CASE REPORT

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Fatal Ephedrine Intoxication

REFERENCE: Backer R, Tautman D, Lowry S, Harvey CM, Poklis A. Fatal ephedrine intoxication. J Forensic Sci 1997; 42(1):157–9.

ABSTRACT: A 28-year-old white female with a history of two prior suicide attempts was found dead in her home by her common law husband. Autopsy findings were unremarkable except for partially dissolved ephedrine tablets in the stomach contents. Quantitation of ephedrine was by gas chromatography/mass spectrometry (GC/MS) following liquid/liquid extraction from alkaline samples and pentafluoropropionic acid derivatization. Significant toxicological finding included ephedrine; blood, 11 mg/L; liver, 24 mg/kg; kidney, 14 mg/kg; brain, 8.9 mg/kg; and amitriptyline; blood, 0.33 mg/kg; liver 7.8 mg/kg. The ephedrine values found far exceed those associated with therapeutic administration and are consistent with the few reported cases of severe ephedrine intoxication. The cause of death was determined to be fatal ephedrine intoxication and manner of death suicide.

KEYWORDS: forensic science, forensic toxicology, ephedrine, overdose, poisoning, fatality

Ephedrine (phenyl-isopropanol-methylamine) an alkaloid present in numerous species of Ephedra, is a prototypical sympathomimetic drug, having both alpha and beta adenergic activity (1,2). Its pharmacological activity is due to indirect adenergic stimulation by releasing norepinephrine and dopamine from neuronal stores, and by direct action on alpha and beta adenergic postsynaptic receptors. The Chinese have used the herb "ma-huang," dried stem of ephedra species as a remedy for various diseases for over 5000 years (1,3). Ephedrine was isolated by Yamanshi in 1885 and the pure drug was introduced into therapeutics as a bronchodilator by the Japanese around the turn of the century. Since then, ephedrine has been indicated for the treatment of enuresis, hypotension, myasthenia gravis, and narcolepsy; but, it was most common use had remained the treatment of asthma at daily doses of 25 to 200 mg, either alone or in combination with theophylline and/or barbiturates (1,2). However, in the U.S.A., the use of ephedrine as a bronchodilator has greatly diminished over the past 20 years. Recently "over the counter" and "natural health" products containing ephedrine have been abused for their stimulant properties (4). Additionally, ephedrine is now used as the primary precursor for the synthesis of methamphetamine and methcathinone in clandestine drug manufacturing laboratories (5).

In instances of ephedrine overdose, cardiovascular and central nervous system stimulant effects predominate including increased blood pressure and heart rate, anxiety and agitation progressing to seizure (1). Chronic abuse of high doses has been associated with the development "stimulant psychosis" (3,6).

Despite its widespread use over many years, ephedrine has rarely been associated with fatal intoxications, usually only in combination with other stimulants. We present a case of fatal ephedrine overdose of a young woman while receiving antidepressant medication.

Case History

A 28-year-old white female was found dead at approximately 11:00 a.m. in her home by her common law husband. He had last spoken by telephone to the decedent the prior evening. At that time, the couple had decided to end their cohabitation. The decedent was found in the bathroom, slumped over, with her head between the tub and toilet. Dried blood was noted on the toilet tank and a bathroom waste basket. The decedent had prescriptions for amitriptyline 50 mg (92/100 tablets remaining) and Tylenol capsules (29/30 remaining). She had a history of two prior suicide attempts, one by firearm and one by overdose of prescription drugs.

Autopsy

The body, 66 in. in length and weighing 124 lb was that of a normally developed adult female of average build and nutritional status exhibiting normal hydration. With the exception of generalized visceral passive congestion, a lower incisor laceration to the lower lip and scars from an old gunshot wound, gross and histological findings were unremarkable. Partially dissolved white tablets were recovered in the gastric and duodenal contents. Specimens were collected and sent for toxicological analysis.

Toxicological Analysis

Initial analysis: Blood was initially screened for ethanol using an enzymatic/radiant energy technique; salicylates by trinders reagent and for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, and phencyclidine by enzyme immunoassay

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Received 31 March 1994; and in revised form 30 May 1994, 7 Feb. 1996, and 15 April 1996; accepted 18 June 1996.

after protein precepitation. GC/MS analysis of a methanolic solution of the recovered tablet fragments disclosed the presence of ephedrine.

Qualitative GC/MS blood analysis: Additionally, blood was extracted and analyzed by GC/MS in the following manner: To 2.0 mL aliquots of calibrator (2.5 mg/L in drug free blood), control (1.8 mg/L, 2 mL blood), drug free blood and autopsy blood was added 5 mg/L ketamine as the internal standard. To each aliquot, 10.0 mL of n-butyl chloride/ether (3:1) was added. The aliquots were vortexed for 15 min, then centrifuged for 5 min and the organic top layer was drawn off into a new tube. 2.0 mL of 2 N HCl was added to each extract which was the vortexed for 15 min and centrifuged for 5 min. The bottom aqueous layers were then removed using a 2-mL glass pipette and placed into clean 15-mL centrifuge tubes. Dry nitrogen was gently bubbled through the extracts at 80°C for 3 min until the ether odor had dissipated. The pH of the solutions were then adjusted to between 8 and 9 with the addition of 3.0 mL of pH 9 carbonate buffer. The solution was extracted with 100 uL of chloroform by vortexing for 1 min followed by centrifuging for 5 min. Two microliter aliquots from the bottom chloroform layer were then injected into the GC/MS.

GC/MS analysis was performed on a Hewlett-Packard 5890 GC equipped with a 12.5 m by 0.2 mm (ID) by 0.33 μ (film thickness) cross linked 5% phenyl silicone capillary column connected to a Hewlett-Packard 5971-A mass selective detector. Data processing was performed with a HP Chemstation (Version 3.2 software) in the scan mode monitoring m/z ions from 44–600. The GC/MS was operated in the splitless mode for 0.1 min with a helium carrier gas linear velocity of 20 mL/min. Initial oven temperature was 70°C for 1 min with an injection port temperature of 250°C. The temperature was ramped at 20°C/min to a final temperature of 280°C which was held for 10 min.

Qualitative tissue analysis: To separate 5.0 g samples of liver, kidney, and brain tissue were added 10 g of distilled water. The samples were then homogenized in a mini-adapted Waring Blender. Drug free samples of liver were treated in the same manner and used for the preparation of assay controls and calibrators. Two-mL aliquots of each tissue homogenate were then extracted and analyzed as described above for qualitative blood analysis.

Quantitative ephedrine analysis: GC/MS quantitation of ephedrine was based on the method of Thurman et al. (7). To 2.0-mL aliquots of calibrator (500 ng/mL of ephedrine in drug free blood), control (625 ng/mL of ephedrine in drug free blood), drug free blood and autopsy samples was add 500 ng/mL of amphetamine-d5 as the internal standard. Aliquots were extracted as described above except that the final chloroform extracts were evaporated and the residues were dissolved in 50 μL of ethyl acetate and 50 μL of pentafluoropropionic anhydride for derivatization of ephedrine. The mixtures were heated for 15 min at 80°C and then evaporated to dryness at 80°C under dry nitrogen. The residues were reconstituted with 100 uL of ethyl acetate and 2-uL aliquots were injected into the GC/MS.

GC/MS analysis was performed with the same instrumentation and settings as described above with the following exceptions: The temperature program rate was 25°C/min to 175°C, 50°C/min to 280°C; data was collected in the SIM mode monitoring m/z ions 204, 205, 160 (ephedrine) and 194, 123 (amphetamine-d5) with a dwell time of 50 ms for each ion. Under the conditions of the assay ephedrine is well resolved from pseudoephedrine, phenylpropanolamine, and other common phenylisopropylamine derivatives.

Results

The results of the toxicological analysis are presented in Table 1. Amitriptyline concentrations in blood and liver were consistent with antidepressant therapy (8). Further, there were the expected number of amitriptyline tablets remaining in the prescription bottle had she been taking her medication as directed. Therefore there is no evidence that an overdose of amitriptyline was ingested. Ephedrine blood and tissue concentrations greatly exceed those associated with therapeutic administration by two orders of magnitude (9,10). Additionally, the ephedrine blood concentration was consistent with those of previously reported instances of toxicity (11) and fatalities (4,12). No container of ephedrine or ephedrine drug mixtures was found at the sence. The source of the ephedrine tablets remains unknown.

Discussion

Ephedrine is readily absorbed after oral administration with peak plasma concentrations within an hour of ingestion. A single oral dose of 24 mg, seldom results in peak plasma concentrations exceeding 0.1 mg/L (9). Following oral daily dose of 33 mg, peak plasma concentrations ranged from 0.07–0.12 mg/L (mean, 0.08 mg/L) in 10 study subjects (10). The plasma half-life of ephedrine ranges from 3–11 h and is dependent on urinary pH (13). The drug is primarily eliminated by the kidney with 70–80% of a dose excreted unchanged in urine (14).

Ephedrine has rarely been associated with fatal intoxications, usually only in combination with other stimulants. Nevertheless, taken in large doses, it is a potentially toxic substance and should be administered with care. In experimental animals, a fatal dose produces both respiratory and cardiac failure and it is difficult to determine which of these is the primary cause of death (1). Both in intact animals and in perfused isolated mammalian hearts, ephedrine has demonstrated direct cardiac depression (15,16). Single large doses or repeated small doses weaken ventricular contraction. Convulsions due to either direct central stimulation or asphyxia are also characteristic of ephedrine poisoning in animals (1,15,16).

The estimated lethal dose of ephedrine in man is 2 g; however, 400-mg doses have been given without causing serious toxic effects (17). A 20-year-old woman survived the ingestion of 7.5 g after developing agitation, anxiety, tachycardia, hypertension, and emesis (11). Her plasma ephedrine concentration was 23 mg/L, 1.5 h post ingestion. Ephedrine blood concentrations in a series of fatalities due to the ingestion of ephedrine/caffeine stimulant "look-a-like" combinations ranged from 3.5 to 20 mg/L (4). Similarly in a single fatality due to ingestion of 2.1-g ephedrine and 7.0-g caffeine, blood and liver ephedrine concentrations were 5 mg/L and 15 mg/Kg, respectively (12). The ephedrine values in the presented case are consistent with these previous cases.

TABLE 1—*Toxicology results.*

Specimen	Amitriptyline	Ephedrine
Blood	0.33 mg/L	11 mg/L
Brain	NA*	8.9 mg/Kg
Kidney	NA*	14 mg/Kg
Liver	7.8 mg/Kg	24 mg/Kg
Gastric	negative	positive

*NA = not analyzed.

Conclusion

Based upon the lack of significant anatomical pathology and the toxicology findings, the cause of death was determined to be fatal ephedrine intoxication. From the case investigation and autopsy findings, the manner of death was ruled suicide. This is an unusual case in that ephedrine, ingested in a large overdose quantity, was successfully used for suicidal purposes.

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