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# Amphetamine Derivative Fatalities in South Australia—Is "Ecstasy" the Culprit?

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**Objective:** To analyze features of a series of fatalities caused by amphetamine-derivative designer drugs marketed as "Ecstasy" in South Australia, and to identify reasons for the recent marked increase in number of these deaths.

**Materials and Methods:** Following the death of a 26-year-old woman after alleged ingestion of Ecstasy tablets, a retrospective search of files at State Forensic Science, Adelaide and the South Australian State Coroner's Department was undertaken from February 1992 to January 1997 to identify similar cases.

**Results:** Six fatalities were found, all of which have occurred since September 1995 (M:F ratio, 1:1; age range, 22 to 36 years; average age, 27.7 years). All individuals had histories of recent ingestion of illegal drugs thought to be Ecstasy (methylenedioxymethamphetamine, MDMA) at the time of purchase. Delay occurred in seeking medical attention, despite severe symptoms. Causes of death involved documented hyperthermia in 3 cases (temperatures of 41.5–46.1°C), with features of hyperthermia in one other case, and intracranial hemorrhage in another. Drugs in toxic/lethal amounts identified at postmortem included paramethoxyamphetamine (PMA) in all cases, amphetamine/methamphetamine in 4 cases, and methylenedioxymethamphetamine (MDMA or Ecstasy) in only 2 cases. Interaction with a prescription medication (fluoxetine) may have occurred in 1 case.

**Conclusions:** The number of deaths due to amphetamine derivatives apparently due to substitution of PMA for MDMA (Ecstasy) have recently increased markedly in Adelaide. Potential users should be warned that PMA has been associated with a much higher rate of lethal complications than other designer drugs, and that no guarantee can be made that tablets sold as Ecstasy are not PMA.

**Key Words:** Ecstacy—PMA—MDMA—Drug fatalities.

The use of amphetamines for recreational purposes is commonplace in many countries, including Australia (1–3). For example, it was estimated in the early 1990s that 500,000 people in Great Britain used amphetamines on a weekly basis (4). In recent years, use of ring-substituted amphetamines (i.e., so-called amphetamine derivatives) such as methylene-dioxyamphetamine (MDA or the "love pill"), 3,4-methylenedioxymethamphetamine (MDMA, "Adam," or "Ecstasy") and 3,4-methylenedioxyethamphetamine (MDEA, or "Eve") has been increasing.

Although used initially for psychotherapy or appetite suppression, medical use of amphetamine derivatives has now ceased and these drugs are banned in most countries (4). Their use persists, however, particularly among young people attending dance clubs and rave parties in which sustained dancing is common. Deaths have occurred in the United States, the United Kingdom, and Australia following adverse reactions to Ecstasy (MDMA), however, deaths following paramethoxyamphetamine (PMA) have been rarely reported. Six deaths occurring in Adelaide between September 1995 and January 1997 prompted concerns as to the reasons for this alarming local increase in fatalities.

## MATERIALS AND METHODS

It is a legal requirement that all violent or unusual deaths in South Australia must be reported to the South Australian State Coroner. Deaths from possible drug overdose or toxicity fall within that description. Most autopsies ordered by the State Coroner are performed by pathologists at Forensic Science in Adelaide. Retrospective review of files at both Forensic Science and the South Australian State Coroner's Office over the 5-year period from February 1992 to January 1997 was undertaken to identify all fatalities attributable to ring-substituted

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amphetamine derivatives such as MDA, MDMA and PMA. Police records and autopsy files were analyzed in detail.

## RESULTS

Six fatalities were identified, all of which occurred after September 1995.

### Case 1

A 35-year-old man had been rolling around on the floor of a club house following ingestion over a period of 5.5 hours of at least 5 tablets believed to be Ecstasy. Witnesses had attempted to cool him down and revive him with water; however, his condition continued to deteriorate and death ensued. On examination at the scene several hours after death, rigor mortis was fully established in all four limbs, the body was clothed only in blue shorts, and the body's core temperature was 41.2°C, with a room temperature of 19°C. Autopsy examination revealed superficial abrasions consistent with carpet burns. The only other finding was of mature scar tissue within the myocardium in the absence of significant atherosclerotic coronary artery disease. Toxicologic analysis of blood revealed lethal levels of PMA, with high levels of amphetamine and methamphetamine. Ecstasy was not detected.

### Case 2

A 36-year-old woman died while at home with her boyfriend following ingestion of a tablet believed to be Ecstasy on the preceding evening. After taking the tablet, she had complained of feeling hot with a headache, had taken her clothes off, and had lain down in the hallway. Her boyfriend attempted to cool her by sponging her. Later, she had crawled into the shower cubicle and was found dead the following morning. Death was estimated to have occurred 9 to 10 hours prior to discovery of the body. The significant finding at autopsy was massive intracerebral hemorrhage within the posterior right frontal lobe with no evidence of underlying aneurysm or vascular malformation. Scattered bruises were also noted over the arms and legs. Toxicologic analysis of blood revealed elevated, but apparently not lethal, levels of PMA, with therapeutic levels of fluoxetine (Prozac). Ecstasy was not detected.

### Case 3

A 22-year-old woman died in the hospital 12 hours after being admitted unconscious and fitting with a core temperature of 42.5°C. Information from police indicated that she had taken both methamphetamine and 3 tablets believed to be Ecstasy and had spent the preceding night at dance clubs. She had complained of feeling hot prior to collapse and when the ambulance arrived she was dressed only in underpants. During her hospital stay, she developed disseminated intravascular coagulation, rhabdomyolysis, and hyperkalemia. Evidence of coagulopathy was noted at autopsy with widespread subcutaneous and intraparenchymal hemorrhage. Histologic evidence of rhabdomyolysis was also present. Toxicologic analysis of blood revealed lethal levels of PMA with high levels of MDMA and methamphetamine.

### Case 4

A 23-year-old man ingested an unknown number (''1 tablet every half hour or so'') of tablets believed to be Ecstasy, overnight at a friend's house. He collapsed and was taken to the hospital where he was noted to feel hot. Cardiac arrest occurred soon after arrival, followed by death. Autopsy examination revealed microscopic evidence of early acute tubular necrosis within the kidneys and changes of rhabdomyolysis. Toxicologic analysis of blood revealed lethal levels of PMA with high levels of amphetamine and methamphetamine. MDMA (Ecstasy) was not detected.

### Case 5

A 24-year-old man died while apparently sleeping on the living room floor at his girlfriend's house after taking 3 tablets believed to be Ecstasy. At autopsy, minor abrasions were found on the face, shoulder, and lower legs consistent with carpet burns sustained in a convulsive phase prior to death. Toxicologic analysis of blood revealed lethal levels of PMA. MDMA (Ecstasy) was not detected.

### Case 6

A 26-year-old woman died at home following the ingestion of at least 5 tablets believed to be Ecstasy over a period of at least 12 hours. Witnesses described her as feeling hot, becoming agitated after having a bath, and having difficulty breathing. She was naked for some time prior to her terminal collapse. After several hours of progressively worsening symptoms, she was taken to the hospital where she was noted to have cyanosis, fits, and hyperthermia, with cardiac arrhythmias. Her highest core temperature was recorded at 46.1°C and terminal cardiac arrest occurred within 30 minutes of arrival. At autopsy, scattered intrathoracic petechial hemorrhages with marked pulmonary congestion and edema were noted. Toxicologic analysis of blood revealed lethal levels of

PMA and MDMA, with high levels of methamphetamine.

It is often difficult to state with certainty drug levels that are potentially toxic or lethal, because levels normally found in habitual abusers may greatly exceed those which would be injurious or fatal to persons not previously exposed to the drug. For example, although levels of more than 1 mg/L of amphetamines within the blood have been deemed fatal (5), steady-state levels of 2.0 to 3.0 mg/L have been reported in an addict (6). Similarly, although a level of blood methamphetamine more than 0.1 mg/L may be lethal (7), concentrations of 1.4 to 13 have been found in abusers dying of trauma (6). PMA levels of more than 0.3 mg/L and MDMA levels of more than 0.6 mg/L have been found in individuals whose deaths were attributed to those drugs (6).

None of the reported victims showed evidence of assault, the bruising noted being attributable to drug-induced coagulopathy. Alcohol was not detected in the blood in any of the cases, the details of which are summarized in Table 1. The pathologic features of Case 1 have been previously reported (8).

## DISCUSSION

Ingestion of ring-substituted amphetamines such as MDMA results in heightened sensations and euphoria. An incorrect belief exists that these substances are relatively safe hallucinogens (10) and locally there has been a marked increase since the early 1990s in their use at dance clubs as mood enhancers. Affected individuals have described an increase in alertness, confidence, and physical and mental activity (8). However, higher doses produce sympathomimetic effects such as anxiety, agitation, and dysphoria with physical manifestations of nausea, insomnia, ataxia, trembling, and sweating (9). Tachycardia and hypertension may also occur.

In toxic amounts, the effects may be extremely serious with the development of hyperthermia, convulsions, rhabdomyolysis, disseminated intravascular coagulation, and multiorgan failure. Deaths have also resulted from cardiac arrhythmias, electrolyte derangements, cerebral hemorrhage, and infarction (10–17). The use of these drugs in association with prolonged strenuous physical activity in hot environments, such as dancing at rave parties, is a well-documented situation that increases the risk of hyperthermic death. Dehydration exacerbated by the use of alcohol, is an additional problem in such settings. Termed the "dance of death" by Henry in a paper in the *British Medical Journal*, some venues provide special rooms with air-conditioning for participants to recover from such exertion (18).

It is significant that the literature deals predominantly with deaths and adverse effects due to MDMA (Ecstasy), MDEA (Eve) and MDA (the love pill), rather than PMA (10–17,19–23). In fact, the most detailed description of deaths due to PMA that we were able to find describes a series of nine deaths in Ontario, Canada, more than 20 years ago, following the first appearance of the drug in the province (24). PMA does not appear to be a favored recreational drug in either the United States or Great Britain, and we are not aware of PMA being widely used in other Australian centers, although occasional deaths have been reported (1,2). Although a recent analysis in Sheffield, Great Britain, of 12 street drugs sold as Ecstasy demonstrated MDMA in only 3 of the preparations, none contained PMA (4).

The ring-substituted amphetamines produce their effects through the noradrenergic, dopaminergic, and serotoninergic neurotransmitter pathways. The role of serotonin in thermoregulation most likely explains the propensity for hyperthermia that occurs in overdose cases, exacerbated by noradrenergic effects (4). Animal studies have also shown that MDMA causes hyperthermia (25). Three of our victims had markedly elevated temperatures, even allowing for a postmortem delay in measurement in one case. There was also additional postmortem evidence of hyperthermia in another case. It is possible that individual susceptibility to the adverse effects of the amphetamine derivatives exists, with deficient demethylation of MDMA by debrisoquine hydroxylase (CYP2D6) being shown in certain individuals (26). The absence of CYP2D6, a member of the cytochrome P450 superfamily of enzymes, in 5% to 9% of whites (26) may be another factor explaining apparently idiosyncratic or severe responses to the drug.

It is also possible that inhibition of CYP2D6 by other illicit or prescribed drugs may inhibit the clearance of amphetamine derivatives. For example, death from cerebral hemorrhage occurred in the woman in Case 2 in spite of levels of PMA not normally considered to be associated with a lethal outcome. However, it may be that fluoxetine, which was also present, had either reduced clearance or had in other ways enhanced the untoward effects of PMA. In support of this possibility is the fact that some users will simultaneously take fluoxetine to increase the effects of MDMA (2). Cocaine also acts through the dopaminergic pathways and may cross react (4). Alcohol intoxication may be another factor to consider, particularly with possible

**TABLE 1.** *Summary of features of 6 fatalities due to ring-substituted amphetamine toxicity in South Australia from September 1995 to January 1997*

| Case no. | Age (years) | Year (month) | Gender | Circumstances of death | Drugs identified at postmortem | Cause of death |
|---|---|---|---|---|---|---|
| 1 | 35 | 1995 (Sept) | M | Collapse at clubhouse | PMA (1.7 mg/L)<br>Methamphetamine (0.23 mg/L)<br>Amphetamine (1.6 mg/L)<br>Cannabinoids | Hyperthermia (temperature = 41.2°C) |
| 2 | 36 | 1996 (Jan) | F | Collapse at home | PMA (0.24 mg/L)<br>Fluoxetine (Prozac, 0.1 mg/L)<br>Cannabinoids | Intracerebral hemorrhage |
| 3 | 22 | 1996 (Mar) | F | Collapse after night in dance club | PMA (1.32 mg/L)<br>MDMA (0.3 mg/L)<br>Cannabinoids | Hyperthermia (temperature = 42.5°C) |
| 4 | 23 | 1996 (Aug) | M | Collapse at friend's home | PMA (3.7 mg/L)<br>Methamphetamine (3.1 mg/L)<br>Amphetamine (0.26 mg/L) | Amphetamine toxicity |
| 5 | 24 | 1996 (Nov) | M | Collapse at friend's home | PMA (4.9 mg/L) | PMA toxicity |
| 6 | 26 | 1997 (Jan) | F | Collapse at home | PMA (2.2 mg/L)<br>MDMA (0.82 mg/L)<br>Methamphetamine (0.09 mg/L) | Hyperthermia (temperature = 46.1°C) |

PMA, paramethoxyamphetamine; MDMA, methylenedioxymethamphetamine.

cardiac arrhythmia, although alcohol was not detected in any of our cases. There are, however, few data available to date on mechanisms of potential cross-reactivity of these substances. It is likely that the elevated levels of amphetamine and methamphetamine also acted synergistically with PMA.

Over the 5 years of the study, routine screening of urine for amphetamines using the EMIT system (Syua, CA, U.S.A.) has been carried out at Forensic Science. Positive results have been followed up by gas chromatographic analysis of blood minimizing the chances of cases of amphetamine toxicity not being detected during that period. The sudden increase in deaths in Adelaide over the past 17 months, widely assumed to be due to Ecstasy ingestion, have been shown by this analysis to be due instead to PMA, which has been sold to users as Ecstasy. The involvement of PMA in these recent deaths suggests that local manufacture and/or distribution of this substance, thought by buyers to be MDMA or its equivalent, has only recently commenced. Although production may have been influenced by the availability of suitable chemical precursors, it has been suggested that producers of PMA may be aware of its lethal nature and have been deliberately marketing it as another drug (1). If this has been the case, this may have implications for criminal liability. Given that PMA could be substituted for MDMA by manufacturers in other countries, such as the United States or the United Kingdom, it is important that the potential results of such activities are known.

A major problem with designer drugs is that buyers and sellers usually have no idea of the strength or precise composition of the merchandise. For example, drugs that have been sold as Ecstasy have contained not only MDA and MDEA, but also other substances including triprolidine, pseudoephedrine, and even caffeine. It has been proposed that some of the toxic effects associated with MDMA may be due to such contaminants (4). Unfortunately, although it would have been of interest to obtain certain local hospital admission figures for amphetamine-related disorders to determine whether a recent increase in the number of cases of PMA-related illness existed, these are not available because they have not been specifically coded for, or recorded. However, over the past 7 months, the Institute of Medical and Veterinary Science (IMVS) laboratories in Adelaide have received urine samples from 16 nonfatal cases of amphetamine derivative toxicity, 14 of which contained PMA. Prior to this, few cases were referred or detected (Prior M, Senior Scientist, IMVS, personal communication, January 1997).

The average age of our victims was 27.6 years, suggesting that amphetamine derivative abuse is not just restricted to a particular adolescent drug scene but may occur at different ages and in different social settings. For example, there was a history of dance club attendance in only one of our cases, with other victims ingesting PMA at private homes or other venues. This widens considerably the group usually considered at risk of exposure to

the drug. Potential users should be aware that there is no way to guarantee the composition or strength of tablets termed Ecstasy. Ecstasy itself may kill and cocktails of drugs sold as Ecstasy may consist partially or completely of other compounds, such as PMA, which appear to increase significantly the risk of life threatening illness and/or death. Such substances should therefore be screened for in all presumed Ecstasy related deaths.

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