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Healthcare

Poisoning with the recreational drug paramethoxyamphetamine ("death")

Liang Han Ling, Colin Marchant, Nicholas A Buckley, Michael Prior and Rod J Irvine

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Abstract

Objective: To describe the clinical features of paramethoxyamphetamine (PMA; "death") poisoning and to compare these with those of people with self-reported "ecstasy" poisoning.

Design: Retrospective casenote review.

Participants and setting: 22 patients who presented to the Emergency Department of the Royal Adelaide Hospital (RAH), a major metropolitan teaching hospital, between 1 January 1996 and 31 December 1998 with PMA poisoning identified through urine drug screens; and 61 patients with self-reported ecstasy poisoning between 1 September 1997 and 31 December 1998 found through the hospital databases.

Results: Patients with PMA poisoning presented with tachycardia (64%), hyperthermia (temperature > 37.5°C; 36%), coma (41%), seizures (32%), arrhythmias (23%), and QRS intervals > 100 ms (50%) with greater frequency and often greater severity than those with self-reported ecstasy poisoning. Two patients with PMA poisoning presented with severe hypoglycaemia (blood glucose level, < 1.5 mmol/L) accompanied by hyperkalaemia (K⁺ concentration, > 7.5 mmol/L).

Conclusions: At our hospital, PMA poisonings accounted for most of the severe reactions among people who believed they had taken ecstasy. Hypoglycaemia and hyperkalaemia may be specific to PMA poisoning. PMA toxicity should be suspected with severe or atypical reactions to "ecstasy", and confirmed by chromatographic urine drug screens.

The recreational use of amphetamine derivatives among young people is common, particularly at dance clubs and dance parties ("raves"). 3,4-Methylenedioxymethamphetamine (MDMA), popularly known as "ecstasy", was first identified in street use in 1972.¹ Another amphetamine derivative, paramethoxyamphetamine (PMA), also appeared in recreational use during the 1970s. PMA, and other amphetamine derivatives, such as 3,4-methylenedioxyethylamphetamine (MDEA) and 3,4-methylenedioxyamphetamine (MDA), are known to have been sold on the street

as ecstasy. Within a few years, PMA was associated with several fatalities in Canada and earned the street-name "death".⁴ Further fatalities associated with PMA toxicity have only been reported in significant numbers in South Australia,^{2,5,6} where at least eight deaths have occurred since September 1995, while no deaths from MDMA alone were reported in the same period (P D Felgate, Scientist, Forensic Science Centre, South Australia, personal communication).

The toxic effects of MDMA are well described,⁷⁻¹⁰ and the few previous case reports of PMA poisoning showed similar toxic effects.^{2,4,5} Serotonergic and sympathomimetic symptoms include anxiety, agitation, nausea, and palpitations. Life-threatening adverse effects of MDMA include severe hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, multiorgan failure, arrhythmias, intracerebral haemorrhage, seizures, and hyponatraemia leading to cerebral oedema.^{3,11}

While case reports of PMA deaths collectively suggest that PMA is more toxic than MDMA, the clinical effects of PMA have not yet been studied systematically. Here, we report a series of non-fatal, confirmed PMA poisonings, all in patients presenting to the emergency department of a metropolitan hospital in South Australia.

Methods

We conducted a retrospective casenote review of all PMA poisonings identified through urine drug screens of patients presenting to the Royal Adelaide Hospital (RAH) Emergency Department between 1 January 1996 and 31 December 1998. We included PMA poisonings involving the coadministration of MDMA or other substances. Urine drug screens had been performed by enzyme immunoassay, with confirmation of positive results by gas chromatography and mass spectrometry, according to Australian Standard 4308 (1995). Data were retrieved from casenotes by means of standardised forms and entered into a computer database.

Findings were compared with those for all other patients presenting to the RAH between 1 September 1997 and 31 December 1998 because of adverse effects after the self-reported use of "ecstasy". These patients were identified by reviewing casenotes of all stimulant drug poisonings through admission diagnosis-related group coding and recorded in the RAH Emergency Department database; a few additional cases that had been wrongly coded were identified through urine drug screens. Confirmation of MDMA exposure by urine drug screens was not available for most patients in this comparison group.

Ethical approval for this study was granted by the Royal Adelaide Hospital ethics committee.

Results

Twenty-two PMA poisonings were confirmed by urine drug screens between 1 January 1996 and 31 December 1998. These occurred in the first eight months and last eight months of the study period, with 16 months of no confirmed PMA poisonings in between. The casenotes of 15 of these 22 patients recorded that they believed they had taken ecstasy. No patient's records showed that he or she knowingly took PMA. Sixty-one patients with self-reported ecstasy (MDMA) poisoning presented to RAH between 1 September 1997 and 31 December 1998. Their characteristics and clinical features are compared with the PMA group in the [Box](#).

Eleven patients with PMA poisoning had only relatively minor symptoms (anxiety, agitation, delirium, hallucinations, headache, involuntary movements, vomiting). Frequent signs recorded in these patients included tachycardia (heart rate > 100 bpm), mild hyperthermia (temperature, > 37.5°C) and a prolonged QRS interval on electrocardiogram, often with a right bundle branch block pattern.

A much larger proportion of patients with ecstasy poisoning presented with relatively minor

symptoms.

The other 11 patients with PMA poisoning had life-threatening toxicity with coma, generalised seizures, severe hyperthermia (temperature, > 40°C) or hypothermia (temperature, < 34.5°C), and some had arrhythmias (atrial fibrillation [2], multifocal ventricular ectopic beats [2], supraventricular tachycardia [1]). Two patients with PMA poisoning presented with severe hypoglycaemia (blood glucose level, < 1.5 mmol/L; normal range, 3.8-5.5 mmol/L), accompanied by hyperkalaemia (K^+ , > 7.5 mmol/L; normal range, 3.1-4.2 mmol/L).

Discussion

PMA and MDMA are structurally and pharmacologically similar, producing their effects through serotonergic, dopaminergic, and noradrenergic mechanisms. The recent case reports of PMA-related deaths in South Australia^{5,6} suggest that PMA is more toxic than MDMA, but do not provide a clinical explanation for this difference. Our retrospective study showed that most people with PMA poisoning present with clinical features that are qualitatively similar to those of people with ecstasy poisoning (ie, hyperthermia, coma, and seizures), but that these symptoms occur more frequently and are more severe in those who took PMA.

Certain features, such as QRS interval prolongation, hypoglycaemia and hyperkalemia, appear unique to PMA poisoning, suggesting there may be toxicological mechanisms different from those of MDMA contributing to PMA's adverse effects. Our patients with PMA poisoning did not have significant acidosis, haemolysis or tissue damage to explain the hyperkalaemia. The high frequencies of prolonged QRS intervals and seizure suggest that PMA may have sodium-channel-blocking properties.

Severe hypoglycaemia has never previously been reported as an adverse effect of PMA. The affected patients did not have liver failure at the time, nor were other drugs detected that might explain the hypoglycaemia. However, PMA is a monoamine oxidase (MAO) inhibitor,¹² and other MAO inhibitors have been reported to stimulate insulin release.¹³ There are only two human studies on PMA, neither of which provides an explanation for serious toxic effects.

Sustained blood pressure elevation of up to 240/130 mmHg occurred in some people taking PMA at a dose of 1 mg/kg bodyweight,⁴ and PMA was found to be three times as potent as the amphetamine derivative MDA as a hallucinogen.¹⁴

Our retrospective study design makes direct comparison between PMA and MDMA impossible. As urine drug screens were not routinely performed in presentations involving stimulant use, it is impossible to determine the exact frequency of PMA and MDMA poisonings presenting over the study period, or to identify a large enough cohort of people poisoned with MDMA alone to serve as a control group. Coadministration of other drugs and inconsistencies in casenote reporting are further factors which would have confounded the comparison of PMA and MDMA poisonings. However, the coronial data and the unique toxicological features of the known PMA poisonings we identified are sufficient to demonstrate that PMA accounts for most severe adverse events after apparent ecstasy ingestion in Adelaide. As PMA does not account for the majority of ecstasy use, this implies that PMA is substantially more toxic than MDMA.

The serious acute toxic effects of MDMA are generally related to hyperthermia, which results from a combination of temperature deregulation, excessive physical activity and high ambient temperatures.³ This knowledge has led to moderately successful public health and education programs to highlight these dangers and encourage users of MDMA at "rave" parties to ensure adequate hydration and to take breaks to cool down. However, much of the serious toxicity we describe with PMA, such as sudden collapse and seizures, may not be amenable to such harm-

minimisation approaches.

Although the actual doses ingested by our patients are not known, only one person reported taking more than two tablets and none were deliberate overdoses. Estimates of dose are unreliable, not only because of the difficulty in obtaining a reliable history of illicit drug use, but also because of variations in tablet strength. However, analysis of recently confiscated ecstasy capsules and tablets shows similar mean concentrations of the active ingredient in those containing PMA (73 mg) and MDMA (106 mg) (P D Felgate, Forensic Science Centre, South Australia, personal communication). Thus, the apparent greater toxicity of PMA is unlikely to be explained by the dose received.

Despite the poor reputation of PMA, its use remains a continuing health concern in Australia. Deaths from PMA use have been reported most frequently in Adelaide, but also in Queensland and Western Australia.² PMA toxicity should be suspected in patients presenting with severe or atypical reactions to ecstasy and the diagnosis can be confirmed by chromatographic urine drug screens.

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Demographic and clinical data for patients confirmed to have ingested paramethoxyamphetamine (PMA) compared with others who reported ingesting "ecstasy"

	PMA (n=22)	"Ecstasy" (n=61)	% Difference (95% CI)	P*
Median age (range)	23 (18-32)	22 (17-35)		0.1115
Males	15 (68%)	33 (54%)	14% (-10% to 38%)	0.3176
Cardiovascular effects				
Median pulse (range)	118 (52-218)	88 (46-160)		0.0156
No. (%) with:				
Pulse >100bpm	14 (64%)	25 (41%)	23% (-1% to 46%)	0.0842
QRS interval >100ms	11 (50%)	3 (5%)	45% (23%-67%)	<0.0001
Arrhythmias	5 (23%)	3 (5%)	18% (-1% to 36%)	0.0278
Metabolic effects				
Median temperature	37°C	36°C		
Range	32-42°C	32-38°C		0.1185
No. (%) with:				
Temperature >37.5°C	8 (36%)	3 (5%)	31% (11%-52%)	0.0008
Temperature >40.0°C	4 (18%)	0	18% (2%-34%)	0.004
Neurological effects				
Median Glasgow coma score	12.5	15		
Range	3-15	4-15		0.0018
No. (%) with:				
Glasgow coma score < 8	9 (41%)	4 (7%)	34% (13%-56%)	0.0005
Seizures	7 (32%)	2 (3%)	29% (9%-49%)	0.001
No. (%) with life-threatening toxicity†	11 (50%)	4 (7%)	43% (22%-65%)	<0.0001

*Fisher's exact test or Mann-Whitney *U* test.

†Seizures, temperature >40°C or Glasgow coma score <6.

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