Case Report

Three Fatal Cases of PMA and PMMA Poisoning in Denmark

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Abstract

Paramethoxyamphetamine (PMA) and paramethoxymetamphetamine (PMMA) are methoxylated phenylethylamine derivatives with effects similar to methylenedioxymetamphetamine (MDMA) and sold as such. However, PMA and PMMA are more potent than MDMA, but have a slower onset of action, which encourages users to take more. Three fatal cases involving PMA and PMMA in Denmark in year 2000 are investigated including history, pathological, and toxicological findings. The methods used for extraction, identification, and quantitation of PMA and PMMA are described. In two of the cases, lethal postmortem blood concentrations of PMA and PMMA were determined at 3.4 and 3.3 mg/kg (case 1) and 0.78 and 0.68 mg/kg (case 3), respectively. In addition, other drugs such as MDMA, tetrahydrocannabinol, cocaine, and alcohol were involved in these cases. In the third case, death occurred four days after the ingestion of tablets containing PMA and PMMA, and therefore only low postmortem concentrations of PMA and amphetamine were detected. However, in a serum sample taken at admission to the hospital, PMA and PMMA were found, but not quantitated. It is believed that the cause of death in case 2, multiple-organ failure, was caused by overdoses of PMA and PMMA.

Introduction

Paramethoxyamphetamine (PMA) and paramethoxymetamphetamine (PMMA) are methoxylated phenylethylamine derivatives that were first encountered in the 1970s on the illegal market. The substances are similar to and sold as methylenedioxymetamphetamine (MDMA), but have a slower onset of action and higher toxicity (1,2). Their chemical structures are shown in Figure 1. PMA is a weak central stimulant, whereas PMMA has effects more similar to those of MDMA than to other structurally-related amphetamine derivatives. PMMA may be considered to be qualitatively similar to methyl-benzodioxolbutanamine (MBDB) because of its lack of stimulus- or hallucinogen-like stimulus qualities. Structurally, PMMA is simpler than either MDMA or methylenedioxymetamphetamine (MBDB) (Figure 1), and the discriminative stimulus is several times more potent than MDMA (3).

In 1973, PMA was produced by clandestine laboratory facilities in Canada, and that year approximately ten deaths related to PMA occurred in Canada and the U.S. (4,5). From 1974 to early 2000, only one death related to PMA was reported in Canada and the U.S. (6). However, several deaths in Australia, which were primarily reported as being caused by MDMA in the period from 1995 to 1997, were later determined to be caused by PMA sold as ecstasy (6,7). Then again in 2000, several deaths involving PMA were reported in Canada, the U.S., and Europe

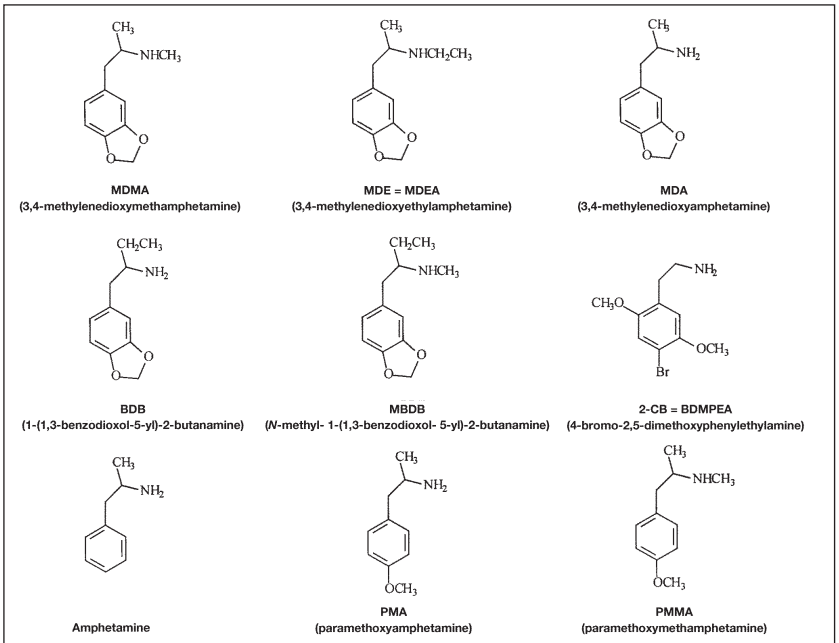

Figure 1. The chemical structures of amphetamine derivatives.

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(6,8,9). None of these cases involved PMMA. This paper describes three fatal cases involving mixtures of PMA and PMMA in Denmark in 2000. Lack of reference substances delayed the quantitation of PMMA and, therefore, the publication of the toxicological findings.

Case Histories

Case 1

A 20-year-old male was admitted to the hospital early in the morning with strong hallucinations. During the previous evening, he was observed drinking heavily (one bottle of strong alcohol and 6–8 beers). Friends witnessed him taking four ecstasy tablets with the Mitsubishi logo. At the hospital, he was initially treated with diazepam. Thereafter, he developed arrhythmia followed by cardiac arrest. A rectal temperature of 42°C was measured. At autopsy, lung oedema and enlargement of the spleen were observed, as well as a slight degree of sclerosis in the coronary arteries. The microscopy showed stasis and oedema of the lungs and brain.

Case 2

A 20-year-old male died four days after admission to the hospital in a condition resembling ecstasy intoxication. Before admission, he was seen taking tablets, which he himself had claimed were ecstasy. During the evening, he had developed paranoia and was brought to hospital in a coma with spasms. Multiorgan failure developed despite intensive treatment and was confirmed by the autopsy, as well as the microscopy. The neuropathological examination showed signs of incarceration and cerebral vasculitis.

Case 3

A 24-year-old male was seen taking three tablets of ecstasy. He and two friends had initially taken one tablet. Shortly thereafter, he took two additional tablets. He began sweating intensively and became hyperactive with excessive walking. Friends tried to make him drink water, but he aggressively refused. Approximately two-and-a-half hours later, he became lifeless. At the hospital, resuscitation was tried unsuccessfully. His rectal temperature was 42.8°C.

The autopsy demonstrated no signs of violence. Severe oedema of the brain and moderate stasis of the organs were found.

Experimental

Materials

Blood, urine, and tissues samples were obtained at the autopsies, and samples were preserved and frozen until analysis. Information was provided by the police reports. All the routine samples from cases 1 and 2 and the serum samples taken at the hospital in case 2 were destroyed before the necessary reference substances for quantitation purposes were obtained. However, in cases 1 and 2, 2-mL samples of postmortem blood were preserved for scientific purposes and were used for quantitation.

Analysis

Routine toxicological analyses were applied for common drugs, narcotics, and poisons. In the screening procedure for basic compounds, both PMA and PMMA were detected. The basic screening was performed on liver tissue. Homogenated liver samples were extracted by diethyl ether under basic pH using back-extraction with sulphuric acid into chloroform or dichloromethane. The organic phase was evaporated (11) and the remanence dissolved in methanol. Two microliters were injected in split mode (1:10) on a gas chromatograph. Mepivacaine or lidocaine was used as the internal standard (IS).

Gas chromatographic (GC) analysis was performed on a Hewlett-Packard 6890 GC-system (Agilent Technologies Denmark A/S, Naerum, Denmark) with Chemstation software. The separation was performed on an Ultra 2 20-m HP capillary column (Agilent Technologies Denmark A/S), which consisted of 5% phenylmethylsiloxane (0.32-mm i.d., 0.52-µm film thickness). The initial column temperature of 160ºC was held for 1 min, then programmed to 320ºC at a rate of 10ºC /min, and held for 13 min at 320ºC. The carrier gas was nitrogen with a head

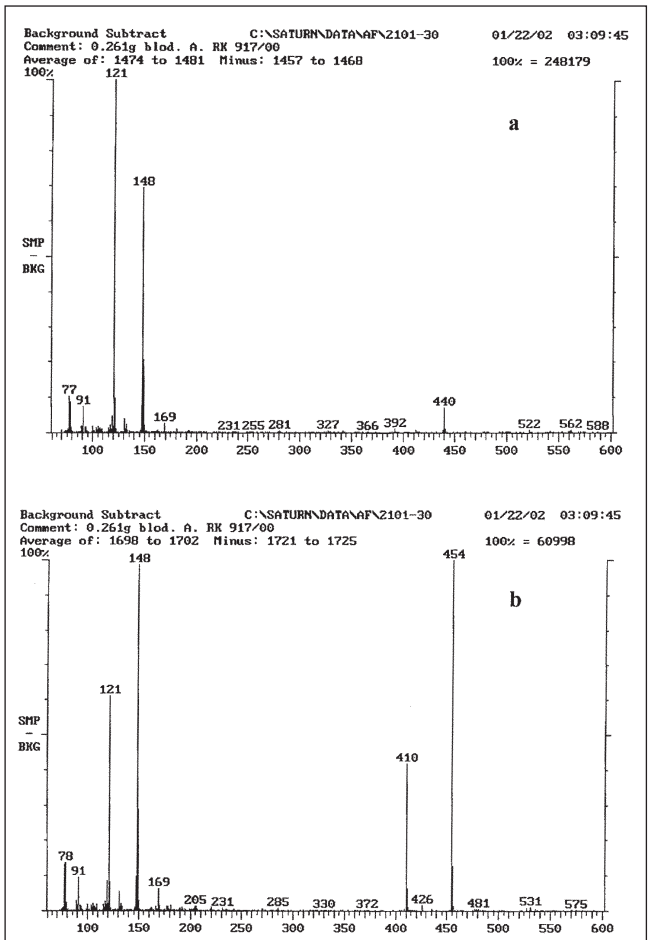

Figure 2. Mass spectra of derivatized PMA (a) and PMMA (b) in postmortem blood from case 3 obtained by GC–mass spectrometry analysis. The molecular ions *m/z* 562 and *m/z* 576 for PMA and PMMA, respectively, were only observed in traces.

pressure of 63 kPa. The temperature of the injector was 300ºC and the nitrogen–phosphorus detector was 325ºC.

The quantitation of amphetamines including PMA, PMMA, and MDMA in postmortem blood was performed by liquid–liquid extraction, followed by derivatization with perfluorooctanyl chloride and GC–mass spectrometry (MS) analysis (12). The derivatized amphetamines were analyzed by GC–MS using deuterated internal analogs for the common amphetamine derivatives, but 2,4-dimethoxyamphetamine (DMA) was used as the IS for PMA and PMMA. Reference compounds were obtained from Radian (Promochem LTD, Hertfordshire, U.K.) and Sigma Chemical (Sigma Aldrich Denmark A/S, Vallensbaek Strand, Denmark). Calibration standards were prepared in whole blood from horses in a range of 0.01–0.5 (1.0) mg/kg (compound dependent). Samples were diluted if beyond the linear range.

Quantitative analysis was performed on a Varian Star 3400 CX gas chromatograph with a Varian 8200 CX autosampler coupled to a Varian Saturn 4D mass spectrometer. For data treatment, Varian Saturn was applied (all from Analytical Instruments A/S, Naerløse, Denmark). The separation was performed on a 30 m HP5-MS capillary column (Agilent Technologies Denmark A/S) (0.25-mm i.d., 0.25-µm film thickness). One microliter of injected splitless into an injector at 210°C, an interface at 290°C, and an ion source (ion trap) at 210°C. The temperature program of the GC was 110°C for 1 min, then increased 6°C/min to 160°C, then 5°C/min to 210°C, and finally 250°C/min to 300°C. The MS was used in scan mode and the quantitation was done using three characteristic ions of each compound, namely *m/z* 121, 148, and 440 for PMA and *m/z* 148, 410, and 454 for PMMA, respectively (Figure 2). The retention times of PMA and PMMA were 12.3 and 14.2 min, respectively.

Results

PMA and PMMA were found in the liver tissue and the peripheral blood in all three cases. The identifications were made by their mass spectra and the National Institute of Standards and Technology library. The cases occurred in the summer of 2000, but because of a lack of reference compound the quantitation could not be finished until recently. The postmortem blood concentrations of PMA, PMMA, and other drugs determined in each of the three cases are listed in Table I. In case 1, 3.4 mg/kg PMA and 3.3 mg/kg PMMA were found, whereas case 3 involved 0.78 mg/kg PMA and 0.68 mg/kg PMMA, respectively. In both cases, MDMA, tetrahydrocannabinol (THC), and alcohol were also found (Table I). Only 0.02 mg/kg PMA and 0.02 mg/kg amphetamine were detected in case 2. However, PMA and PMMA were detected in serum and liver tissue in high concentrations, which was assessed by the response observed in the GC–MS analyses.

The verifications of PMA and PMMA in postmortem blood are illustrated in Figure 2 by mass spectra of the derivatized PMA and PMMA in case 3. The characteristic ions were *m/z* 121, 148, 440 and *m/z* 121, 148, 410, 454 for PMA and PMMA, respectively. The molecular ions *m/z* 562 and *m/z* 576 were only observed in traces.

Table I. Findings for Three Fatal Cases Involving PMA and PMMA

	Case 1	Case 2	Case 3
Age	20	20	20
Sex	Male	Male	Male
Body temperature	42°C	40.2°C	42.8°C
Time of death	Several hours after ingestion	4 Days after ingestion	A few hours after ingestion
Liver screening	+PMA +PMMA	+PMA +PMMA	+PMA +PMMA
Blood concentration	3.4 mg/kg PMA 3.3 mg/kg PMMA 1.6 mg/kg MDMA +THC (not quantitated because of lack of material –	0.02 mg/kg PMA – – 0.02 mg/kg Amphetamine Serum +PMA and PMMA (not quantitated)	0.78 mg/kg PMA 0.68 mg/kg PMMA 0.08 mg/kg MDMA 0.08 mg/kg Benzoylecgonine –
Blood alcohol content	0.066%	Not detected in serum	0.029%
Effects	–	2 Tablets with PMA and PMMA	–
Cause of death	MDMA and PMA/PMMA overdoses	Multiple-organ failure because of PMA/PMMA	PMA/PMMA overdoses

Discussion

The determined postmortem blood concentrations of PMA and PMMA in cases 1 and 3 were associated with fatal overdoses of PMA assessed by Felgate et al. (7). They found that blood concentrations greater than 0.5 mg/L PMA seemed likely to be associated with toxic effects, and this was supported by Kraner et al. (8). Acute intoxication by PMA and PMMA may involve some of the following symptoms: restlessness, agitation, rigidity, tachycardia, convulsions, and coma. Several of these symptoms were observed in the cases. Hyperthermia, typically induced by PMA/PMMA, was also observed in these cases.

PMMA has previously been described in two fatal cases. The first was a case in Spain in 1993, which determined 1.7 mg/L PMMA (unknown analysis and reference substance for quantitation) together with MDA, a high concentration of MDEA, and some alcohol in a 17-year-old male (10). No further details were given about the case. The other case was a 17-year-old male from Austria who in 2000 died from multiorgan failure 57 h after the ingestion of PMA and PMMA. It was reported that he had ingested five to six tablets with PMA and PMMA under the assumption that these were ecstasy. A blood concentration of 1 mg/L PMA and 0.4 mg/L PMMA (serum/plasma unspecified) were found in blood taken at the time of admission to the

hospital (13). These concentrations were comparable to the cases reported in this paper. The concentration ratios of PMA and PMMA between plasma and blood are unknown. The measured concentrations in postmortem samples were unfortunately not reported, although they were determined (13).

In cases 1 and 3, other drugs were present in combination with PMA and PMMA at either "therapeutic" or lethal levels. MDMA was found in lethal concentration in case 1. Furthermore, interaction may have occurred in case 1, as some alcohol also was detected. In case 3, low concentrations of MDMA and benzoylecgonine were observed. The presence of benzoylecgonine indicates cocaine use prior to death. Interaction between these central nervous system-stimulating compounds including alcohol, probably also occurred in case 3.

PMA is often seen in the form of a white tablet with a Mitsubishi logo. This design has been confirmed in case 2. It has been reported that PMA and PMMA are cheaper, less controlled by legislation, and easier to make than MDMA, and therefore manufacturers may substitute it for ecstasy (13,14). The effects of PMA and PMMA are similar to MDMA, but with a slower onset, which encourages the user to take more. However, this leads to an increase in blood concentration, body temperature, and blood pressure that occurs much more rapidly and more severely than with MDMA (3). Cases 1 and 3 are examples of this that illustrate the major risk of overdose for users taking multiple doses.

In case 2, death occurred 4 days after ingestion, and knowing that from 49 to 83% of PMA is excreted in urine over 24 h mainly as metabolites (1) explains the very low postmortem concentrations of PMA and amphetamine. Unfortunately, the serum samples were destroyed before the reference substances were obtained, and the drug concentrations in these samples could therefore not be determined.

The police in Denmark have made several seizures of tablets containing PMA and PMMA within the last years. The PMA/PMMA ratio in these tablets was 1:1, 1.5:1, and 2:1 (15). The ratio between PMA and PMMA in cases 1 and 3 was 1:1, which agreed with tablets of ratio 1:1 because high similarities of the compounds indicate similar absorption and metabolism in humans. Case 2 might have involved a mixture of 2:1, which may explain why PMMA was not detected because it was below the level of quantitation. The ratio was not assessed on tablets found on the victim.

It is assumed that acute fatal intoxication with PMA and PMMA was the cause of death in case 3, however the cause of death in case 1 involved intoxication with both MDMA and PMA/PMMA. In case 2, it was concluded that the cause of death most probably was multiple-organ failure caused by overdoses of PMA and PMMA, and that the incarceration of the brain and the cerebral vasculitis were caused by the intoxication. Amphetamines taken by any route can cause cerebral vasculitis and intracranial hemorrhage (16).

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