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CRITICAL CARE

Severe paramethoxymethamphetamine (PMMA) and paramethoxyamphetamine (PMA) outbreak in Israel

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Context. Paramethoxymethamphetamine (PMMA) is a hallucinogenic synthetic substituted amphetamine that was not included in the Israeli Controlled Substance Act (CSA). *Objective.* To report a severe PMMA and paramethoxyamphetamine (PMA) outbreak. *Patients and methods.* The Israeli national forensic toxicology laboratory analyzes the body fluids of unnatural deaths by means of screening immunoassays and chromatographic confirmation and quantification. Samples are referred to this laboratory by the Israeli Forensic Medicine Institute and by hospitals following consultation with the Israel Poison Information Center. The forensic toxicology laboratory began determining PMMA and PMA in February 2007. In all fatal cases with a positive immunoassay screen for amphetamines, a chromatographic analysis of PMA and PMMA was performed. The laboratory and demographic data of consecutive patients in whom PMMA or PMA were detected, were collected during 1 year and subjected to descriptive analysis. *Results*. Of 108 fatal cases with a positive screen for amphetamines, 32 were confirmed. Twenty-four of the 32 cases tested positive for PMMA and PMA – age 27 ± 5 years, 79.2% males, post mortem whole blood PMMA and PMA concentrations 0.35 ± 0.24 and 2.72 ± 1.67 mcg/mL, respectively. Co-exposures were detected in 17 (70.8%) fatalities; including methylenedioxymethamphetamine, methylenedioxyamphetamine, cocaine, cannabinoids, cathinone derivatives, ephedrine/pseudoephedrine, opiates, and ethanol. In addition, five non-fatal male cases were identified; age 32 ± 5 years, four had co-exposures to cocaine, cathinone derivatives, and cannabinoids. These findings led to the inclusion of PMMA in the CSA in July 2007, resulting in only three more fatalities in the following year. *Discussion*. We report an outbreak of PMMA and PMA poisoning resulting in 24 fatalities, and the post mortem whole blood and urine concentrations of these two compounds. PMA was probably the result of PMMA metabolism. Stimulant co-exposures may have contributed to the severity of the poisoning. *Conclusion*. Forensic laboratory and poison center co-operation is important in identifying a new drug of abuse.

Keywords Paramethoxymethamphetamine; Paramethoxyamphetamine; Poisoning; PMMA; PMA

Introduction

Paramethoxymethamphetamine (PMMA), a hallucinogenic synthetic substituted amphetamine, was marketed in Israel because it was not included in the Israeli Controlled Substances Act (CSA). It was found in tablets seized by the Israeli police and identified by the analytical laboratory, Division of Identification and Forensic Sciences, Israel Police.

PMMA and paramethoxyamphetamine (PMA) belong to a group of methoxylated phenethylamine derivatives that includes the naturally occurring compound mescaline and synthetic compounds, such as methylenedioxymethamphetamine (MDMA) and methylenedioxyamphetamine (MDA).[1]

Until 2007, PMMA and PMA were neither seized nor detected in clinical or forensic specimens in Israel. In February 2007, the Israeli forensic toxicology laboratory (Institute of Clinical Toxicology and Pharmacology, Sheba Medical Center, Tel Hashomer, Israel) began testing for PMMA and PMA after encountering a fatal case where amphetamines were detected by immunoassay screening but not in routine chromatographic analysis. Since then, every fatal case with the suspected involvement of drugs of abuse in which amphetamines are detected in the screen has been tested for PMMA and PMA. The detection of new designer drugs, such as PMMA and PMA, is an analytical challenge and there is limited information on their post mortem levels.

During 2007 and the start of 2008, a cluster of 29 patients involving exposure to PMMA and PMA was recorded in Israel. The study objective was to report the analytical findings of the outbreak of PMMA and PMA poisoning and the result of outlawing these designer drugs.

Patients and methods

The study design is a case series.

Between February 2007 and January 2008, all consecutive patients in whom PMMA or PMA were detected in biological samples referred to the Israeli forensic toxicology laboratory were recorded.

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Samples from unnatural deaths are referred to this laboratory by the Israeli National Forensic Medicine Institute, and from patients admitted to hospitals following consultation with the Israel Poison Information Center, Rambam Health Care Campus, Haifa. The forensic toxicology laboratory and the poison center collaborate by continuous exchange of information.

The forensic toxicology laboratory analyzes body fluids in cases of unnatural deaths. The initial screening analysis for drugs of abuse (opiates, cocaine, methadone, cannabis, barbiturates, benzodiazepines, and amphetamines) is performed by an enzyme immunoassay in two different body fluids (blood and urine) when available. This screening uses DRI® homogeneous enzyme immunoassay (Microgenics Corp., Fremont, CA) and Olympus AU640 automated chemistry analyzer (Tokyo, Japan).

Samples that are tested positive in the drugs of abuse screening tests are re-analyzed by gas chromatography/electron ionization-mass spectrometer (EI GCMS) following extraction and derivatization for confirmation and quantitation of the appropriate drugs and metabolites. If amphetamines are tested positive in the screening test (cutoff 1000 ng/mL), the extracted samples are first identified using EI GCMS by comparing the mass spectrum and the retention time to both reference material and library data. PMMA and PMA are further identified and quantitated using liquid chromatography/mass spectrometry-mass spectrometry (LC/MS-MS) operating in the multiple reaction monitoring (MRM) mode. All chemicals used are of analytical grade. PMMA and PMA were purchased from Sigma-Aldrich, and MDMA-D5 and MDA-D5 (Cerrilliant Corp., Round Rock, TX) were used as the internal standard in PMMA and PMA quantitation, respectively. Mass spectrometric confirmation and quantitation were performed either by GCMS 5975A MSD mass spectrometer connected to a 7890A gas chromatograph (Agilent Technologies Inc., Santa Clara, CA) and/or by a triple quadrupole mass spectrometer, Micromaass Quattro Ultima PT, connected to an Alliance 2695 HPLC separation module (Waters, Manchester, UK).

Ethanol was measured in all the available samples using a Hewlett Packard 5890 gas chromatograph connected to a Hewlett Packard 7694 headspace sampler (Hewlett Packard Co., Wilmington, DE). Blood testing was done on whole blood drawn from the femoral vein. Data, including age, gender, site of death, PMMA and PMA concentrations and co-exposures, were subjected to descriptive analysis. The results are expressed as mean ± SD. The study was approved by the Institutional Review Board of Rambam Medical Center, Haifa, Israel.

Results

During the study period, 29 consecutive cases were found to be positive for PMMA and PMA; 24 fatalities and 5 survivors.

During that period, samples from 982 autopsies were referred to the forensic toxicology laboratory, and 108 were found to be positive for amphetamines in the immunoassay screen. The presence of PMMA and PMA was confirmed and quantitated in 24 of the 108 cases. The data of the 24 fatal cases are shown in Table 1. The mean age of these cases was 27 ± 5 years, 19 (79.2%) were males. Seventeen (70.8%) patients were pronounced dead at the scene, three (12.5%) died en route to the hospital while being resuscitated, and four (16.7%) died in the hospital. The mean post mortem whole blood PMMA and PMA concentrations were 2.72 ± 1.67 and 0.35 ± 0.24 mcg/mL, respectively. The mean urine PMMA and PMA concentrations in the fatal cases were 2.72 ± 1.67 and 0.35 ± 0.24 mcg/mL, respectively. Co-exposure to other drugs of abuse was detected in 17 (70.8%) fatal cases; MDMA (45.8%), MDA (37.5%), cocaine (25%), ephedrine/pseudoephedrine (16.7%), tetrahydrocannabinoids (16.7%), cathinone derivatives (16.7%), opiates (8.3%), and diazepam (4.2%). Ethanol was found in 4 (16.7%) of the fatalities. The cause of death was determined as acute poisoning from drugs of abuse; the drugs were listed according to the findings of the forensic toxicology laboratory.

All five non-fatal cases identified were males, age 32 ± 5 years. Four of them were from the scene of a fatal case. Their blood and urine samples were positive for PMMA and PMA using confirmatory chromatographic analysis; the small blood volume in the samples referred to precluded quantitation. Co-exposures were found in four (80%) cases – cocaine (4), cathinone derivatives (2), and tetrahydrocannabinoids (1). Parahydroxymethamphetamine (pholedrine) was detected in the blood or urine samples of all fatal cases and in three of the five survivors.

The clinical manifestations reported included combinations of coma, seizures, headache, tremor, dilated pupils, diaphoresis, acute respiratory failure, cardiac arrhythmias, acute myocardial infarction, hyperthermia, rhabdomyolysis, acute renal failure, and liver injury.

The clinical and analytical identification of these two new drugs of abuse and the associated fatality were reported by the national forensic laboratory and the Israel Poison Information Center to the Israeli Ministry of Health. Emergency departments across the country were notified by the Ministry of Health and the national poison center. In July 2007, PMMA was included in the Israeli CSA; PMA was included in 2004. Only three more fatal cases were detected during the following year.

Discussion

We report an outbreak of severe PMMA and PMA toxicity including 24 fatalities in the course of 1 year. The victims were predominantly young males, most were pre-hospital deaths. In 70.8% of the fatal cases there was co-exposure to other drugs of abuse (mainly MDMA, MDA, and cocaine, and, to a lesser extent, cathinone derivatives and cannabinoids) and ethanol.

The post mortem PMMA and PMA blood concentrations in our series are similar to those found by Lin et al. in Taiwan in 2000 (Table 2).[2] The finding of PMA in our cases is probably due to PMMA metabolism because it was not found in tablets seized by the police. The wide presence of pholedrine

Table 1. Demographic and post mortem analytical data of fatal cases associated with PMA and PMMA.

No.	Age (years)	Gender	Site of death	PMMA blood* (mcg/mL)	PMMA urine (mcg/mL)	PMA blood* (mcg/mL)	PMA urine (mcg/mL)	Co-exposures
1	28	Male	Pronounced dead by paramedics		67.59	0.35	8.38	Ephedrine/pseudoephedrine†
2	22	Male	Found dead in the street	1.96	238.65	0.23	22.29	
3	25	Male	Died en route to hospital	5.10	14.85	0.32	1.40	
4	25	Male	Found dead in friend's home	1.23		0.46		
5	27	Male	Pronounced dead by paramedics	2.23	89.73	0.31	12.41	
6	27	Male	Found dead at home	1.18	69.37	0.36	10.26	
7	27	Male	Found dead at home	0.16	28.26	0.00	3.55	MDMA, MDA, opiates
8	31	Male	Died in the hospital	0.08	46.18	0.04	61.56	MDMA, MDA, cocaine
9	18	Female	Found dead in friend's home	3.07		0.34		MDMA, MDA, cocaine, THC
10	26	Male	Died en route to hospital	1.00	18.32	0.53	5.91	MDMA, MDA
11	18	Male	Pronounced dead by paramedics	4.79	77.41	0.21	3.61	MDMA, MDA
12	26	Male	Found dead at home	2.58	4.33	0.45	4.92	MDMA, cocaine, THC, ethanol
13	24	Female	Found dead in hotel room	3.60	64.62	1.15	37.80	MDMA, MDA
14	24	Male	Found dead in the street	1.69	120.09	0.15	4.06	THC, ethanol
15	26	Male	Died en route to hospital	2.82	12.14	0.12	0.26	Ethanol
16	35	Female	Died in hospital		29.18		0.82	MDMA, MDA, ethanol
17	35	Male	Found dead at home	2.12		0.08		MDMA, MDA, cathinone derivatives, ephedrine/ pseudoephedrine†
18	26	Male	Pronounced dead in prison	1.01	100.00	0.27	6.63	
19	25	Female	Found dead at home	6.02		0.56		Cocaine, cathinone derivatives
20	35	Female	Died in hospital	‡	‡	‡	‡	MDMA
21	35	Male	Found dead at home	4.28		0.34		MDMA, MDA, cathinone derivatives, THC, ephedrine/pseudoephedrine†
22	35	Male	Died in hospital	4.44		0.53		Cocaine, THC, ethanol, diazepam
23		Male	Found dead in the street	3.88		0.55		Cocaine, cathinone derivatives, opiates, ephedrine/ pseudoephedrine†
24	27	Male	Found dead in prison	3.84		0.28		

PMA = paramethoxyamphetamine, PMMA = paramethoxymethamphetamine, MDMA = methylenedioxymethamphetamine, MDA = methylenedioxyamphetamine, THC = tetrahydrocannabinoids.
*PMA and PMMA blood concentrations were determined in whole blood drawn from the femoral vein post mortem.
†The results of ephedrine/pseudoephedrine also included metabolites.
‡Muscle sample, qualitatively positive for PMMA and PMA.

Table 2. Post mortem PMMA and PMA blood concentrations reported in the literature and in our study.

Study (reference)	No. of cases	PMMA	PMA
Spain 1993[18]	1	1.51 mcg/mL	
Denmark 2000[3]	3*	3.3 mg/kg 0.68 mg/kg	3.4 mg/kg 0.78 mg/kg 0.02 mg/kg
Germany 2002[4]	1	0.85 mcg/mL	0.61 mcg/mL
Taiwan 2006[2] (mean ± SD)	8	4.312 ± 4.806 mcg/mL	0.213 ± 0.144 mcg/mL
Israel 2007 (mean ± SD)	24	2.72 ± 1.67 mcg/mL	0.35 ± 0.24 mcg/mL

PMA = paramethoxyamphetamine, PMMA = paramethoxymethamphetamine.
*PMMA was not quantified in one case.

is most probably due to the metabolism of PMMA. As in other reports,[2–4] co-exposure to other drugs of abuse was found in most of our fatal cases (70.8%); two or more co-exposures in 58.3%. MDMA and MDA were not found in the non-fatal cases, but cocaine was found in 80% of them. The high frequency of stimulant co-exposures may have contributed to the severity of the poisoning because these compounds can interact to potentiate their cardiovascular, neurologic, and thermoregulatory toxicities.

The collaboration between the national forensic laboratory and the national poison information center resulted in the outlawing of PMMA and banning its use. A sharp decrease in PMMA forensic identification and associated deaths followed this measure.

PMA deaths were first reported in Ontario in 1973,[5] followed by similar reports from the USA,[6] Canada,[7] Australia,[8–10] and Europe.[11]

Animal data suggest that PMA enhances the release of serotonin, inhibits its reuptake and metabolism, with little effect on the dopaminergic system.[12] Another study suggested that PMA has monoamine oxidase (MAO)-A inhibitory properties.[13] PMA is about five times more potent than mescaline and has been used as an illicit drug both orally and intravenously in doses of 50–100 mg.[1] The pharmacokinetic profile of PMA is not well defined. In humans, it is metabolized mainly via CYP2D6 to the active metabolite p-hydroxyamphetamine (PHA)[14,15] with intersubject variability due to genetic CYP2D6 polymorphism.[16] Fatalities from PMA were first reported in Canada in the early 1970s.[5] Since then, it has been known as a "dirty" drug, notorious for its street name "death."[17]

PMMA is the N-methylated analogue of PMA. It is newer than PMA on the illicit drug scene and human data are limited. The first reported death from PMMA was in Spain in 1993,[18] followed by more cases thereafter.[2–4] The limited pharmacokinetic data suggest that PMMA is extensively metabolized by CYP2D6 (O-demethylation), mainly to 4-parahydroxymethamphetamine (4-HMA, pholedrine) and to a lesser extent to dihydroxymethamphetamine, 4-hydroxy 3-methoxymethamphetamine, and PMA.[15]

The clinical features of PMA poisoning are similar to those of MDMA and other ring-substituted amphetamines, including tachycardia, hypertension, hyperthermia, nystagmus, muscle spasm, bruxism, visual hallucinations, and, in severe cases, cardiac arrhythmias, respiratory failure, renal failure, seizures, and death.[17] Most fatal cases published in the literature had hyperthermia with a core temperature ranging between 39 and 42.8°C.[8,10,17] Although unproven, PMA is considered to be more toxic than MDMA, with a higher rate of electrocardiographic abnormalities, seizure activity, and hyperthermia.[19,20] In addition, its pharmacologic profile may facilitate overdosing. PMA is often sold as Ecstasy or Ecstasy substitute, but its onset of action is delayed and its initial effect is milder compared with MDMA. Therefore, users who are disappointed with the initial effect of PMA can ingest several tablets within a relatively short time, eventually resulting in severe toxicity.[17]

The pharmacodynamic profile of PMMA is even less understood. In animal behavioral studies, the effect of PMMA is more similar to MDMA than to other structurally related amphetamine derivatives.[21] The first report was on the death of a 17-year-old male in Spain in 1993. Methylenedioxyethamphetamine (MDEA), MDA, and ethanol were also found in this case.[18] Additional fatal cases were reported from Europe and Taiwan[2–4] (Table 2). The main clinical manifestations reported were agitation, hallucinations, coma, convulsions, hyperthermia, rhabdomyolysis, respiratory distress, and cardiac arrhythmias.[2,3] PMA is an active metabolite of PMMA and may partly account for the alleged PMMA toxicity.

Conclusion

We report an outbreak of severe PMA and PMMA poisoning resulting in 24 fatalities, and the post mortem blood and urine levels of these two hallucinogenic amphetamine derivatives. The inclusion of these designer drugs in the CSA resulted in a sharp decrease in their laboratory identification, presumably due to reduced marketing and consumption. The identification of new designer drugs presents an analytical challenge, as they are absent from mass spectrometry libraries, and adequate standards are lacking. Forensic laboratory and poison center co-operation is important in the detection of new drugs of abuse. It is an essential part of the national and global efforts to reduce morbidity and mortality from drugs of abuse.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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