Recent Paramethoxymethamphetamine (PMMA) Deaths in Taiwan

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Abstract
Paramethoxymethamphetamine (PMA) and paramethoxymethamphetamine (PMMA) are methoxylated phenylethylamine derivatives that have been banned in Taiwan since December 2005. The case history and pathological and toxicological findings of eight recent PMMA fatalities were investigated. All specimens from these cases were initially identified by an AxSYM fluorescence polarization immunoassay screening test for amphetamines with a 300 ng/mL cutoff. Specimens screened positive were confirmed and quantitated by gas chromatography-mass spectrometry. The mean age of these PMMA-related fatalities was 18.9 ± 4.4 years in the range of 14-25. Seven (87.5%) of these eight cases were men. The mean, standard deviation, and range of PMA found in the heart blood collected from these 8 cases were 0.213, 0.144, and 0.079-0.489 µg/mL, respectively. The corresponding data for PMMA were 4.312, 4.806, and 1.208-15.824 µg/mL, respectively. Other drugs, such as MDA, MDMA, ketamine, norketamine, hydroxymidazolam, methamphetamine, and pentobarbital, were also found in these cases.

Introduction
Like 3,4-methylenedioxymethamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA), and 3,4-methylenedioxyethylamphetamine (MDEA), paramethoxyamphetamine (PMA) and paramethoxymethamphetamine (PMMA) are methoxy-derivatives of phenylethylamines. All drugs exhibit hallucinogenic properties; however, para-methoxy-derivatives have a slower onset of action and higher toxicity than their methylenedioxy counterparts (1,2). PMMA is sold in tablets, and its appearance and cost are similar to MDMA, causing it to be mistakenly ingested as "ecstasy," sometimes with lethal consequences. In the last few years, an increasing number of fatal intoxications involving PMA have been reported (3-11).

The lack of reference substances delayed the quantitation of PMMA and, therefore, the publication of the toxicological findings in fatal cases. Recently, Becker et al. (12) published blood PMMA concentrations (0.85 µg/mL) in a fatal case in Germany. Johansen et al. (11) described three fatal cases involving PMA and PMMA in Denmark in 2000. Postmortem blood concentrations of PMA and PMMA in two of these cases were reportedly at 3.4 and 3.3 mg/kg and 0.78 and 0.68 mg/kg, respectively.

The metabolism of PMMA in humans has been addressed in several studies. Staack et al. (13) identified metabolites in rat urine by GC-MS, indicating that PMMA was extensively metabolized mainly by O-demethylation to pholedrine and, to a minor extent, 3,4-methyloxyamphetamine, 1-hydroxypholedrine diastereomers, 4-hydroxy-3-methoxymethamphetamine, and 4-hydroxy-3-methoxymethamphetamine. They have also shown that cytochrome P450 2D6 catalyzes the demethylation of PMMA to phenol in humans (14).

Taiwan has, during the last few years, experienced a very significant increase in the abuse of PMA and PMMA. The police have made 52 seizures of PMMA-containing tablets during the January–June 2006 period (Table I). In Taiwan, PMA has long

Table 1. Number of PMMA-Related Seizures in Taiwan Reported for the January–June 2006 Period

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
<th>Jun</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>PMMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>PMMA + PMA</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>5</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>PMMA + Ketamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>PMMA + MDEA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>PMMA + MAP*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>PMMA + MDA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PMMA + MDMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PMMA + Heroin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>52</td>
</tr>
</tbody>
</table>

* MAP = methamphetamine.
been classified as a controlled drug (Schedule II) under the Statute for Narcotics Hazard Control list (15), though PMMA was not a controlled substance until recently (included in the Schedule II list on August 8, 2006). This paper describes eight fatal overdose cases caused by PMMA ingestion during the April-July 2006 period.

Case Histories

Case 1
A 14-year-old male was found unresponsive at a party in the home of a friend. Friends witnessed him taking 2½ ecstasy tablets at 10:30 a.m. At 1:00 p.m., friends found him unresponsive, lying on the bed. An ambulance was called to the scene, and paramedics found him to have no vital signs. An autopsy revealed no remarkable findings and no anatomic cause of death. A toxicological analysis of blood revealed lethal levels of PMMA, with low levels of ketamine and norketamine. Ecstasy was not detected.

Case 2
The deceased was a 15-year-old male who attended the same party as Case 1 and was reportedly taking two ecstasy tablets at 10:30 a.m. At 1:30 p.m., he witnessed his friend (the subject in Case 1) transported to the hospital and then went home. Approximately 1½ h after arriving at home, he convulsed and was then unresponsive. He was sent to a local hospital. Despite aggressive resuscitation attempts, death ensued 1 h after convulsion. During his hospital stay, he developed disseminated intravascular coagulation, rhabdomyolysis, and hyperkalemia. Pulmonary edema/congestion, renal hemorrhage, and renal tubular necrosis were noted at autopsy. A toxicological analysis of blood revealed lethal levels of PMMA, with low levels of ketamine and norketamine. Ecstasy (MDMA) was not detected.

Case 3
In one early morning, the face of the subject (an 18-year-old female) was found showing strong cyanosis. The mother called an ambulance to the scene, but the subject was pronounced dead before arriving at the hospital. More than 100 tablets of unknown ecstasy were found at the scene. The deceased had a history of attempted suicide by cutting her wrists and taking sleeping pills. A toxicological analysis of blood revealed lethal levels of PMMA, with high levels of ketamine and norketamine and low levels of methamphetamine. Ecstasy was not detected.

Case 4
A 19-year-old male was found collapsed and lying on the bedroom floor. He was later sent to the hospital. Respiratory distress developed, followed by cardiac arrest. He was pronounced dead in the emergency department. A toxicological analysis of blood revealed lethal levels of PMMA, with therapeutic levels of pentobarbital. Ecstasy was not detected.

Case 5
A 25-year-old male attended a friend’s birthday party one night. He was seen taking one tablet of ecstasy with wine. The next day morning, he was convulsing, vomiting, and disordered language developed. He was sent to the hospital and was pronounced dead before arrival. High levels of pulmonary congestion and edema were noted at autopsy. A toxicological analysis of blood revealed lethal levels of PMMA, with low levels of MDMA, ketamine, and norketamine.

Case 6
A 14-year-old male was found dead at home following the ingestion of at least 4 tablets, believed to be Ecstasy, over a period of 12 h (or longer). Brain edema/congestion, subendocardial hemorrhage with marked pulmonary congestion, and edema were noted in the autopsy report. A toxicological analysis of blood revealed lethal levels of PMMA and MDMA, with low levels of ketamine, norketamine, MDA, and methamphetamine.

Case 7
A 22-year-old male ingested an unknown number of tablets, believed to be Ecstasy, during a hotel party. He collapsed and was taken to the hospital where he was pronounced dead before hospital arrival. Pulmonary edema was noted at autopsy. A toxicological analysis of blood revealed lethal levels of PMMA, with low levels of ketamine. Ecstasy was not detected.

Case 8
A 24-year-old male ingested an unknown number of tablets, believed to be Ecstasy, while staying overnight at a friend’s house. The next morning, friends found him unresponsive, lying on the bed. He was sent to the hospital and was pronounced dead before hospital arrival. Toxicological analysis of blood revealed lethal levels of PMMA and MDMA, with low levels of MDA.

Experimental

Test procedure
All PMMA case specimens were initially identified by an AxSYM fluorescence polarization immunoassay screening test for amphetamines with 300 ng/mL as the cutoff. Positive screens were confirmed and quantitated using gas chromatography–mass spectrometry (GC–MS). Biological fluid specimens (heart blood, gastric, bile, and urine) were routinely tested for opiates, amphetamines, benzo diazepines, and barbiturates by the fluorescence polarization immunoassay. All samples were also screened for basic or acidic drugs by GC–MS and then quantitatively confirmed (also by GC–MS) for the drugs found. Biological fluid specimens were also analyzed for ethanol by headspace GC with flame-ionization detection.

Sample preparation
Aliquots (2 mL) of biological fluid specimens (blood, gastric, bile, and urine) were spiked with 50 μL of the internal standard (20 μg/mL methamphetamine-d8) and 1 mL 2N NaOH was added. The resulting solution was extracted with 5 mL ethyl acetate on a horizontal shaker for 5 min. The mixture was then centrifuged for 5 min and the upper ethyl acetate phase was

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transferred to a clean screw-cap test tube. Two milliliters of 0.5N HCl was added, and the mixture was shaken for 5 min. After centrifugation, the acidic layer was transferred and made basic with 1 mL 2N NaOH. The basicity was checked with pH paper before it was extracted with 5 mL ethyl acetate for 5 min. After centrifugation, the upper ethyl acetate phase was transferred to a clean screw-top tube containing 50 μL methanol-HCl mixture (20 mL methanol + 0.1 mL concentrated HCl) and evaporated to dryness under a stream of nitrogen at 60°C.

For derivatization, 50 μL of ethyl acetate and 50 μL of heptafluorobutyric anhydride (HFBA) were added to the residue in the screw-top tube previously prepared. The capped tube was vortex mixed for 20 s and then heated at 70°C for 30 min. The reaction mixture was evaporated to dryness under a stream of nitrogen at 50°C and reconstituted in 100 μL ethyl acetate prior to GC-MS analysis.

**GC–MS analysis**

An Agilent 6890N GC–5973N MSD, operated at 70 eV with an ion-source temperature of 230°C, was used in this study. The GC was equipped with a 30-m Hewlett-Packard (Andover, MA) HP-1MS fused silica capillary column (0.25-mm i.d., 0.25-μm film thickness). The injector and interface temperature were maintained at 260°C and 280°C, respectively. The inlet pressure was held at 5 psi for 1 min, then programmed to 20 psi at 2 psi/min, and held for 4.5 min. The oven temperature was held at 60°C for 1 min, then programmed to 300°C at 20°C/min, and held at the final temperature for 1 min. The following parameters were used for injecting samples into the GC–MS system: sample size, 1 μL; injection mode, splitless; and injector purge-off duration, 1 min.

Ions selected for monitoring the resulting HFB-derivatives were: m/z 261, 213, and 123 for methamphetamine-d₈; 121, 148, and 240 for PMA; and 254, 148, and 121 for PMMA. The mass spectra of HFBA-derivatized PMA, PMMA, and methamphetamine-d₈ are shown in Figure 1. The first ion listed for each compound was used for quantitation using a linear regression line derived from five calibrators at 100, 250, 500, 1000, and 2000 ng/mL. Corresponding drug-free matrixes were used for the preparation of these calibrators.

**Results and Discussion**

To access the epidemiology and causes of death for the PMMA-positive fatalities, all eight deaths that tested positive for PMMA during the April–July 2006 period were reviewed. The mean age of these PMMA-related fatalities was 18.9 ± 4.4 years in the range of 14–25. Seven (87.5%) of these eight cases were men. Acute intoxication by PMA and PMMA may show some of the following symptoms: restlessness, agitation, rigidity, tachycardia, convulsion, and coma. Several of these symptoms were observed in this series of cases hereby reported. Hyperthermia, typically induced by PMA/PMMA, was also observed in these cases. Common autopsy findings (Cases 1, 2, 5, 6, and 7) included pulmonary edema/congestion, multiple organ congestion, pulmonary hemorrhage, brain edema/congestion, subendocardial hemorrhage, and portal vein congestion. Subarachnoid hemorrhage or subdural hemorrhage was also presented. Other observations included renal hemorrhage, renal tubular necrosis, hepatic necrosis, splenic congestion, rhabdomyolysis, acute hypoxic brain, and coronary atherosclerosis.

![Figure 1. Total ion chromatogram; peak identification: 1, methamphetamine-d₈; 2, PMA; and 3, PMMA (A). Mass spectra of HFB-derivatized methamphetamine-d₈ (B), PMA (C), and PMMA (D).](https://academic.oup.com/jat/article-abstract/31/2/109/851145)
Table II. Postmortem Distribution of PMA and PMMA (µg/mL) Found in Specimens Collected from Eight Fatal Cases in Taiwan

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Drug Ratio</th>
<th>Heart Blood</th>
<th>Urine</th>
<th>Other Drugs (Blood, µg/mL)</th>
<th>Cause of Death</th>
<th>Manner of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>M</td>
<td>PMA</td>
<td>0.145</td>
<td>6.263</td>
<td>Ketamine, 0.018</td>
<td>PMMA</td>
<td>Accidental</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PMMA</td>
<td>3.017</td>
<td>157.51</td>
<td>Norketamine, 0.017</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PMA/PMMA</td>
<td>0.048</td>
<td>0.040</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>M</td>
<td>PMA</td>
<td>0.196</td>
<td>1.808</td>
<td>ND*</td>
<td>PMMA</td>
<td>Accidental</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PMMA</td>
<td>1.554</td>
<td>7.646</td>
<td></td>
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<tr>
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<td>PMA/PMMA</td>
<td>0.126</td>
<td>0.237</td>
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<tr>
<td>3</td>
<td>18</td>
<td>F</td>
<td>PMA</td>
<td>0.367</td>
<td>—</td>
<td>Ketamine, 1.210</td>
<td>PMMA</td>
<td>Suicide</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>PMMA</td>
<td>15.824</td>
<td>—</td>
<td>Norketamine, 0.558</td>
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<tr>
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<td></td>
<td></td>
<td>PMA/PMMA</td>
<td>0.023</td>
<td>NA*</td>
<td>Methamphetamine, 0.139</td>
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<tr>
<td>4</td>
<td>19</td>
<td>M</td>
<td>PMA</td>
<td>0.489</td>
<td>—</td>
<td>Pentobarbital, 0.283</td>
<td>PMMA</td>
<td>Accidental</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PMMA</td>
<td>4.014</td>
<td>—</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PMA/PMMA</td>
<td>0.122</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>M</td>
<td>PMA</td>
<td>0.122</td>
<td>0.379</td>
<td>MDMA, 0.199</td>
<td>PMMA</td>
<td>Accidental</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PMMA</td>
<td>1.208</td>
<td>11.857</td>
<td>Ketamine, 0.154</td>
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<td>PMA/PMMA</td>
<td>0.101</td>
<td>0.032</td>
<td>Norketamine, 0.177</td>
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<tr>
<td>6</td>
<td>14</td>
<td>M</td>
<td>PMA</td>
<td>0.205</td>
<td>5.964</td>
<td>Methamphetamine, 0.109</td>
<td>Multiple-drug</td>
<td>Accidental</td>
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<tr>
<td></td>
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<td>PMMA</td>
<td>2.193</td>
<td>88.706</td>
<td>MDMA, 0.134</td>
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<tr>
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<td></td>
<td>PMA/PMMA</td>
<td>0.093</td>
<td>0.067</td>
<td>MDMA, 14.637</td>
<td></td>
<td></td>
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<tr>
<td></td>
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<td>Ketamine, 0.199</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Norketamine, 0.326</td>
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</tr>
<tr>
<td>7</td>
<td>22</td>
<td>M</td>
<td>PMA</td>
<td>0.097</td>
<td>0.263</td>
<td>Ketamine, 0.041</td>
<td>PMMA</td>
<td>Accidental</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>PMMA</td>
<td>1.969</td>
<td>14.208</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PMA/PMMA</td>
<td>0.049</td>
<td>0.019</td>
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<tr>
<td>8</td>
<td>24</td>
<td>M</td>
<td>PMA</td>
<td>0.079</td>
<td>—</td>
<td>MDMA, 0.172</td>
<td>Multiple-drug</td>
<td>Accidental</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PMMA</td>
<td>4.718</td>
<td>—</td>
<td>MDMA, 4.322</td>
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<td></td>
<td>PMA/PMMA</td>
<td>0.017</td>
<td>NA</td>
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</tbody>
</table>

* ND = Not detected; 
  a Sample for information not available; 
  * NA = Not applicable.

The postmortem blood concentrations of PMA, PMMA, and other drugs found in these cases are listed in Table II. Postmortem blood PMA concentrations were 0.145, 0.196, 0.367, 0.489, 0.205, 0.097, and 0.079 µg/mL, and the corresponding PMMA concentrations in these cases were 3.017, 1.554, 15.824, 4.014, 2.193, 1.969, and 4.718 µg/mL, respectively. Average postmortem blood concentrations and standard deviations for PMA and PMMA were 0.213 ± 0.144 and 4.312 ± 4.806 µg/mL, respectively. The mean of PMMA concentration found in the heart blood collected from these 8 cases was higher than the published postmortem blood PMMA concentrations 0.85 µg/mL in Germany (12) and 0.78, 0.68 mg/kg in Denmark (11). The PMA-to-PMMA concentration ratios in the postmortem blood (n = 8) ranged from 0.017 to 0.126, with an average of 0.072 ± 0.043.

Urine specimens contained significant amounts of PMMA and PMA. The PMA-to-PMMA concentration ratios in the postmortem urine (n = 5) ranged from 0.019 to 0.237, with an average of 0.079 ± 0.090. The concentrations of PMMA appeared to be higher than PMA in postmortem blood and urine. The drug is primarily metabolized in the liver, where it undergoes N-dealkylation with PMA as the minor metabolite (13). Most PMMA is excreted unchanged in the urine.

Blood specimens from cases 1, 3, 5, 6, and 7 also contained ketamine and norketamine. The police have seized several ecstasy tablets containing ketamine (25.23%) (16). This appears to be a characteristic of a drug combination unique to Taiwan. In each case, it is likely that the deceased thought they were ingesting MDMA; however, MDMA was found only in Cases 5 (0.199 µg/mL), 6 (14.637 µg/mL), and 8 (4.322 µg/mL). PMA or PMMA was found in street drugs offered as ecstasy. These compounds exhibit a higher toxicity than the methylene-dioxyamphetamine derivatives. This paper describes eight cases of fatal overdoses from PMMA ingestion that occurred during the April–July 2006 period in the greater Taipei metropolitan area (population = approximately 7 million). These cases reflect the well-known fact that the contents of street drugs offered as ecstasy pills may not necessarily be MDMA, even if they have the same logo as those found to be ecstasy. Users of these pills,
therefore, always take the risk of consuming pills with
dangerous life-threatening ingredients.

Acknowledgment

The authors are thankful to Professor Ray H. Liu (Fooyin
University, Kaohsiung Hsien, Taiwan) for his assistance in
the preparation of the manuscript.

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Manuscript received July 22, 2006;
revision received August 30, 2006.