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CASE REPORT

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Distribution and Optical Purity of Methamphetamine Found in Toxic Concentration in a Civil Aviation Accident Pilot Fatality*

ABSTRACT: Toxicological evaluation of postmortem samples collected from a pilot involved in a unique fatal civil aircraft accident is described in this paper. A one-occupant airplane was substantially damaged upon colliding with terrain in poor visibility. Remains of the pilot were found outside the aircraft. Pathological examination revealed multiple blunt force injuries and vascular congestion. The fluorescence polarization immunoassay disclosed 8.0 μg/mL amphetamines in urine. Gas chromatographic/mass spectrometric analyses determined the presence of methamphetamine (1.13 μg/mL in blood and 59.2 μg/mL in urine) and amphetamine (0.022 μg/mL in blood and 1.50 μg/mL in urine). Methamphetamine was distributed throughout the body, including the brain. The amount of methamphetamine in gastric contents was 575-fold higher than that of amphetamine. The (+)- and (−)-forms of methamphetamine were present in equal proportions in gastric contents. The methamphetamine concentration found in blood was in the range sufficient to produce toxic effects, causing performance impairment.

KEYWORDS: forensic science, toxicology, methamphetamine, amphetamine, distribution, stereochemical analyses, fatal aviation accident investigation

Methamphetamine, a sympathomimetic amine (1), exists in optical isomeric forms. Its *dextrorotatory* [*dextro-;* (+)-] form has central nervous system (CNS) stimulant effects (1,2) and has been used in the treatment of obesity, while its *levorotatory* [*levo-;* (−)-] form has been used as a nasal decongestant in nonprescription inhalers (2) and as a precursor in selegiline manufacturing (3). The latter isomeric form has weaker CNS stimulant and greater peripheral sympathomimetic effects than those of the former isomeric form (1,2). Methamphetamine is an abused drug of concern (4–6); and unless specifically excepted, its isomers are considered controlled substances under the "food and drugs" regulations of the United States (7). This secondary amine is sold in illegal drug markets in the forms of (+)-methamphetamine, (−)-methamphetamine, and (±)-methamphetamine (2,8–10). (±)-Methamphetamine, also known as racemic methamphetamine or methamphetamine racemate, consists of *dextro-* and *levo*-forms in equal proportions. Methamphetamine mixtures of enantiomeric excess of one isomeric form over another isomeric form in variable proportions are also sold in the drug markets. These mixtures could be easily prepared by physically mixing *dextro-* and *levo*-forms together or by adding either of the isomers to methamphetamine racemate or vice versa.

In biological samples, a legitimate source of (−)-methamphetamine could be nasal inhalers or selegiline (11–13) and of (+)-methamphetamine could be legally prescribed Desoxyn® (14). Methamphetamine is primarily biotransformed by *N*-demethylation to the active metabolite amphetamine (2,15). Biotransformation of optical isomers of methamphetamine and amphetamine is stereospecific—*dextro*-isomers of these amines are metabolized at faster rates than their corresponding *levo*-isomers (2,15–17).

Several methamphetamine-abuse-associated cases of violent and irrational behaviors (blood concentration: 0.15–0.56 μg/mL), of erratic driving (blood concentration: 0.05–2.6 μg/mL), and of deaths with traumatic injuries (blood concentration: 1.4–13 μg/mL) have been reported in the literature (2,18–20). Blood concentrations of methamphetamine in the range of 0.09–18 μg/mL have been documented in fatal poisonings attributed to overdoses of this amine (2,21). Also, a toxic range of methamphetamine in blood has been considered to be 0.6–5.0 μg/mL (22), but a 0.23-μg/mL concentration of methamphetamine in blood has been reported as lethal (23). Therefore, there is a considerable amount of overlap in the toxic and lethal blood levels of methamphetamine. Although toxic and lethal blood levels of methamphetamine have been well documented, its stereospecificity was not established in those cases—it was not known whether methamphetamine found

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in those cases was *dextrorotatory*, *levorotatory*, or optical isomeric mixtures of equal or non-equal proportions. Knowing the stereospecific composition of methamphetamine in biological samples could assist in concluding the source of the amine and in accurately predicting the level of the adverse effects caused by the substance.

In the present study, toxicological findings of a unique civil aviation accident pilot fatality involving methamphetamine are described. Additionally, distribution and stereospecificity of this amine and its metabolite—amphetamine—were determined in the various submitted postmortem biological samples. Also included are pathological findings and aircraft accident case history.

Case History

A Cessna airplane was substantially damaged upon colliding with terrain at approximately 1700 h in an isolated area. The only occupant, the pilot, was fatally injured. In the general area of the accident, heavy snow conditions were observed, and the visibility was 0.5 mile (805 m) with fog and scattered overcast. An airman's meteorological information for mountain obscuration was in effect in the area at the time of the accident. There was no sign of fire in the crash. A strong odor of gasoline was present near the wreckage. Seat belts and shoulder harnesses were not buckled. The remains of the pilot were found on the ground outside the airplane. The autopsy was conducted 69 h after the accident.

Pathology

The pilot was a well-developed and well-nourished 44-year-old Caucasian male, weighing approximately 180 lb (82 kg). The length of the body was about 70 in. (1.8 m). The body was cold. Anatomical examination of the body revealed multiple blunt force injuries—bone fractures and internal lacerations—in the chest, abdomen, and lower back; and a small focus of subdural hemorrhage over the left parietal region of the cerebral cortex. Lacerations, contusions, and abrasions were noted practically all over the body. Vascular congestion was found in the kidneys, lungs, heart, spleen, and left frontal/parietal cortex. There was no evidence of medical therapy. Autopsied biological samples—blood, brain, gastric contents, heart, liver, muscle, spleen, urine, and vitreous fluid—were submitted for toxicological evaluation to the Federal Aviation Administration's Civil Aerospace Medical Institute in Oklahoma City, OK.

Materials and Methods

Materials

Drug standards, reagents, and solvents were obtained from commercial sources. The AxSyM® Amphetamine/Methamphetamine II assay kits were purchased from Abbott Laboratories (Abbott Park, IL). This screening assay utilizes fluorescence polarization immunoassay (FPIA) technology. Standards of (+)- and (−)-amphetamines and of (+)- and (−)-methamphetamines were obtained from Alltech-Applied Science Labs (State College, PA). Internal standards were supplied as racemic mixtures, (±)-amphetamine-d_8 and (±)-methamphetamine-d_8, by Cerilliant Corporation (Austin, TX). Pentafluoropropionic anhydride (PFPA) was purchased from Pierce Chemical Company (Rockford, IL). The chiral probe, (*S*)-(−)-*N*-(trifluoroacetyl)prolyl chloride (TPC), was obtained from Aldrich Chemical Company, Inc. (Milwaukee, WI). This probe has previously been used in the stereospecific analysis of amphetamines (11–13). Calibrators and controls were prepared in bovine whole blood.

Analytical Toxicology

The submitted biological samples were analyzed for combustion gases (carbon monoxide and hydrogen cyanide), alcohol/volatiles, and drugs (24–28). Carbon monoxide in blood was analyzed spectrophotometrically as carboxyhemoglobin (29) and hydrogen cyanide colorimetrically as cyanide (30). Alcohol/volatile analysis in vitreous fluid was performed by headspace gas chromatography. The urine sample was screened for abused drugs by FPIA and for prescription and nonprescription drugs by high-performance liquid chromatography and by gas chromatography/mass spectrometry (25).

Instrumentation

An Agilent gas chromatograph/mass spectrometer (Model 6890/Model 5973; GC/MS; Agilent Technologies, Wilmington, DE) was used for the confirmatory/quantitative and stereochemical analyses of methamphetamine and amphetamine. A crosslinked 100% methylsiloxane wall-coated open tubular column (12.5 m × 0.2-mm i.d.; 0.33-μm film thickness) was used in the GC. Helium was the carrier gas with a constant flow of 1 mL/min. The injection volume was 1 μL in the splitless mode, with a splitless time of 0.5 min. The injector temperature was maintained at 250°C, and the transfer line was set at 280°C. The acquisition was in the electron impact mode of ionization using selected ion monitoring.

Confirmatory/Quantitative Analyses

Extraction—Amphetamines from samples were extracted by the solid phase extraction (SPE) technique using Bond Elut Certify™ columns (Varian Sample Preparation Products, Harbor City, CA). Suitable amounts of aliquots of each calibrator, control, fluid specimen, diluted specimen, tissue homogenate, and gastric content supernatant in glass tubes were spiked with 400 ng of (±)-amphetamine-d_8 and (±)-methamphetamine-d_8. To each of the tubes containing blood and tissue homogenate, 10.0 mL of cold acetonitrile was added: Acetonitrile was not added to the tubes containing urine, vitreous fluid, and gastric content supernatant samples. After extraction, acetonitrile supernatants were decanted into a new set of tubes and evaporated to less than 1 mL. Subsequently, 2.0 mL of 0.10 M phosphate buffer (pH 6.00) was added to each tube, including those tubes that contained urine, vitreous fluid, and gastric content supernatant samples.

The SPE columns were conditioned with 2.0 mL of methanol, followed by 2.0 mL of the phosphate buffer. The buffered sample solutions were transferred onto the columns and allowed to pass through. Then the columns were rinsed with 1.0 M acetic acid and dried. Subsequently, 6.0 mL of methanol was passed through the columns, and they were then allowed to dry for 2 min. Analytes were eluted from the columns into conical glass tubes by using 4.0 mL of 2% NH_4OH in ethyl acetate. Hydrogen chloride was bubbled through the collected eluates to minimize the loss of amphetamines.

PFPA Derivatization—The obtained eluates were dried and reconstituted with ethyl acetate, and the PFPA derivatization was conducted as reported earlier (13). The mixtures were incubated at 70°C, dried, and reconstituted with ethyl acetate. The PFPA products were analyzed by the GC/MS.

GC/MS Conditions for PFPA Derivatives—The initial GC oven temperature of 70°C was increased to 150°C at 15°C/min and then to 290°C at 40°C/min with no hold times. The retention times (±0.01 min) for PFPA derivatives of (±)-amphetamine-d_8, (±)-amphetamine, (±)-methamphetamine-d_8, and (±)-methamphetamine were 3.72, 3.75, 4.54, and 4.57 min, respectively. The ions (m/z) monitored were 193, 126, and 96 for PFPA-(±)-amphetamine-d_8; 190, 118, and 91 for (±)-amphetamine; 211, 163, and 123 for PFPA-(±)-methamphetamine-d_8; and 204, 160, and 118 for PFPA-(±)-methamphetamine. The first of the three ions of each of these analytes was used as their quantifying ions, while the remaining two ions of each of the analytes were used as their qualifying ions. Calibrators of both amines for obtaining calibration curves were 0.025, 0.050, 0.100, 0.200, and 0.400 μg/mL ($r \geq 0.9990$).

Stereochemical Analyses

Extraction—Amphetamines were extracted from gastric content, blood, and urine samples by the liquid-liquid extraction method. Two-hundred-μL aliquots of each control (200 μg/mL) and sample were transferred into test tubes. To each tube were added 400 ng of (±)-amphetamine-d_8 and (±)-methamphetamine-d_8, four drops of concentrated NH_4OH, and 10.0 mL of *n*-butyl chloride. Tubes were shaken and centrifuged, and the organic phase was transferred into a new set of test tubes. After adding 4.0 mL of 1.0 N HCl to each of the tubes, they were shaken and centrifuged. The upper phase was discarded, and 1.0 mL of concentrated NH_4OH was added to each tube. Tube contents were vortexed, and chloroform was added. Subsequently, tubes were shaken and centrifuged, the chloroform phase was decanted into 10-mL screw-cap conical glass tubes, and hydrogen chloride was bubbled through each chloroform solution.

TPC Derivatization—The chloroform solutions were evaporated to dryness, and then 50.0 μL of the TPC solution was added to each tube (11–13). The reaction mixtures were incubated for 30 min at 70°C and evaporated to dryness. To each tube was added 50.0 μL of ethyl acetate to reconstitute the residue, and then the ethyl acetate solutions were injected onto the GC/MS.

GC/MS Conditions for TPC Derivatives—The GC oven temperature was set at 70°C; it was then increased to 290°C at a rate of 30°C/min with a final hold time of 2.67 min. The retention times (±0.01 min) of the TPC-derivatized diastereomers, (−)-amphetamine-d_8, (−)-amphetamine, (+)-amphetamine-d_8, (+)-amphetamine, (−)-methamphetamine-d_8, (−)-methamphetamine, (+)-methamphetamine-d_8, and (+)-methamphetamine, were 4.94, 4.95, 5.01, 5.02, 5.40, 5.42, 5.45, and 5.47 min, respectively. The ions (m/z) monitored were 240, 241, and 242 for TCP-(−)-amphetamine-d_8 or TCP-(+)-amphetamine-d_8; 237, 238, and 239 for TCP-(−)-amphetamine or TCP-(+)-amphetamine; 258, 259, and 260 for TCP-(−)-methamphetamine-d_8 or TCP-(+)-methamphetamine-d_8; and 251, 252, and 253 for TCP-(−)-methamphetamine or TCP-(+)-methamphetamine. The first of the three ions of each of these analytes was used as a quantifying ion for the determination of enantiomeric percentages, while the remaining two ions of each of the analytes were used as qualifying ions.

Enantiomeric Percentages—These percentages were determined by separately calculating ratios of TCP-(−)- and TCP-(+)-amine peak areas to the peak areas of respective isomeric-d_8 internal standards and then dividing each of the obtained ratios with the sum of both ratios as expressed in the following formula.

$$\left[\left\{PA_{\text{TCP-}(-\text{or}+)\text{-amine}} \div PA_{\text{TCP-}(-\text{or}+)\text{-amine-}d8}\right\} \times 100\right] \div \left[\left\{PA_{\text{TCP-}(-)\text{-amine}} \div PA_{\text{TCP-}(-)\text{-amine-}d8}\right\} + \left\{PA_{\text{TCP-}(+)\text{-amine}} \div PA_{\text{TCP-}(+)\text{-amine-}d8}\right\}\right]$$

where PA = peak area of amphetamine or methamphetamine TCP derivatives.

Results and Discussion

Analysis of the blood sample failed to disclose the presence of carbon monoxide or cyanide in a detectable amount. Ethanol was not detected in vitreous fluid. However, the FPIA screening revealed the presence of 8.0 μg/mL amphetamines in urine. The presence of amines was confirmed by the GC/MS analysis. Methamphetamine was distributed throughout the body, including the brain (Table 1). The blood methamphetamine level of 1.13 μg/mL was in the range sufficient to produce toxic effects, including erratic behavior (2,18–20). This level overlapped the lethal concentration range of methamphetamine (0.09–18 μg/mL) reported in the literature (2,21). The 575-fold higher amount of methamphetamine found in the gastric contents than that of amphetamine suggested that methamphetamine might have been taken orally. The relatively small amount of amphetamine found in the gastric contents was potentially the result of the low-pH associated ion trapping of the methamphetamine metabolite in the stomach (31).

Blood methamphetamine concentrations reported in the literature do not specifically mention stereospecificity of the amine (2,18–23). The amine could be in the (+)- or (−)-optical form or could be a mixture consisting of both optical forms in equal or non-equal proportions. Since pharmacological effects of methamphetamine are stereospecific [the (+)-form has stronger central stimulant effects than the (−)-form] (1,2), racemic methamphetamine [(±)-methamphetamine] would have pharmacological effects falling somewhere between the degree of effects caused by each of the optical isomers alone. Additionally, (−)-methamphetamine and its metabolite could legitimately be found in biological samples of individuals who use nasal inhalers or the anti-Parkinson's medication selegiline (11–13). Therefore, there is a genuine need for analytically determining stereospecificity of methamphetamine and its metabolite (amphetamine) for establishing the degree and type of biological effects and the source of the amines as a particular optical

TABLE 1—*Distribution of methamphetamine and amphetamine and their concentration ratios in various biological samples from the pilot fatality.*

Sample Type	Methamphetamine (μg/mL or μg/g)	Amphetamine (μg/mL or μg/g)	[Methamphetamine] / [Amphetamine]
Blood	1.13	0.022	51.4
Urine	59.2	1.50	39.5
Brain	1.53	0.038	40.3
Vitreous fluid	0.23	Not detected	–
Heart	1.06	0.017	62.4
Liver	5.53	0.13	42.5
Spleen	3.35	0.084	39.9
Muscle	0.327	Not detected	–
Gastric contents	5.75 mg*	0.010 mg*	575

*Total present in 78.0 g of the submitted gastric content sample.

TABLE 2—*Optical purity of methamphetamine and of amphetamine in biological samples from the pilot fatality.*

	Methamphetamine		Amphetamine	
Sample Type	(+)-Form %	(−)-Form %	(+)-Form %	(−)-Form %
Gastric contents	50	50	60	40
Blood	66	34	54	46
Urine	48	52	58	42

isomer may produce a selective biological effect, may be more potent than the other isomer (1,2,15), or could be considered a controlled substance (7).

As is given in Table 2, (+)- and (−)-forms of methamphetamine were present in almost equal proportions in gastric contents and in urine, but the percent concentration ratio of (+)-methamphetamine to its (−)-form was 2:1 in blood. The biotransformation of methamphetamine and amphetamine is stereoselective; their (+)-form is metabolized faster than their (−)-form (2,15–17). Therefore, the (+)-form should be present in the lesser amounts than the (−)-form in various body compartments. However, in vivo stereoselective pharmacokinetic processes other than metabolism may prevent these isomers from reaching such an anticipated concentration pattern in a particular body compartment. Since biotransformation is essentially negligible in the stomach, the stereoselective effect of the process will also be minimal on the concentrations of optical isomeric forms of methamphetamine. Thus, the concentration ratio found in the gastric contents more likely reflects the optical purity of methamphetamine ingested by the deceased.

Considering the isomeric ratio of methamphetamine in blood, concentrations of its (+)- and (−)-forms could be calculated as to be 0.75 and 0.38 μg/mL, respectively. Therefore, the net biological effect on the deceased was caused by both isomers, and the intensity of the effect would have been less than that would have been caused by only *dextro*-methamphetamine at 1.13 μg/mL. The possibility for reaching the *levo*-isomer's concentration at the calculated value from a legitimate use of a non-prescription inhaler or from selegiline is remote, particularly in the presence of the *dextro*-isomer and in the absence of selegiline itself.

Toxicological findings suggested that the deceased took racemic methamphetamine orally. The origin of (±)-methamphetamine could have been a chemically synthesized product from phenylacetone and *N*-methylformamide (2,8–10) or a physically prepared product from mixing (+)- and (−)-forms of methamphetamine in equal amounts. The oral ingestion allowed the blood methamphetamine concentration to reach a level sufficient to produce some degree of central stimulant effects, causing performance impairment. Findings of this study supported the National Transportation Safety Board's determination of factors of the accident as "meteorological conditions obscuring the pilot's visibility and incapacitation due to illegal substances."

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