Category:

Interaction with monoamine oxidase inhibitors.

50. Friedman, R.B., Kindy, P., Jr., and Reinke, J.A. What to tell patients about weight-loss methods. 2.Drugs. Postgrad. Med. 72, 85-88 (1982).

No new information on adverse effects of phenylpropanolamine is presented.

Category:

Review.

50 a. Phenylpropanolamine effects. Psychosomat. 23, 1055 (1982).
Marshall, T.J.
Stoudemire, A.

A letter by Dr. Marshall states that phenylpropanolamine should be listed as an etiologic agent for catatonia.

A letter in reply by Dr. Stoudemire states that he is unaware of sympathomimetics causing catatonia, and at the present time, such a listing would be inappropriate.

No new information is thus provided.

Category:

Review.

51. Mueller, S.M., and Solow, E.B. Seizures associated with a new combination "pick-me-up" pill. Ann. Neurol. 11, 322 (1982).

This is a case report involving 2 seizures in a 17-year-old female who reportedly took a "look-alike" tablet thinking it was an amphetamine compound. Analysis of a tablet provided later by the patient indicated a large amount of caffeine with lesser amounts of phenylpropanolamine and pseudoephedrine. The report does not discuss possible prior drug abuse by the patient. It seems likely that she may have taken more than the one tablet she admitted to taking.

Category:
Overdoses, combinations of drugs, drug misuse.

52. Altschuler, C., Conte, A. Sebok, M, Marlin, R.L., and Winick, C. Three controlled trials of weight loss with phenylpropanolamine. Internat. J. Obesity 6, 549-556 (1982).

This was reviewed under Reference No. 36.

53. Weesner, K.M., Denison, M., and Roberts, R.J. Clin. Pediat. 21, 700-701 (1982).

A 14 year old female apparently ingested 15 to 18 capsules of a "look-alike" labelled RJ8 (25 mg ephedrine, 200 mg caffeine, and 50 mg phenylpropanolamine per capsule) in a suicide "gesture." Complex cardiac arrythmias were unresponsive to lidocaine but converted with propanolol.

The authors proposed a treatment plan to deal with arrythmias and hypertension induced by the "look-alike" stimulant preparations. They also pointed out the likelihood of the incidence of such toxicity increasing as the use of "look-alikes" increases.

Category:

Overdoses, combinations of drugs, drug misuse.

54. Greenblatt, D.G., and Shader, R.I. Phenylpropanolamine (Editorial). J. Clin. Psychopharmacol. 2, 369-370 (1982).

The authors of this editorial stated that phenylpropanolamine "is a stimulant and is marketed as such." They did not provide documentation for this statement. Hypertensive crisis as a result of interaction of MAO inhibitors and phenylpropanolamine was reemphasized in the editorial, along with a brief report of such a case in which the authors were involved.

Category:

Interaction with monoamine oxidase inhibitors.

54 a. Finton, C.A., Barton, M., and Chernow, B. Possible adverse effects of phenylpropanolamine (diet pills) on sympathetic nervous system function - - caveat emptor! (Editorial) Mil. Med. 147, 1072 (1982).

This editorial reviewed some of the adverse effects attributed to phenylpropanolamine. The authors averred that Horowitz et.al. (Reference No. 24) stated that "the advisory panel to the FDA has recommended an increase in the amount that could be put in the proprietary drugs." Not even an allusion to such a statement could be found in that journal article.

Category:

Review.

54 b. Silverstone T. Psychopharmacology of hunger and food intake in humans. Pharmacol. Therap. 19, 417-434 (1983).

This article reviews very briefly the anorexiant effect of phenylpropanolamine in humans reported by Hoebel et al., Obesity Bariat. Med. 4, 200-206 (1975) and by Griboff et al., Current Therap. Res. 17, 535-543 (1975). It does not provide information of use in assessing safety of the drug.

Category:

Review.

55. Howrie, D.L., and Wolfson, J.H. Phenylpropanolamine-induced hypertensive seizures. J. Pediat. 102, 143-145 (1983).

A 13-year-old female, during an office visit because of severe headache and nausea (blood pressure was found to be 210/100 mm Hg) vomited and had a seizure. Approximately 20 minutes later, in the emergency room, blood pressure was 170/100 mm Hg. About 4 hours after the first seizure, she had a second one. Following this episode, blood pressure was 120/60 mm Hg. The patient admitted to taking Dex-A-Diet II capsules (75 mg phenylpropanolamine and 200 mg caffeine, sustained release) for 2 weeks because a boyfriend told her she was "fat." She said she had taken 2 capsules on the morning of admission in "an effort to increase weight loss."

Because of her apparent intense desire to lose weight, it seems very likely that she may have ingested several more capsules that she admitted to.

Category:
Overdoses, combinations of drugs, drug misuse.

55 a. Soloway, R.A. Poisonings in the otolaryngologist's office. E.N.T.J. 62, 112-115 (1983).

A brief (unreferenced) mention of phenylpropanolamine being associated with "intractible" hypertension adds nothing to the literature on the drug.

Category:

Review.

56. Smith, D.E. Look-alike drugs and drugs of deception--epidemiological, toxicological, and clinical considerations. Internat. Drug Report 24(3), 3-7 (1983).

This is a rather comprehensive review of "look-alike" drugs. The author, based on his experience as Director of the Haight-Ashbury Free Medical Clinic, reported that the primary toxicity associated with these preparations are arrythmias and hypertensive episodes which are relatively short-lived. He stated that there is little clinical data on ephedrine toxicity in humans. His contention is that hypertensive crises, seizures, and intracranial hemorrhages have been ascribed to the phenylpropanolamine component, but most clinical situations "involve the high dose use of look-alike stimulants containing PPA with caffeine and/or ephedrine."

Category:
Review.

56 a. Bernstein, E., Diskant, B., Troutman, W., and Spaulding, C.T. Safety of phenylpropanolamine. Ann. Emerg. Med. 12, 130/591 - 592/131 (1983).

The authors stated that a review of the 1982 data from the New Mexico Poison Center showed that phenylpropanolamine-containing diet aid preparations "appear to have replaced the 'look-alikes'." Twenty-two patients were hospitalized after apparent ingestion of these preparations (20 had diastolic blood pressure in excess of 90 mm Hg). They admitted that most patients took large doses, but stated that two patients developed hypertension after one capsule, two after 2 capsules, one after 3 capsules, and 2 after 4 capsules. It would appear that the latter 5 patients were indeed overdosed. The authors cite the lack of an effective national data collection system for reporting toxic effects and overdose situations associated with diet aid preparations, but it would seem that the American Association of Poison Control Centers might be a useful avenue of approach to this problem, since this organization has in the past had a large degree of success in documenting poisonings from a wide variety of drugs and other chemicals.

Category:
Overdoses, combinations of drugs, drug misuse.

57. Mueller, S.M. Phenylpropanolamine, a nonprescription drug with potentially fatal side effects. N.E.J. Med. 308, 653 (1983).

The author briefly reviewed reports of toxic reactions to phenylpropanolamine-containing medications. The author appears to lump such drugs sold as nasal decongestants and diet aids with"look-alikes," sold for the (illicit) purpose of CNS stimulation as substitutes for amphetamine. A noteworthy comment was made that one commonly-used drug screening method, EMITR was demonstrated (at least by one laboratory) not to differentiate between amphetamine and phenylpropanolamine.

Category:

Review.

58. Nicholl, A.M., Jr. The nontherapeutic use of psychoactive drugs. N.E.J. Med. 308, 925-933 (1983).

Phenylpropanolamine in only briefly mentioned in this article, in the context of "look-alikes." No new information on this drug is presented.

Category:
Review.

59. Lake, C.R., Tenglin, R., Chernow, B., and Holloway, H.C. Psychomotor stimulant-induced mania in a genetically predisposed patient: a review of the literature and report of a case. J. Clin. Psychopharmacol. 3, 97-100 (1983).

This is a case of a 21-year-old male who had apparently ingested 4 "look-alike" capsules; during the next 4 days, his behavior became increasingly aberrant. He admitted to prior drug abuse (alcohol, marijuana, and LSD). Two of his older siblings were hospitalized with the same diagnosis as the patient (major bipolar affective disorder, manic) on "several occassions." The authors "speculate that accelerated release of norepinephrine following the ingestion of a central nervous system stimulant triggering a cycling or one-time manic episode lasting several weeks, especially in subjects genetically predisposed to bipolar affective disorder."

It is quite possible that the patient took many more capsules of the "look-alike" than he admitted to.

Category:
Overdoses, combinations of drugs, drug misuse.

60. Elkins, B.R., and Spoerke, D.G., Jr. An estimation of the toxicity of non-prescription diet aids from seventy exposure cases. Vet. Human Toxicol. 25, 81-85 (1983).

This is essentially a review of information accumulated by the Intermountain Regional Poison Control Center in a 5-month prospective study. Seventy patients met the criteria of the study (history of ingestion of a phenylpropanolamine-containing anorexiant, subsequent treatment, follow-up or evaluation by the Center staff or at a treatment facility). Ten cases involved products only containing phenlypropanolamine; 60 involved preaprations in which this drug and caffeine were both present. Children ages 0-5 years of age represented 56% of the cases; here, accidental ("exploratory") ingestion was presumed. "Young adults," 13-25 years of age, were responsible for 30% of all cases and 75% of the group taking the drugs for "self-destruction" or abuse purposes. Physician evaluation was required only in 16 cases. Only 2 patients were admitted to the hospital. The authors state that "the lack of serious side effects in either the cases with only PPA or combinations of PPA with caffeine raises questions about the serious reactions noted in earlier published reports."

The main criticisms than be levelled at this report are that it was a study of rather short term (5 months) conducted in a medium-sized city (Salt Lake City) whose population is largely composed of people belonging to a religious group (Mormons) who strongly condemn nonmedical use of drugs. Nonetheless, the study has set forth a model which could be implemented by other Poison Control Centers to result in a nation-wide survey of frequency and severity of toxic effects from the use of phenyl-propanolamine-containing preparations, not only from diet aids but also from oral decongestants ("cold" medications).

Category:

Overdoses, combinations of drugs, drug misuse.

60 a. Lund, M.E. Over the counter overdose. Emerg. Med. 15, 175-188 (1983).

No new information is presented re toxicity of phenylpropanolamine. Several errors of fact are apparent.

Category:
Overdoses, combinations of drugs, drug misuse.

61. Greenwood, [illegible] The case against phenylpropanolamine. Pharmaceut. J., May 21, 1983, pp. 585-586.

No new information on toxicity of phenylpropanolamine is presented.

Category:
Review.

62. Krenzelok, E.P. Street speed. The Pennsylvania Pharmacist, May, 1983, pp. 149-150.

This article mainly addresses "look-alikes." It presents a useful aid to presumptive identification of the more common forms based on the color of the capsules or tablets, the "product identification codes," and the shapes of the tablets.

Category:
Review.

62 a. Mueller, S.M. Neurologic complications of phenylpropanolamine use. Neurol. 33, 650-652 (1983).

Abstracted information from case reports of 11 patients who took "look-alikes" was presented. The authors did not mention the almost universal inclusion of ephedrine or pseudoephedrine, along with large amounts of caffeine, in these "street" forms.

Category:

Overdoses, combinations of drugs, drug misuse.

63. Renal failure, rhabdomyolysis, and phenylpropanolamine. J. Amer. Med. Assoc. 249 (1983).

Blewitt, G.A. and Siegel, E.B., p. 3017

Golper, T.A., Bennett, W.M., and Swenson, R.D., pp. 3017-3018

This is an exchange of letters which contains no new factual information.

Category:

Review.

63 a. Cohen, S. The rise and fall of the look-alikes. Drug Abuse and Alcoholism Letter 12 (4), June 1983.

This is a highly readable short article on the history of "look-alikes." No new information on phenylpropanolamine is presented.

Category:

Review.

64. Caperton, E. Raynaud's phenomenon -- role of diet pills and cold remedies. Postgrad. Med. 72, 290-291 (1983).

Three young women presented with Raynaud's phenomenon which apparently promptly disappeared upon discontinuation of use of "diet pills" or "cold remedies" which contained phenylpropanolamine.

Not enough information is presented in this report to evaluate the role of this and other drugs contained in the preparations in the patients' conditions.

Category:

Raynaud's phenomena.

64 a. Phenylpropanolamine. Amer. Fam. Physician 27, (1983)
Saltzman, M.B., pp.23and 26
Calesnik, B., pp.26 and 28

This is an exchange of letters which contribute no new information to the literature.

65. George, E. Lawsuit claims Dexatrim pill caused stroke. Arlington Journal, July 15, 1983.

This newspaper article reported on a case wherein the plaintiff "said he used the diet aid not to help him lose weight but in the hopes that it would help him stay awake during a long auto trip." Another statement attributed to the plaintiff was, "people said it (Dexatrim) was like speed." If these statements are true, then this use of the preparation is clearly a misuse. Insufficient information on clinical course, use of other drugs, etc. is presented for any further evaluation of the case.

Category:

Overdoses, combinations of drugs, drug misuse.

65 a. McEwan, J. Phenylpropanolamine-associated hypertension after the use of "over-the-counter" appetite suppressant products. Med. J. Austral. 2, 71-73 (1983).

This report summarizes data from 8 apparently normotensive women who developed hypertension after taking appetite suppressant preparations containing approximately 60-85 mg phenylpropanolamine hydrochloride. Two of the patients admitted to taking twice the recommended dose. Details on prior blood pressures were not available.

Very little definitive information is presented. Several of the patients admitted taking other drugs. The patients' severe headaches, anxiety, and mental trauma on admission to the hospital could have contributed markedly to increased blood pressures.

Category:
Overdoses, combinations of drugs, drug misuse.

66. Krupka, L. R., and Vener, A.M. Over-the-counter appetite suppressants containing phenylpropanolamine hydrochloride (PPA) and the young adult: usage and perceived effectiveness. J. Drug Education 13, 141-152 (1983).

This is an "opinion-type" study without controls. Validation of the instrument employed (self-administered questionnaire) was not mentioned. The report contributes little to information on the adverse effects of phenylpropanolamine.

Category:

Overdoses, combinations of drugs, drug misuse.

66a. Committee on Drugs. "Look-alikes." Pediat. 72, 256-257 (1983).

This position paper does not add any new information about either "look-alikes" or other phenylpropanolamine-containing preparations.

Category:

Review.