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The Detection of a Metabolite of α-Benzyl-N-methylphenethylamine Synthesis in a Mixed Drug Fatality Involving Methamphetamine

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ABSTRACT: A 37-year-old, white male collapsed at his home following a party. He reportedly had a history of unspecified cardiac arrhythmia. The ambulance crew found him unresponsive and an ECG revealed ventricular tachycardia/fibrillation. Following one hour of resuscitative efforts in the ambulance and emergency room of a local hospital, he was pronounced dead. An antemortem urine toxicology screen performed at the hospital was "positive" for benzodiazepines, cocaine and amphetamine/methamphetamine. At autopsy, there was generalized organ congestion with no evidence of trauma or other significant pathology except mild, left ventricular hypertrophy. Quantitation by gas chromatography/mass spectrometry (GC/MS) of methamphetamine in bile, blood, urine and gastric contents yielded 21.7, 0.7, 32.0 and 2.9 mg/L, respectively. Liver and brain contained 2.2 and 2.7 mg/kg, respectively. A trace amount of p-OH-α-benzyl-N-methylphenethylamine (p-OH-BNMPA), a metabolite of α-benzyl-N-methylphenethylamine (BNMPA), an impurity of illicit methamphetamine synthesis, was also detected in the urine. Since these impurities can be characteristic of a particular synthetic method, their presence in seized samples or their detection in biological samples from methamphetamine users can further be used to monitor the sales of precursor chemicals, group seized compounds to common sources of illicit production or provide links between manufacturers, dealers and users.

KEYWORDS: forensic science, methamphetamine fatalities, illicit synthesis, substance abuse testing

Methamphetamine ("speed") continues to rank among the top twenty drugs in emergency room and medical examiner mentions. However, in 1993, drug abuse deaths involving methamphetamine accounted for only 0.5% of total drug abuse deaths in 14 large metropolitan areas (including Washington D.C. and Norfolk, Virginia) east of the Mississippi River compared to 12% of total drug abuse deaths in 11 large metropolitan areas west of the Mississippi River (1).

Methamphetamine is readily synthesized in clandestine laboratories. Illicitly obtained methamphetamine is frequently impure, containing various purposefully added diluents and adulterants, as well as impurities of manufacture and origin. One such impurity is α-benzyl-N-methylphenethylamine (BNMPA). We have previously demonstrated the four major metabolites of BNMPA to be the N-demethyl compound, diphenyl-2-propanone (DP2P), p-hydroxy-N-demethyl BNMPA, and p-hydroxy-BNMPA (2). We have also shown that these metabolites are detectable in known methamphetamine users in sufficient quantities to provide a marker of use of illicitly synthesized methamphetamine (3).

Because of methamphetamine's rare occurrence in east coast medical examiners cases and because of our interest in the detection of impurities of illicit methamphetamine manufacture in biological samples as a means of tracking supply sources, we present a case of a "mixed drug" fatality involving methamphetamine.

History

A 37-year-old, white male collapsed at his home at approximately 3:00 a.m. following a party. The ambulance arrived at approximately 4:30 a.m. where an ECG revealed ventricular tachycardia/fibrillation. Resuscitative efforts were initiated and the patient was transported to the emergency room at a major local teaching hospital where he was pronounced dead at 5:05 a.m. An antemortem urine toxicology screen performed at the hospital was "positive" for amphetamine, benzodiazepines and cocaine. Family and friends reported a history of unspecified cardiac arrhythmia or "other cardiac problem."

Autopsy Findings

At autopsy there was generalized organ congestion but no evidence of trauma or other significant pathology apart from cardiomegaly (510 g). There was mild left ventricular hypertrophy. Postmortem toxicology revealed blood concentrations of 0.21 mg/L benzoylecgonine, 0.09 mg/L morphine, 0.68 mg/L methamphetamine and 0.13 mg/L diazepam. No ethanol, methanol, isopropanol or acetone was detected. The death was classified as an accidental, mixed drug toxicity.

Methamphetamine/BNMPA Analysis

We were interested in this case because of the presence of methamphetamine and the possible presence of BNMPA/its metabolites. Quantitation of methamphetamine and BNMPA and metabolites in blood, urine, bile liver, brain and gastric samples was by gas chromatography/mass spectrometry (GC/MS). Blank tissue

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samples were drug-free autopsy specimens obtained from a major local teaching hospital. Tissue samples were homogenized and suspended in twice their volume of normal saline. Bile samples were diluted 1:3 with normal saline. A total of 4 mL of homogenate, diluted bile, urine or blood was used for blanks, calibrators and samples. β-glucuronidase hydrolysis, extraction, derivatization and GC/MS conditions were as described in a previous publication (2). Methamphetamine and amphetamine concentrations in bile, blood, urine, gastric contents, liver and brain are summarized in Table 1. A trace amount of p-OH-BNMPA was also detected in the urine.

Discussion

The case presented here is not unusual in that it was a fatality associated with relatively low levels of methamphetamine. Rather, its uniqueness lies in the fact that it occurred on the east coast where methamphetamine is an uncommonly abused drug, the presence of significant amounts of methamphetamine/amphetamine in the bile and the detection of a primary metabolite of BNMPA, an impurity of illicit methamphetamine synthesis.

The acute lethal dose of amphetamines is generally thought to be in the range of 20–25 mg/kg, and, in animals, may be as low as 5 mg/kg. The lowest reported lethal dose is 1.5 mg/kg (4). However, as tolerance develops, dosages as high as 800 mg (10–12 mg/kg) have been ingested without significant effects (5). In fact, chronic abusers may use as much as 5000 to 15,000 mg (70–200 mg/kg) per day (6). As is true with most abused drugs, this phenomena of tolerance makes blood and tissue levels as predictors of cause or contribution to death very difficult. This variability in blood and tissue concentrations of methamphetamine in fatalities can be seen in the cases summarized in Table 2. Blood concentrations of methamphetamine in fatal cases have ranged from less than 1 mg/L to over 14 mg/L (7–10). Since the degree of tolerance for any drug is impossible to determine at autopsy, attributing significance to isolated amounts is unwise (11). Low levels, thought to be incidental findings, are hard to interpret. As in the case presented here, very low concentrations (0.7 mg/L) have been observed in patients dying of what is now described as "classic stimulant toxicity" with agitation, hypertension, tachycardia and hyperthermia (12).

We also found intriguing the presence of significant quantities of methamphetamine/amphetamine in the bile from this case. It is well established that bile may be an important route of excretion for many drugs and that enterohepatic circulation of drugs may contribute to their total pharmacokinetic profile (13). The biliary excretion of many amphetamines has been studied in the rat with 15 to 20% of the dose excreted in the bile with enterohepatic circulation. However, the molecular weight requirement for significant biliary excretion varies with species, being 325 ± 50 in the rat. In humans, the cut-off is not so clear, but it has been thought that only compounds with molecular weight of 500 to 1000 are excreted significantly in human bile. Since virtually all amphetamines and metabolites have molecular weights less than 375, it has not been expected that biliary excretion is an important route for these compounds in man. In fact, bile concentrations of methamphetamine/amphetamine are rarely reported in the literature. Di Maio and Garriott (14) reported a bile concentration of 135 mg/L in an amphetamine ingestion overdose fatality. That report, coupled with the finding of 21.7 mg/L methamphetamine and 0.58 mg/L amphetamine in the bile in the case we present here, suggests that bile may be a useful tissue for the detection of these compounds in suspected methamphetamine fatalities.

Finally, impurities arising from the illicit synthesis of methamphetamine can be characteristic of a particular synthetic method. Therefore, their presence in seized samples or their detection in biological samples from methamphetamine users can further be used to monitor the sales of precursor chemicals, to group seized compounds to common sources of illicit production or provide

TABLE 1—*Tissue concentrations of methamphetamine (meth) and amphetamine (amph) in current case.*

Bile*		Blood*		Brain†		Gastric*		Liver†		Urine*	
Meth	Amph	Meth	Amph	Meth	Amph	Meth	Amph	Meth	Amph	Meth	Amph
21.7	0.58	0.68	0.03	2.7	0.25	2.9	0.13	2.2	0.1	32.0	1.6

* = mg/L. † = mg/kg.

TABLE 2—*Methamphetamine (meth) and amphetamine (amph) tissue concentrations in overdose fatalities involving methamphetamine.*

		Blood*		Brain†		Gastric		Liver†		Urine*		
Ref	N	Meth	Amph	Meth	Amph	Meth	Amph	Meth	Amph	Meth	Amph	Comments
(6)	1	1.3	X	X	X	X	X	X	X	X	X	
(20)	1	40	X	X	X	X	X	X	206	X	X	
(21)	1	4.3	X	X	X	X	X	X	X	28	X	
(21)	1	2.0	X	X	X	1.5 mg	X	4.8	X	28	X	
(22)	1	5.6	0.35	102	0.8	11.6 mg	0.2 mg	175	1.3	320	10.0	
(23)	11	0.02–3.05	NMA-0.32	X	X	X	X	0.17–11.6	NMA-1.06	X	X	Meth-related deaths (AO)
(23)	6	0.08–1.01	0.03–0.17	2.99 (N = 1)	0.4 (N = 1)	X	X	0.45–1.29	0.11–0.73	X	X	Mixed cocaine/meth deaths (AO)
(24)	1	9.0	0.2	22	X	51 mg/L	X	45	X	103	0.53	

* = mg/L; † = mg/kg; X = not done; NMA = No measurable amount; AO = Accidental overdoses.

links between manufacturers, dealers and users. Methamphetamine laboratories comprised more than 50% of all laboratories seized by the DEA during a 45-month period ending in September 1981 (15). One of the most popular methods of synthesis during the 1980s used the Leukart reaction, refluxing phenyl-2-propanone (P2P) with either methylamine and formic acid or N-methylformamide with hydrochloric acid.

Until 1981, P2P was available commercially. Because of its importance in illicit synthetic methods, it is now listed as a Schedule-II controlled substance with some clandestine laboratories now synthesizing just P2P. The most common synthetic by-product present in P2P prepared from phenylacetic acid is diphenyl-2-propanone (DP2P) (16). When P2P containing this contaminant is used to synthesize methamphetamine via the Leukart route, BNMPA is a major contaminant (17).

With the growing difficulty in obtaining precursors for these more popular reductive amination routes, and the increasing availability of (−) ephedrine and (+)-pseudephedrine both in this country and the Far East, methamphetamine synthesized from ephedrine has "flooded" the market (18). In calendar year 1993, the DEA participated in the seizure of 270 clandestine laboratories in the United States. Of these laboratories, 218 were methamphetamine labs. The ephedrine reduction method was used in 81% of all methamphetamine labs seized during 1993, whereas the P2P method was used for only 16% (19).

Because the P2P method is currently unpopular, the finding of a metabolite of an impurity arising from this method in this case is unique enough to provide conclusive evidence that the methamphetamine involved in this case was illicitly manufactured. Since the DEA monitors synthetic methods used by various labs, this impurity may also provide a link from user to distributor to manufacturer.

Very little work has been done on the pharmacology/toxicology of impurities of illicit synthesis. While some preliminary investigations have been done on the *in vivo* effects of BNMPA (25,26), the results are not conclusive. We cannot eliminate the possibility that impurities such as BNMPA may be contributing to the toxicity of METH in chronic abusers, especially in "low-concentration" fatalities such as this case.

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