Case Report

Fatality Due to Acute α-Methyltryptamine Intoxication

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Abstract

In February 2003, the Miami-Dade County Medical Examiner Department reported the first known death in the country related to α-methyltryptamine (AMT). AMT is an indole analogue of amphetamine investigated in the 1960s as an antidepressant, stimulant, and monoamine oxidase inhibitor. Today, AMT is recognized as a powerful psychedelic drug among high school and college-aged men and women. Its popularity is partly due to the multitude of anecdotal websites discussing AMT as well as its legality and availability for purchase via the Internet prior to April 2003. Emergency designation of AMT as a Schedule 1 controlled substance by the Drug Enforcement Administration occurred shortly after the death in Miami-Dade County. The case in Miami involved a young college student who, prior to death, advised his roommate that he was "taking hallucinating drugs" and as a result had "discovered the secret of the universe". Approximately 12 h later, the roommate discovered the deceased lying in bed unresponsive. An empty 1-g vial of AMT was recovered from the scene and sent to the toxicology laboratory. Initial screening of urine by enzyme-multiplied immunoassay technique was positive for amphetamines, and the basic drug blood screen detected a small peak later identified by mass spectrometry as AMT. For quantitation, AMT was isolated using solid-phase extraction, derivatized with pentafluoropropionic anhydride, and analyzed using gas chromatography–mass spectrometry. Quantitative analysis was based upon *m/z* 276, 303, and 466 for AMT and *m/z* 306, 333, and 496 for the internal standard, 5-methoxy-alpha-methyltryptamine. A linear calibration curve from 50 to 500 ng/mL was used to calculate the concentration of AMT in the samples and controls. Blood, tissue, and gastric specimens were diluted to bring the observed concentration within the limits of the standard curve. Matrix matched controls were extracted and analyzed with each run. Postmortem iliac vein blood revealed 2.0 mg/L, gastric contents (48 g collected at autopsy) contained 9.6 mg total of AMT, liver contained 24.7 mg/kg, and the brain contained 7.8 mg/kg. An additional Medical Examiner case from another jurisdiction revealed 1.5 mg/L in antemortem serum.

Introduction

α-Methyltryptamine (AMT) is a synthetic drug of the tryptamine family. It is an indole analogue of amphetamine initially investigated as a monoamine oxidase inhibitor. In the 1960s, the Soviet Union marketed AMT as an antidepressant under the name of Indopan. During the same period, Sandoz (as IT-290 and IT-403) and the Upjohn Company (as U-14 and 164E) studied AMT and its commercial use as a stimulant, but found it to be of little medicinal value. Although clinical use of AMT is obsolete today, recreational use has gained popularity because of the intense hallucinogenic properties lasting up to 16 h. To illustrate recreational use of AMT in the 1960s, Alexander Shulgin, in his book *TiHKAL*, references the author Ken Kesey and his experiences with AMT and other hallucinogenic drugs (1).

There has been a wide range of reported effects for AMT, indicating a great deal of individual variability. For some, AMT has a fast onset, whereas for others it has a relatively slow onset. Some individuals find AMT to be a powerful psychedelic, whereas others are disturbed by the negative physical side effects. In general, at low dosages (15–30 mg orally, 5–20 mg smoked), AMT produces powerful hallucinations. Depending on the individual, however, AMT can cause negative effects that are more typical at higher dosages (80–100 mg orally). Neurologic manifestations that may occur at low or high dosages include agitation, restlessness, confusion, and lethargy. Physical manifestations including vomiting, pupillary dilation, jaw clenching, tachycardia, mydriasis, salivation, diaphoresis, and mild elevations in blood pressure, temperature, and respiratory rate may also occur at low and high dosages (1,2). Generally, at higher dosages, individuals do not experience any visuals or hallucinations but do experience extreme depersonalization.

Because of the hallucinogenic properties of AMT and the multitude of anecdotal reports on drug-related internet websites, it has become recognized as a powerful psychedelic drug among high school- and college-aged men and women who may have experienced the effects of other hallucinogens. Its popularity is partly due to the legality and availability of AMT for purchase via the Internet prior to April 2003 (3). Emergency designation of AMT as a Schedule 1 controlled substance by the Drug Enforcement Administration occurred shortly after the Miami-Dade Medical Examiner reported the death of a 22-year-old college student who ingested a large amount of AMT (4). Prior to death, the deceased advised his roommate that he was "taking hallucinating drugs" and as a result had "discovered the secret of the universe". The roommate reported that the deceased was shaking and sweating profusely, waving a knife, and threatening to commit suicide. The roommate tied the de-

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ceased to the bed for his own protection and left him to "sleep it off". Approximately 12 h later, the roommate discovered the deceased lying in bed unresponsive.

An autopsy by the medical examiner revealed no gross abnormalities of any organs, including the heart and brain, and no evidence of traumatic injuries. Urine, iliac vein blood, gastric contents, liver, and brain specimens were sent for toxicological analysis. Also recovered from the scene and sent to analysis was a 1-g vial labeled α-methyltryptamine containing a trace amount of white residue (Figure 1).

Materials

AMT and cyclizine were purchased from Sigma-Aldrich Company (Milwaukee, WI). The internal standard, 5-methoxy-alphamethyltryptamine (5-MeO-AMT), was provided by the Drug Enforcement Administration. All standards were used without further purification. Standard stock solutions of AMT and 5-MeO-AMT were prepared at a concentration of 1.0 mg/mL in methanol. All reagents utilized were analytical grade.

Toxicological Analysis

Initial drug screening

The initial screening of the gastric contents and the blood and urine specimens was by immunoassay (EMIT, Hitachi 705 Analyzer, Syva® Diagnostic Products and ELISA, P-Lab Analyzer, OraSure Technologies, Inc.) for benzodiazepines, barbiturates, opiates, benzoylecgonine, amphetamines, and phencyclidine. The urine and gastric contents were further screened by thin-layer chromatography (Toxi-Lab® Ansys Technologies, Inc.). Volatile substances were screened using headspace gas chromatography (GC). Collectively, these initial analyses provided negative results for benzodiazepines, opiates, barbiturates, benzoylecgonine, phencyclidine, and ethanol. Immunoassay analysis of the urine and gastric contents provided a positive result for amphetamines.

Figure 1. Vial labeled "α-Methyltryptamine" found with the deceased.

Qualitative blood analysis

The qualitative screening procedure that disclosed the presence of AMT was a general drug screen for chemically basic drugs adapted from Pierce et al. (5). Briefly, 1 mL of saturated sodium borate buffer (pH 9) and 1 mL of cyclizine internal standard (0.50 mg/L in deionized water) were added to 1 mL of whole blood and vortex mixed. After the addition of 8 mL of *n*-butyl chloride, the mixture was rotated for 15 min followed by centrifugation at 3000 rpm for 10 min. The upper organic phase was transferred to a clean test tube containing 1.5 mL of hydrochloric acid (HCl, 0.10M). The mixture was vortex mixed for 1 min and centrifuged at 3000 rpm for 5 min. The upper organic phase was aspirated and discarded, and the remaining aqueous acid layer was alkalinized by the addition of 150 µL of sodium hydroxide (NaOH, 1.0M) and 2.0 mL of saturated sodium borate buffer (pH 9). After the addition of 8 mL of *n*-butyl chloride, the mixture was rotated for 15 min, followed by centrifugation at 3000 rpm for 5 min. The organic phase was transferred to a clean test tube containing 2–3 drops of 1% concentrated HCl in methanol. The extract was evaporated to dryness at 40°C under a stream of nitrogen and reconstituted with 50 µL of methanol. Extracts were transferred to autosampler vials for analysis on a dual-column GC equipped with nitrogen-phosphorus detectors (GC–NPD).

The GC system consisted of a Hewlett-Packard model 5890 series II GC equipped with dual NPDs and a 7673A autosampler. A guard column connected the injection port to a fused silica y-connector joined to two columns. The columns used were a DB-1 (100% dimethylpolysiloxane) and a DB-17 (50%-phenylmethylpolysiloxane) capillary column (30 m × 0.25-mm i.d., 0.25-µm film thickness, Agilent Technologies, Palo Alto, CA). The column temperature was 50°C for 1 min, then increased to 190°C at 20°C/min. The temperature was held at 190°C for 1 min, then ramped to 300°C at 5°C/min, and maintained for 30 min. Identification was based on relative retention times on both columns, and confirmation was by GC–mass spectrometry (MS).

Quantitative AMT analysis

Stock standard solutions of AMT for quantitation were prepared in methanol and stored at –15°C. A working standard of AMT was prepared by serial dilution of the stock standard solution and comprised four concentrations ranging from 50 to 500 ng/mL. The extraction procedure for the samples, standards, and blank was performed using United Chemical Technology Clean Screen solid-phase extraction columns, which were installed on a Zymark RapidTrace System. No sample preparation was required for the iliac vein blood; however, it was necessary to homogenize the liver and brain by blending 5 g of specimen with 20 g of phosphate buffer (pH 6, 100mM). Samples were prepared by diluting 1.0 mL of each with 4.0 mL of sodium phosphate buffer (pH 6, 100mM) and 50 µL of 5-MeO-AMT internal standard (10 mg/L in methanol). The solid-phase

extraction columns were sequentially rinsed with 3 mL of 2% ammonium hydroxide (NH_4OH) in ethyl acetate, 3 mL methanol, 3 mL of deionized water, and 1 mL phosphate buffer (pH 6, 100mM). Samples (5 mL) were loaded onto the columns at a flow rate of 2.0 mL/min. The cartridges were then washed with 3 mL of deionized water, followed by a wash with 2 mL of 0.10M HCl and 3 mL of methanol. The columns were dried under vacuum for 1 min prior to elution with 3 mL of a 2% NH_4OH in ethyl acetate mixture. The eluant was washed with 3 mL of deionized water in order to eliminate the NH_4OH and reduce the loss of drug upon evaporation. The solvent layer was transferred to another tube containing 2–3 drops of 1% concentrated HCl in methanol and was evaporated to dryness at 40°C under a stream of nitrogen. Extracts were derivatized with 100 µL of a 50:50 mixture of ethyl acetate and pentafluoropropionic anhydride (Pierce, Rockford, IL), overlaid with nitrogen, and left to incubate at 75°C for 20 min. Extracts were evaporated to dryness and reconstituted in ethyl acetate before transferring to autosampler vials for analysis on the GC system coupled to an MS.

GC–MS analysis was performed using a Hewlett-Packard 6890 series GC system equipped with a 16.5-m × 0.25-mm i.d. × 0.30-µm film thickness capillary column (Agilent Technologies) connected to a Hewlett-Packard 5973 mass selective detector. Initial oven temperature was 65°C for 0.50 min followed by a temperature ramp of 15°C/min to 290°C. Data processing was performed with an HP Chemstation in the SIM mode monitoring *m/z* 276, 303, and 466 for AMT and *m/z* 306, 333, and 496 for the internal standard, 5-MeO-AMT.

Quantitation was based on the preparation of a calibration curve derived by the addition of known amounts of AMT in normal saline. Concentrations were calculated using linear regression. When necessary, the specimens were diluted to bring

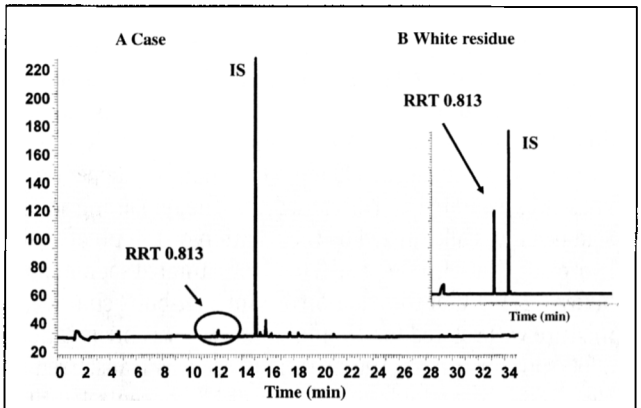

Figure 2. GC–NPD chromatogram of the postmortem iliac vein blood (A) and of the white residue contained in the vial labeled "α-Methyltryptamine" (B).

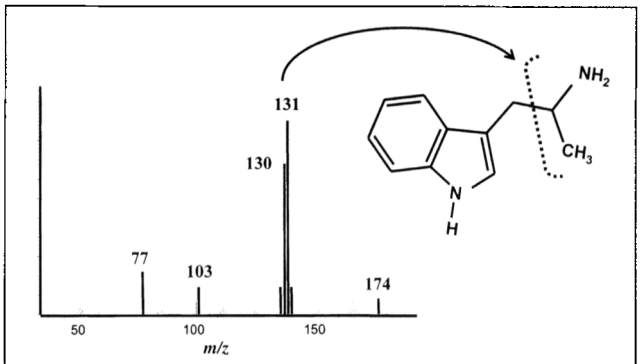

Figure 3. Mass spectra of underivatized AMT with primary cleavage occurring between the carbons alpha and beta to the primary amine nitrogen.

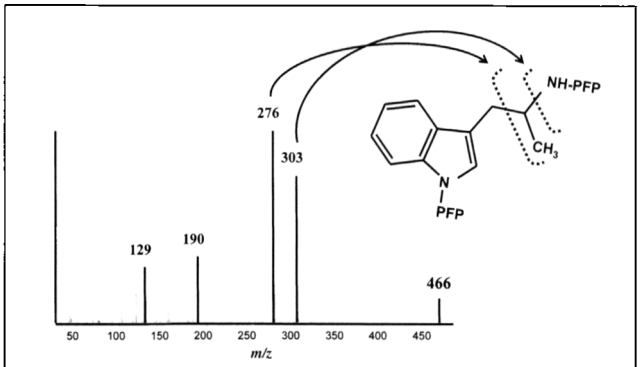

Figure 4. Mass spectra of AMT derivatized with pentafluoropropionic anhydride.

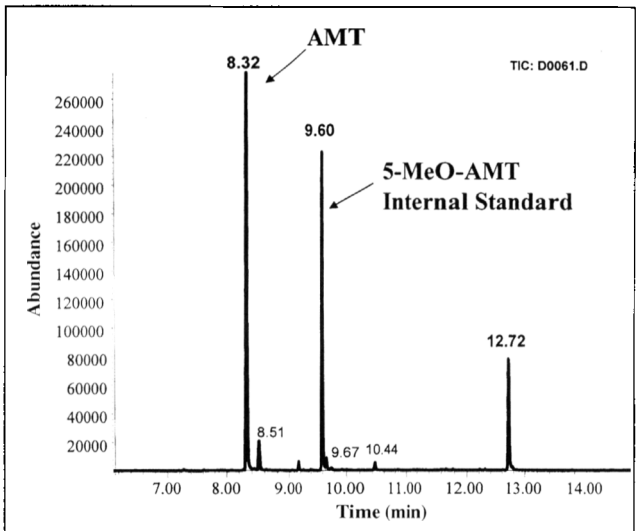

Figure 5. Gas chromatogram of AMT and the internal standard, 5-MeO-AMT.

Table I. Concentrations of AMT in the Miami-Dade County Medical Examiner Case and in an Additional Case from Another Jurisdiction

Specimen	Miami Case	Case 2
Iliac vein blood	2.0 mg/L	
Gastric	9.6 mg total*	
Liver	24.7 mg/kg	
Brain	7.8 mg/kg	
Serum	not analyzed	1.5 mg/L

* 48 g of stomach contents was collected at autopsy.

the observed concentration within the limits of the standard curve. Matrix matched controls were extracted and analyzed with each run.

Results and Discussion

AMT was qualitatively identified and quantitated in postmortem iliac vein blood, liver, and brain specimens, as well as in the gastric contents of the deceased. The basic drug screen analysis of both the white residue in the vial labeled α-methyltryptamine and the postmortem iliac vein blood specimen resulted in a retention time of 0.813 relative to the internal standard, cyclizine (Figure 2). The presence of AMT was confirmed by GC–MS, and the resulting mass spectrum for the contents of the vial, the urine specimen, and the gastric contents are similar to that shown in Figure 3. The molecular ion for AMT is *m/z* 174, with cleavage occurring between the carbons alpha and beta to the primary amine nitrogen to give *m/z* 130. The double peaks, *m/z* 130 and 131, are further confirmation of a monosubstituted amine and an unsubstituted indole portion of the molecule.

The quantitation of AMT involved derivatization using a mixture of ethyl acetate and pentafluoropropionic anhydride (50:50). The derivatization of AMT and the internal standard 5-MeO-AMT, occur at both the indole nitrogen and the primary amine nitrogen to give pentafluoropropionamides. The molecular ion for the derivatized AMT is *m/z* 466, with a fragment occurring at *m/z* 276 and 303. Again, fragmentation occurs between the carbons located alpha and beta to the primary amine nitrogen. An additional fragment at *m/z* 303 is a result of cleavage of the amide bond at the side chain amine (Figure 4). The GC chromatogram of AMT and the internal standard, 5-MeO-AMT obtained from the iliac vein blood extract is shown in Figure 5.

The concentrations of AMT in the postmortem specimens are listed in Table I. The iliac vein blood, liver, brain, and gastric contents (48 g collected at autopsy) revealed 2.0 mg/L, 24.7 mg/kg, 7.8 mg/kg, and 9.6 mg total, respectively. During the analysis of AMT in the Miami-Dade County Medical Examiner case, a death in another jurisdiction was attributed to AMT. This additional case involving AMT revealed a concentration of 1.5 mg/L in the antemortem serum (Table I).

The case received by the Miami-Dade County Medical Examiner Department in February 2003 is the first reported death in the country related to AMT. Up until now, there have been no documents concerning the concentration of AMT in postmortem specimens, nor have there been any reports on the tissue distribution of AMT in a fatality.

Unfortunately, the use and abuse of AMT is expected to increase, and consequently, Medical Examiner departments across the country may see more deaths attributed to this drug.

References

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