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Case Report

Recent Paramethoxyamphetamine Deaths

Heather E. Felgate, Peter D. Felgate, Ross A. James, D. Noel Sims, and **Dominic C. Vozzo**
Forensic Science, 21 Divett Place, Adelaide, South Australia 5000, Australia

Abstract

Paramethoxyamphetamine (PMA) is a methoxylated phenethylamine derivative that has been used illicitly in Australia since late 1994. It is purportedly sold under the guise of "ecstasy", which is the colloquial name for methylenedioxymethamphetamine (MDMA). Methods for extraction, identification, and quantitation are presented. Toxicology findings in six fatalities involving the drug are discussed. Femoral blood PMA levels ranged from 0.24 to 4.9 mg/L (mean, 2.3 mg/L). Liver PMA levels ranged from 1.4 to 21 mg/kg (mean, 8.9 mg/kg). Other amphetamines were found in five of the six cases. Blood PMA levels in three nonfatal cases are also presented. PMA appeared to be more toxic than MDMA, and blood levels greater than 0.5 mg/L seemed likely to be associated with toxic effects.

Introduction

Paramethoxyamphetamine (PMA) is a methoxylated phenethylamine derivative. Structurally related compounds include methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA, ecstasy), methylenedioxyethylamphetamine (MDEA), and mescaline. These drugs all exhibit hallucinogenic properties. MDMA has been available in Australia from illicit sources since the mid-1980s and has become popular among dance-club patrons. A number of deaths involving MDMA toxicity were reported in Britain (1,2) and North America (3), and one death was reported in Australia (4). A Canadian report from 1974 (5) is the most recent report of death due to PMA toxicity.

Here we report the toxicology findings in six cases in which adverse effects due to PMA ingestion have resulted in death. The pathology associated with the first of these deaths has been reported elsewhere (6). A report on the additional pathological details is in preparation. In addition, we report three more cases of PMA abuse, including one case in which hospital treatment was required for toxic reactions.

Case Histories

Case 1

A 31-year-old male was found dead at a party. It was said he had ingested at least five ecstasy tablets and snorted a "line" of amphetamine over a period of 5 ½ h. He was delirious and thrashing about. Witnesses tried to cool him down and revive him with water. Clad only in shorts, he suffered from hyperthermia and had a core body temperature of 41.2°C 3 h after death with rigor mortis fully established in all limbs. Symmetrical brush abrasions were present over his forehead, hands, and knees, which is consistent with carpet burn. Death was attributed to hyperpyrexia with amphetamine abuse. A table allegedly similar to those taken at the party contained 50 mg PMA.

Case 2

A 37-year-old female died at home after ingesting an ecstasy tablet. She had earlier complained of a headache and being hot. A friend attempted to cool her off by sponging her and putting her in the shower. Postmortem examination revealed red bruises on the right arm, knee, and ankle. There was a massive intracerebral hemorrhage within the right frontal lobe that destroyed the basal nucleus and caused a right-to-left midline shift. There was no underlying aneurysm or vascular malformation. Intracerebral hemorrhage is a well-recognized complication of amphetamine abuse.

Case 3

A 22-year-old female died in the hospital 12 h after being admitted unconscious with a temperature of 42.5°C and dressed only in underpants. She developed disseminated intravascular coagulation, rhabdomyolysis, and hyperkalaemia. Autopsy showed evidence of coagulopathy with widespread subcutaneous and intraparenchymal hemorrhage. She attended dance clubs and allegedly ingested three ecstasy capsules and methylamphetamine. A capsule allegedly from her drug supplier contained 60 mg of PMA.

Case 4

A 23-year-old male ingested an unknown number of ecstasy capsules at a friend's house before collapsing and being admitted

to hospital. He was noted to feel hot. He died of cardiac arrest soon after admission. The urine was heavily blood stained, and bruises were present on both legs. Microscopic evidence of early acute tubular necrosis within the kidneys and changes of rhabdomyolysis in skeletal muscle were found at autopsy. Death was attributed to severe hyperkalaemia due to rhabdomyolysis. A capsule associated with the deceased was found to contain 50 mg PMA.

Table I. Toxicology Results in PMA*-Related Deaths

Case no.	Amphetamines	Blood (mg/L)	Liver (mg/kg)	Other drugs in blood
1	PMA	1.7	11	cannabinoids
	amphetamine	1.6	5.9	
	methamphetamine	0.23	1.4	
	MDMA	ND	1.9	
2	PMA	0.24	1.4	tetrahydrocannabinol
				fluoxetine 0.1
3	PMA	1.3	7.4	tetrahydrocannabinol
	MDMA	0.30	3.2	
	amphetamine	ND	0.45	
4	PMA	3.7	7.1	
	methamphetamine	3.1	1.7	
	amphetamine	0.26	0.57	
5	PMA	4.9	21	
	MDMA	ND	2.1	
6	PMA	2.2	5.6	tetrahydrocannabinol
	MDMA	0.82	3.2	cocaine <0.01
	methamphetamine	0.09	0.26	benzoylecgonine <0.01
	amphetamine	0.03	0.35	

*Abbreviations: PMA, paramethoxyamphetamine; MDMA, methylenedioxymethamphetamine; ND, not detected.

Table II. Toxicology Results in Four Other Australian PMA*-Related Deaths†

Case	Amphetamines	Blood (mg/L)	Liver (mg/kg)	Other drugs in blood
WA	PMA	1.7	6	carboxytetrahydrocannabinol
	amphetamine	0.11		
	methamphetamine	0.01		
QLD1	PMA	2.2	7.5	paracetamol 14
	amphetamine	1.2	2.8	
QLD2	PMA	2.0	6.0	
	pseudoephedrine	2.3	5.5	
	methamphetamine	0.18	0.87	
QLD3	PMA	0.53	2.7	
	MDMA	0.51	3.0	
	methamphetamine	0.23	0.76	

*Abbreviations: PMA, paramethoxyamphetamine; WA, Western Australia; QLD, Queensland; MDMA, methylenedioxymethamphetamine.
†Information obtained from references 7 and 8.

Case 5

A 24-year-old male recently released from jail was found d at a friend's house. His core body temperature of 34.4°C appr imately 8 h after his death suggested earlier hyperpyrexia. Auto only revealed superficial abrasions on the knees, shins, and fo head consistent with carpet burns that were likely to have ari during convulsions before death. It was alleged he had inges three ecstasy tablets. There was no evidence intravenous drug abuse.

Case 6

A 26-year-old female collapsed at home s fering hyperthermia. She had attempted cool down in the bath and was naked for s eral hours before hospital admission. She h allegedly ingested at least five ecstasy capsu over a period of at least 12 h. Cardiac arr occurred soon after admission. Her temper ture before death was 46.1°C. Intrathora petechial hemorrhages with marked p monary congestion and edema were found autopsy. Blue bruises were present on the fa right thigh, and right foot. Skeletal and card muscle showed features of rhabdomyolysis capsule allegedly from her drug supplier c tained 90 mg of PMA.

Experimental

Materials

PMA standard was obtained from t Curator of Standards, Australian Governme Analytical Laboratory. Mefenorex was used the internal standard. Stock standard dr solutions were prepared in ethanol at a co centration of approximately 1 mg/mL as fr base. Working standard drug solutions were freshly prepared by a 100-fold dilution of th stock solutions with water. All reagents were analytical grade except for 1-chlorobutane which was BDH HiPerSolv grade.

Instrumentation

PMA and other amphetamines were screened for and subsequently quantitatively analyzed using Hewlett Packard 5890 series II Plus gas chromatograph (GC) equipped with dual nitrogen-phosphorus detectors and a 7673A auto sampler. The columns consisted of a 5-m phenyl-methyl deactivated guard column (0.53-mm i.d.) split equally to a DB-1 capillary column (10 m × 0.32-mm i.d., 1.0-µm fil thickness, J&W Scientific) and a DB-17 capilla column (10 m × 0.32-mm i.d., 0.5-µm fil thickness, J&W Scientific). The oven was held 100°C for 0.5 min and then ramped at 10°C/m

280°C and held for 8.5 min. The injection port temperature was 250°C, and the temperature of the detectors was 280°C. Under these conditions, the retention time for PMA was 4.7 min on the DB-1 column and 3.9 min on the DB-17 column.

PMA was identified by derivatizing the extract with pentafluoropropionic anhydride (Pierce) followed by analysis using a Hewlett Packard 5890 series II GC with a Hewlett Packard 5972 series mass selective detector (GC–MS). The column was a HP-5MS capillary column (15 m × 0.25-mm i.d., 0.25-µm film thickness, Hewlett Packard). The oven was held at 60°C for 2 min and then ramped at 15°C/min to 280°C and held for 3 min. The injection port temperature was 250°C, and the mass detector interface temperature was 300°C. Under these conditions, the retention time of the PMA derivative was 9.0 min.

Extraction

Five grams of liver was finely macerated with 35 g of water. These liquified livers were then treated in the same manner as the femoral blood samples.

Femoral blood or liver homogenate (0.5 mL), 1.5 mL 1% sodium hydroxide, and 5 mL 1-chlorobutane were added to 0.05 mL of a 5-µg/mL aqueous solution of the mefenorex internal standard in a glass screw-top tube, and the contents were rolled on a mechanical mixer for 10 min. After centrifuging, the solvent was drawn off and transferred to a clean glass tube, and 0.05 mL acid alcohol (0.005% hydrochloric acid in methanol) was added. After mixing, the solvent was evaporated to dryness in a Jouan centrifugal evaporator. The residue was dissolved in 0.05 mL ethanol for GC analysis. After the GC screen, the extracts were transferred to glass tubes and evaporated to dryness at 40°C under nitrogen. The residues were dissolved in 0.09 mL ethyl acetate and 0.01 mL pentafluoropropionic anhydride and heated at 70°C for 15 min. After cooling, the derivatizing solution was evaporated at 40°C under nitrogen, and the residue was dissolved in 0.03 mL ethyl acetate for GC–MS analysis.

Quantitative GC analysis of the identified amphetamines was done by comparison of duplicate sample extracts with standard curves constructed by adding known amounts of drug to drug-free blood and following extraction and GC analysis plotting the area-response ratio for drug and internal standard versus drug concentration.

Results and Discussion

The calibration curves for all the quantitative drug analyses included at least five drug concentrations in the range of 0.05 to 8 mg/L and produced linear correlations with the coefficient of regression (r) better than 0.997 in all cases. The recovery of PMA after extraction was approximately 50%. The recoveries from drug spiked blood and drug-spiked liver were found to be similar so drug standard curves were subsequently constructed in drug-free blood only. The limit of detection for PMA, equivalent to three times the background noise, was estimated to be 0.001 mg/L based on a 0.5-mL blood sample.

Table III. Toxicology Results in South Australian PMA* Users

Case no.	PMA blood level (mg/L)
Tablet dealer	0.13
Driving offense	0.09
Hospital admission	0.56

*PMA, paramethoxyamphetamine.

During the period September 1995 to January 1997, six PMA-related deaths have occurred in South Australia. Table I presents the toxicology data from these cases. Peripheral blood PMA levels were all greater than 1 mg/L, except in Case 2. In this case the interaction with fluoxetine may be significant as may the interaction with cocaine in Case 6. Although MDMA was of significance in two of the cases and amphetamine and methamphetamine in one each, the significant factor in each case is the toxic effects of PMA. PMA would appear to be more toxic than other common amphetamine derivatives. Before these six cases, our laboratory had only one case in the last 10 years in which the cause of death was amphetamines poisoning. In that case, a concentration of 1.7 mg/L methamphetamine was found in an intravenous drug user. During this time a variety of amphetamine derivatives including MDMA have been available illegally. Locally, PMA has been sold under the "ecstasy" name normally associated with MDMA. Although MDMA was present in the blood in Cases 3 and 6, the toxic effects of MDMA have not been associated with any other deaths in South Australia.

Significantly all the PMA deaths involved oral administration. Case 1 was associated with a 50 mg PMA tablet while Cases 3, 4, and 6 involved capsules containing 60, 50, and 90 mg PMA, respectively. The PMA levels in the Canadian deaths (5) were considerably lower, being in the range of 0.3–1.9mg/L for the blood samples and 0.5 to 10 mg/kg for the liver samples. This is not surprising as one Canadian case was said to have involved inhalation and at least six of the other eight cases were said to involve intravenous administration. The data presented here may be more relevant to the current availability of PMA in tablets and capsules.

PMA has only been available in Australia since late 1994 and to our knowledge has been associated with 10 deaths. In Western Australia, a death from PMA occurred in late 1994 (7). Subsequent to this case, three deaths involving PMA have occurred in Queensland (8). The toxicology results for these cases are presented in Table II. Oral administration was thought to be involved in these cases, although injection of a powder was said to have occurred in the second report from Queensland.

Between June 1996 and January 1997, there was a sudden increase in admissions at the Royal Adelaide Hospital of patients suffering amphetamine toxicity. In a total of 16 admissions, 14 patients were found to have PMA in their urine (9). Blood PMA levels in three living drug users are presented in Table III. In Queensland, a carbon monoxide poisoning and a trauma victim had blood PMA levels of 0.37 and 0.25 mg/L, repectively (8).

The cases presented here indicate that PMA is available in localised areas. It is routinely sold as "ecstasy" but would appear to be more toxic than MDMA. When used orally, hallucinogenic blood PMA levels range up to approximately 0.4 mg/L. In

general, levels above 0.5 mg/L appear likely to be associated with toxic effects and may be lethal, especially in combination with other amphetamines.

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