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Report of a Fatal, Acute Tripelennamine Intoxication

Tripelennamine[2] is a widely used antihistamine. It has been reported as a drug of abuse ("blue velvet") with multiple deaths being attributed to its chronic intravenous usage [*1*]. Acute oral ingestion resulting in death, however, is unusual. There has been one reported death in a 2-year-old child [*2*], but thus far no deaths have been reported in adults due to tripelennamine overdose. This report presents both autopsy findings and toxicological analysis in what we believe is the first fatal case in an adult.

Case Report

A 19-year-old Caucasian male weighing 170 lb ingested approximately twenty 50-mg tripelennamine tablets following an argument with his wife. He was then noted to fall asleep. Approximately six hours later he began having tonic-clonic grand mal seizures and was taken to the hospital by a rescue squad. En route he suffered cardio-respiratory arrest and arrived without heart action or spontaneous respirations. During externally administered cardiac massage, he regurgitated material recognizable as partially digested tablets (not submitted for toxicological analysis). Resuscitative efforts were unsuccessful. The time lapse between ingestion and death was approximately seven hours. His medical records revealed no evidence of significant medical conditions.

An autopsy was performed five hours postmortem. Multiple small petechial hemorrhages were observed in the soft tissues of the scalp. There was 100 ml of straw-colored fluid in each pleural space. The right lung weighed 750 g and the left 575 g. On sectioning, the lungs exuded a large amount of pink frothy fluid. Microscopic examination confirmed the pulmonary edema. Focal areas of intra-alveolar hemorrhage were also noted. No evidence of aspiration was observed. The brain was unremarkable, both grossly and microscopically. The remainder of the autopsy was unremarkable.

Toxicological analysis was performed on postmortem blood, liver, brain, kidney, urine, and gastric contents. Large concentrations of tripelennamine were detected by

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[2] Pyribenzamine®, manufactured by Ciba Pharmaceutical Co., 566 Morris Ave. Summit, N.J. 07901.

ultraviolet spectroscopy and verified by gas-liquid chromatography (Table 1). No alcohol, acidic drugs, or other basic drugs were detected by ultraviolet spectroscopy or gas-liquid chromatography.

TABLE 1—*Tissue concentrations of tripelennamine.*

Specimens for Analysis	Concentrations of Tripelennamine, mg/100 ml or mg/100 g
Blood	1.0
Liver	8.3
Brain	4.3
Kidney	3.5
Urine	28.7
Gastric contents	107.0

Tripelennamine was detected in routine screening for organic basic compounds. Blood; urine; tissue homogenates of liver, brain, and kidney; and gastric contents were made alkaline and extracted with ether. The organic phase was extracted with 0.5*N* sulfuric acid. The ultraviolet absorption spectrum of tripelennamine is similar to that of methapyrilene, another common antihistamine, with maximal peaks at 238.5 and 312 nm. However, if the pH of the sulfuric extract solution is made alkaline, there is a shift in the maximum absorption of tripelennamine but not methapyrilene. At an alkaline pH tripelennamine has peaks at 248.5 and 310 nm (Fig. 1).

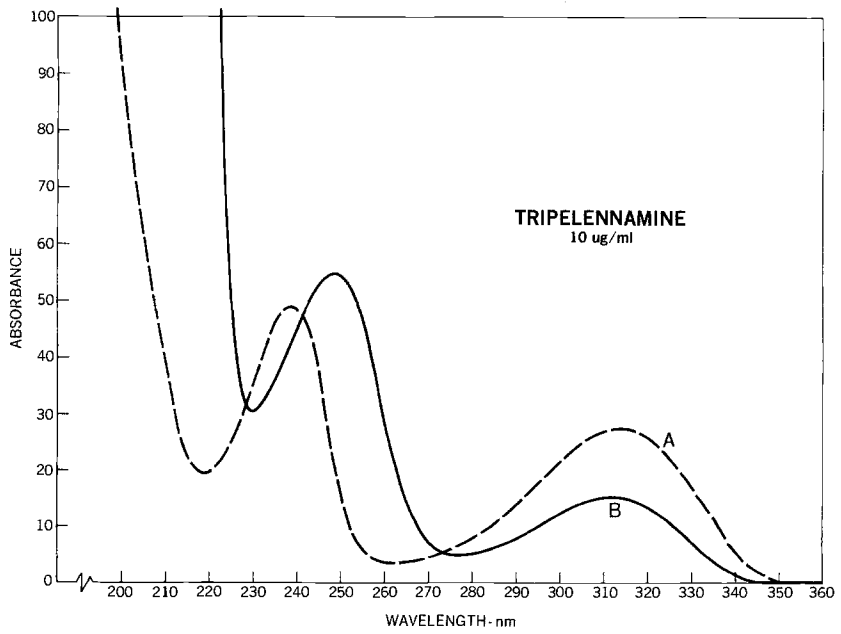

FIG. 1—*Ultraviolet absorption spectra of tripelennamine:* A = *10 μg/ml acid and* B = *10 μg/ml base.*

Analysis by gas-liquid chromatograph was performed employing a Perkin-Elmer Model 900 chromatograph equipped with a flame ionization detector. Extracts were injected into a 3% OV-17 Gas-Chrom W HP 6-ft glass column, using tetraphenylethylene as an internal standard. Tripelennamine had a relative retention time of 0.72 (Fig. 2) under the following conditions:

Injection port temperature: 280°C
Manifold temperature: 280°C
Column temperature program: 115°C for 3 min, increasing 16°C/min to 260°C, holding for 12 min
Gas flow rate: helium (carrier gas), 50 psi
Attenuation: 32 × 10

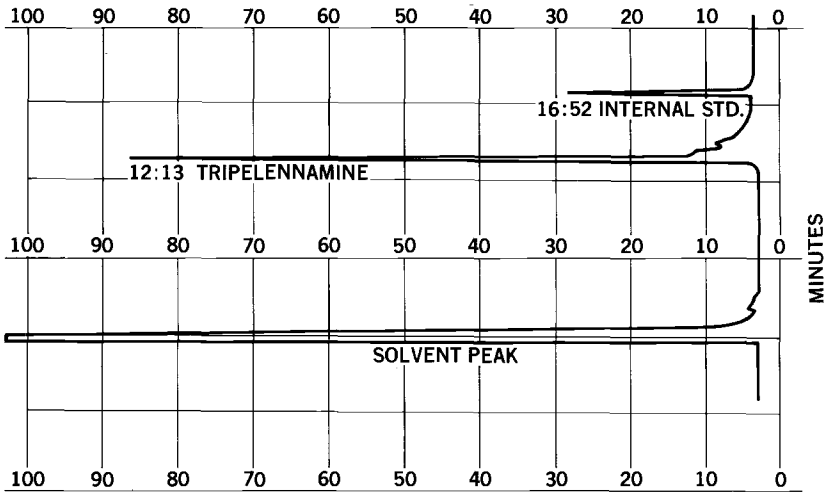

FIG. 2—*Representative chromatogram depicting the relative retention time of tripelennamine.*

Discussion

Tripelennamine is a synthetic antihistamine available as the hydrochloride or citrate salt of 2-(benzyl (2-dimethylamine) ethyl) amino pyridine. The drug is widely prescribed for control of allergic conditions and acts as a competitive antagonist of histamine. Pharmacological effects are evident within 15 to 30 min and maximal effects are reported at 1 to 2 h. The duration of action is 4 to 6 h. The drug is rapidly absorbed and tissues are free of the drug in about 6 h. The majority of the drug is biotransformed primarily in the liver, though some metabolic conversion has been noted in the lung and kidney [*3*]. Tripelennamine is then excreted in the urine and bile. The enterohepatic circulation reabsorbs the compound which is finally excreted in the urine.

The recommended dosage of tripelennamine for an adult is 50 to 100 mg once or twice daily. Serial blood plasma concentrations in subjects receiving a 100-mg oral dose have a maximum concentration of 0.06 μg/ml at 2 and 3 h post ingestion [*4*]. Our patient was alleged to have ingested an oral dose of approximately 1 g (10 times therapeutic). The postmortem blood level represents a concentration reached approximately 7 h post ingestion. The concentration of 1.0 mg/100 ml blood (or 10 μg/ml)

obtained is greater than 100 times the maximum level reached from a single therapeutic dose.

Reports of serious toxicity from antihistamine appear to be relatively rare [5]. The toxic effects of antihistamines have been reviewed by Wyngaarden and Seevers [6] and multiple cases of poisoning, primarily in children, have been reported [6–9]. In a lethal case in which a 2-year, 9-month-old child ingested an unknown number of Plimasin®[3] tablets [2], tripelennamine and methylphenidate drug concentrations were measured in the various tissues with the highest levels being in the bile and liver. The usual symptoms are either excitation or depression of the central nervous system (CNS). At toxic levels children commonly have signs of CNS excitation characterized by nervousness, tremors, hyperactivity, and occasionally convulsions. On the other hand, adults usually show symptoms of CNS depression with dizziness, inability to concentrate, deep sleep, and (in high doses) depression of vital function.

Toxicity studies in animals have shown that high doses of antihistamines produce CNS stimulation which is progressive and characterized by restlessness, irritability, and convulsions [4]. Tripelennamine has been shown to increase petit mal seizure activity in a group of epileptic children [4].

Tripelennamine has not previously been reported as a drug commonly used for suicide. It has, however, been well characterized as a drug of abuse [1], where the oral preparation is injected intravenously by addicts as "blue velvet." The usual cause of death from abuse has not been attributed to overdose but rather acute cor pulmonale as a result of prolonged right-sided failure secondary to increased pulmonary vascular resistance. The pulmonary disease is the result of foreign body granulomas due to the talc present in the oral preparation.

Treatment of an acute overdose requires support of vital function. Gastric lavage with activated charcoal is extremely important, as illustrated by the residual level of tripelennamine in the postmortem gastric contents. CNS stimulants should be used only with extreme caution, *if at all,* in view of the CNS stimulation that occurs from the drug [6].

Summary

A death resulting from tripelennamine overdose in a 19-year-old male Caucasian is reported. The patient died 7 h after ingesting approximately twenty 50-mg tripelennamine tablets. A concentration of 1.0 mg/100 ml was found in the blood. All tissue concentrations were measured by ultraviolet spectroscopy and verified by gas-liquid chromatography. Significant findings included pulmonary edema and multiple small petechial hemorrhages in the soft tissue of the scalp.

Acknowledgments

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[3] Plimasin®, also manufactured by Ciba, contains 25 mg tripelennamine hydrochloride and 5 mg methylphenidate hydrochloride per tablet.

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