Three Cases of Fatal Paramethoxyamphetamine Overdose

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Abstract

Two recent cases of death due to paramethoxyamphetamine (PMA), a methoxylated phenylethylamine derivative, are described and compared with a previous PMA death that occurred in this province in 1985. The deceased were 18 or 19 years of age and were reported to have ingested either methylenedioxyamphetamine (MDA, Ecstasy) or methylenedioxymethamphetamine (MDMA) prior to their deaths. Concentrations of PMA were measured in both peripheral and heart blood samples using gas chromatography equipped with a nitrogen-phosphorus detector. PMA results in the most recent cases were 0.6 mg/L and 1.3 mg/L in the peripheral blood samples, and corresponding heart blood samples were 0.7 mg/L and 2.3 mg/L, respectively. In the 1985 case, the femoral blood concentration was 0.6 mg/L, and the heart blood concentration was 0.8 mg/L. Significant differences between heart and peripheral blood concentrations were observed in two of the three cases, which may indicate the potential for postmortem redistribution of PMA.

Introduction

Phenylethylamine derivative compounds such as methylenedioxyamphetamine (MDA, “Love”) and methylenedioxymethamphetamine (MDMA, “Ecstasy”) have gained attention as a result of their popularity as recreational drugs and their association with rave culture. Users of these drugs cite feelings of euphoria, an increased sociability and a heightened sense of well being as some of the desired effects of the drugs.

The semi-synthetic compound paramethoxyamphetamine (PMA) is also a phenylethylamine derivative. However, the distinguishing feature of PMA is a closer structural resemblance to mescaline which bestows increased hallucinogenic properties to the drug.

PMA has no clinical applications; thus, its pharmacology has not been evaluated in controlled studies. As a result, information on the pharmacokinetics of the drug is currently unavailable. Blood and plasma concentrations following a “typical” or recreational dose are also undetermined. To date, Felgate et al. (1) are the only authors who have published blood PMA concentrations in living subjects. Their analysis of three cases reported PMA blood levels of 0.09 mg/L, 0.13 mg/L, and 0.56 mg/L (1). However, interpreting these values as desired levels in the recreational user is inappropriate because the authors did not indicate whether the subjects took PMA intentionally. Furthermore, resuscitative efforts may have been required for survival at the highest blood PMA level (0.56 mg/L) (1).

Apart from these three living subjects, the only other published information on blood PMA concentrations comes from fatal cases of PMA intoxication (1–6). Twenty-three PMA-related deaths have been described in the literature with blood concentrations ranging 0.2 mg/L to 5.7 mg/L (median 1.9 mg/L) (1–6).

The first published report of PMA use in Canada appeared in 1974, following the deaths of nine individuals who ingested the drug in the province of Ontario (2). Subsequent to these cases, the drug was not detected in any biological sample submitted to this laboratory until April 1985, the details of which are described.

Case Histories

Case 1 (May 2000)

The deceased was a 19-year-old male who ingested unknown quantities of beer, cocaine, methamphetamine, and Ecstasy the night before his death. The next morning he reportedly purchased some additional methamphetamine and two more tablets of Ecstasy. Friends observed the individual to be agitated and “shaky” throughout the afternoon. Sometime later, he was found convulsing and unresponsive and was taken to the hospital. Upon admission he was unconscious with a body temperature of 42.9°F. He developed bradycardia and died of cardiac arrest. An autopsy was conducted, but no anatomic cause of death was found.

Case 2 (April 2000)

An 18-year-old male with a history of drug use ingested cocaine, marijuana, and three tablets of “Ecstasy” over a 5-h period. Following this, the individual felt ill and began to vomit and hallucinate, and he suffered a seizure. An ambulance was
called to the scene where paramedics found him to be without vital signs. The victim was transported to hospital where he died approximately 1 h later. An autopsy revealed no remarkable findings and no anatomic cause of death.

Case 3 (April 1985)
The deceased was a 19-year-old female who attended a party and ingested what she believed was MDA in powder form. She was witnessed to have a seizure during which time she was unable to speak and she stopped breathing. An ambulance was called and paramedics attended. On route to hospital, the victim was intubated and received intravenous fluids, epinephrine, atropine, and Narcan®. Despite these resuscitative efforts, death ensued at the hospital approximately 2 h after her convulsions began. Pulmonary edema was noted at autopsy.

Experimental

Drug screening
PMA was detected during general drug screening for chemically basic drugs. This method, an adaptation of the procedure described by Koves and Wells (7) used a Hewlett-Packard 5890 series II Plus gas chromatograph (GC) equipped with dual nitrogen phosphorus detectors (NPD) and a 7673A autosampler. The columns used were a DB-5 capillary column (25 m x 0.32-mm i.d., 0.52-μm film thickness, Agilent Technologies, Palo Alto, CA) and a DB-17 capillary column (15 m x 0.32-mm i.d., 0.25-μm film thickness, Agilent Technologies). The oven temperature was 90°C for 2 min then ramped at 6°C/min to 290°C and maintained for 17 min. Identification was based on retention times on both columns and confirmation was by gas chromatography–mass spectrometry (GC–MS) (Hewlett-Packard 5973 MSD).

Methodology for the quantitation of PMA is described. Screening for morphine, cocaine and its metabolites, and cannabinoid metabolites was by radioimmunoassay. Tetrahydrocannabinol, cocaine, and benzoylcegonine were quantitated and confirmed by GC–MS.

Blood and urine were analyzed for ethanol and other volatiles using headspace GC with flame-ionization detection (8).

PMA Quantitation

Stock standard solutions of PMA for quantitation were prepared in ethanol and stored at -15°C. Working standards of PMA were prepared by dilution of the stock standard solution and comprised four concentrations ranging 0.125 mg/L to 1.0 mg/L. The extraction procedure for the samples, blood standards, and blank were a modification of the method described by Koves and Wells (7). Briefly, 7.0 mL of toluene and 100 μL of ammonium hydroxide (NH₄OH) were added to 2.0 mL of whole blood and rotated for 20 min. The mixture was centrifuged at 2800 rpm for 10 min at 10°C, and the upper organic phase was transferred to a clean test tube. To the organic phase, 2.0 mL of 2.0N sulfuric acid (H₂SO₄) was added, vortex mixed for 60 s, and centrifuged at 2800 rpm for 5 min at 10°C. The upper organic phase was aspirated using a vacuum pump and discarded. The remaining aqueous acid layer was made alkaline by the addition of 5.0N sodium hydroxide (NaOH) and extracted with 1.0 mL of toluene. After centrifugation for 5 min at 2800 rpm at 10°C, the organic phase was transferred to an automatic injector vial (Chromacol 1.1 autosampler microvials, VWR) that was sealed with Teflon-lined caps. Prior to analysis by GC, the extracts were derivatized by the addition of 2.0 μL of acetic anhydride.

The GC system consisted of a Hewlett-Packard 5890 series II GC equipped with NPDs and a 7673A autosampler. The system included two columns: a DB-1 megabore column (10 m x 0.53-mm i.d., 1.5-μm film thickness, Agilent Technologies) maintained at a temperature of 150°C and a FFAP widebore column (10 m x 0.53-mm i.d., 1.0-μm film thickness, Agilent Technologies) at a temperature of 185°C.

Quantitation was based on the preparation of a calibration curve derived by the addition of known amounts of PMA standard into blank blood. Concentrations were calculated using linear regression. Where necessary, the extract was diluted to bring the observed concentration within the limits of the standard curve.

Results and Discussion

The concentrations of PMA and other drugs determined in each of the three cases are listed in Table I. Other drugs were present in combination with PMA in all three cases at either therapeutic or sub-toxic levels. However, the presence of 0.6 mg/L benzoylcegonine in case 2 indicates cocaine use prior to death. Because both cocaine and PMA are CNS stimulants that act through increased serotonergic activity, the possibility of an interaction between the two drugs should be considered. Similarly, this may apply to case 1 where PMA was present in combination with methamphetamine.

All measured blood PMA concentrations in Table I have been

<table>
<thead>
<tr>
<th>Case</th>
<th>Peripheral Blood</th>
<th>Heart Blood</th>
<th>Other Drugs (mg/L)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>0.6</td>
<td>0.7</td>
<td>Methamphetamine (0.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Amphetamine (traces)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Benzoylcegonine (traces)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cocaine (not detected)</td>
</tr>
<tr>
<td>Case 2</td>
<td>1.3</td>
<td>2.3</td>
<td>Diazepam (0.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Benzyolcegonine (0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cocaine (not detected)</td>
</tr>
<tr>
<td>Case 3</td>
<td>0.6</td>
<td>0.8</td>
<td>Methaqualone (0.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tetrahydrocannabinol (traces)</td>
</tr>
</tbody>
</table>

* All other drugs were quantitated in heart blood, unless otherwise specified.
† Analysis in neck blood.
associated with fatal overdose. Acute intoxication by PMA is characterized by restlessness, agitation, rigidity, tachycardia, and convulsions. A prominent symptom associated with PMA-induced toxicity is hyperthermia. Although information on body temperature was not available for two of the cases presented here, the individual in case 1 presented to the hospital with a body temperature of 42.9°C. This is consistent with the body temperatures recorded for victims of PMA intoxication described in the literature. For example, among the nine previous PMA deaths in Ontario, body temperatures of 42.8°C were described in each of three cases (2), whereas Felgate et al. (1) reported temperatures ranging from 41.2°C to 46.1°C in their case histories.

In two of the present cases, the detected level of PMA was substantially higher in the heart blood sample than the peripheral blood sample. Because previously published data on PMA levels were for peripheral samples (1) or blood samples of unspecified source (2–6), this paper provides the first indication that post-mortem redistribution of PMA may occur. Further data are required to verify this finding; however, site-dependent concentration differences have also been shown for related compounds such as methamphetamine (9–11), amphetamine (9,11) and methylenedioxyethylamphetamine (MDEA) (12). The data from these publications are limited but also support the possibility that postmortem redistribution of this drug may occur.

Despite the 15-year time gap between the three cases presented, the circumstances surrounding the deaths are similar. All three victims were teenagers aged 18 to 19 years, and all of the decedents were reported to ingest either MDMA (Ecstasy) or MDA (Love). However, neither of these drugs was present in any of the blood samples analyzed. This is a common finding among published cases of death due to PMA. Of the nine previous PMA deaths that occurred in Ontario, it was reported that at least five of the individuals believed they were taking MDA (2). Felgate et al. (1) have also indicated that PMA is routinely sold as Ecstasy in Australia. This demonstrates the need to screen for all amphetamine derivatives when case history indicates death has occurred following Ecstasy use.

**Acknowledgments**

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**References**