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Research

Deaths from exposure to paramethoxymethamphetamine in Alberta and British Columbia, Canada: a case series

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Abstract

Background: Paramethoxymethamphetamine (PMMA) is a ring-substituted amphetamine similar in structure to 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"), but substantially more toxic. We describe the clinical features of fatal exposures in the provinces of Alberta and British Columbia, Canada.

Methods: We conducted a retrospective case series on deaths in Alberta and BC between June 2011 and April 2012 for which forensic toxicologic analysis was positive for PMMA and the drug was implicated as the primary toxic agent. Data collected included patient demographics, exposure history, clinical features, investigations, therapy provided and postmortem toxicologic findings.

Results: A total of 27 PMMA-associated deaths (20 in Alberta, 7 in BC) were reported in the 11-month period. The median age was 24 (range 14–52) years, and 22 (81%) were male. Ten patients were pronounced dead at the scene, and 17 died in hospital. The median time from exposure to death was 17 (range 5–264) hours. The median first-recorded vital signs (and ranges) were: heart rate 160 (86–201) beats/min, blood pressure 89/43 (69/30–162/83) mm Hg, respiratory rate 40 (26–48) breaths/min, oxygen saturation 81% (68%–100%) and temperature 39.4°C (34–43.8°C). Sixteen of the 17 people who died in hospital presented with clinical features consistent with serotonin syndrome. End-organ dysfunction included hepatic (30%) and acute kidney injury (85%), rhabdomyolysis (54%), coagulopathy (61%) and cardiac ischemia (15%). Other drugs identified on toxicologic analysis were MDMA (n = 27), cocaine or its metabolite benzoylecgonine (n = 14) and methamphetamine (n = 12).

Interpretation: Exposure to PMMA was characterized by multiorgan dysfunction and serotonin syndrome, followed by cardiovascular collapse. In addition to PMMA, multiple synthetic amphetamines were present on toxicologic analysis. When evaluating patients suspected of exposure to sympathomimetic drugs of abuse, clinicians must anticipate multiple clinical effects from the increased release of dopamine, serotonin, norepinephrine and other neurotransmitters.

Paramethoxymethamphetamine (PMMA) is a ring-substituted amphetamine, similar in structure to 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") but substantially more toxic (Figure 1).[1] With nearly 50 documented deaths in Europe, Asia, Australia and Israel, PMMA has earned the street names "Death" and "Dr. Death."[2] Although the drug has been found in a small fraction of ecstasy pills confiscated during drug seizures, it is responsible for a disproportionate number of deaths.[3] Clinical features include hyperthermia, serotonin syndrome and multiorgan dysfunction.[2,4–8]

Prior information on PMMA exposures has been limited to case reports or case series that focused on either the clinical or the postmortem features. Furthermore, descriptions of strategies adopted in response to outbreaks of PMMA-associated deaths are limited. Over an 11-month period from June 2011 to April 2012, there were 27 confirmed deaths from exposure to ecstasy containing PMMA in the provinces of Alberta and British Columbia, Canada. We describe the clinical features observed with fatal PMMA exposures in Alberta and BC. We also describe the public health interventions that were implemented in response to the deaths, to provide an overview of the different services and organizations involved.

Competing interests: None declared.

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Methods

Study design

We conducted a retrospective case series of deaths in Alberta and BC between June 2011 and April 2012 for which forensic toxicologic analysis was positive for PMMA and the drug was implicated as the primary toxic agent on the antemortem or postmortem toxicologic analysis. The Office of the Chief Medical Examiner in Alberta and BC Coroners Service identified the cases (i.e., PMMA-associated deaths). The research ethics boards of the University of Calgary and the University of British Columbia approved the study. The need for informed consent was waived by both institutions.

Data collection and definitions

We reviewed the medical records of identified cases at the Office of the Chief Medical Examiner in Alberta (J.N. and I.W.) and BC Coroners Service (D.T.). Using a predefined medical-record review tool, we collected data on patient demographics, exposure history, clinical features, laboratory investigations, therapy provided and hospital course. We also obtained postmortem toxicology results and autopsy findings from the records. All measured laboratory values, including blood and tissue concentrations of PMMA and other substances, that had been obtained from the hospital records were also collected from the coroners' records. Time from exposure to hospital presentation was obtained for the patients who died in hospital. Time from exposure to death was obtained for those whose death was pronounced at the scene only if time of exposure and time of death were known.

Serotonin syndrome was defined as per the criteria of Dunkley and colleagues[9] by the presence of neuromuscular abnormalities, mental status changes and hyperthermia. These criteria were applied only to patients who presented to hospital.

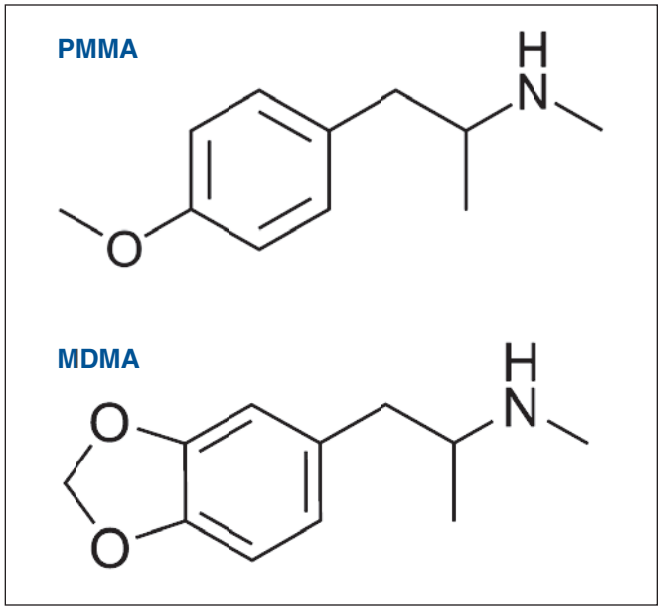

Figure 1: The chemical structures of paramethoxymethamphetamine (PMMA) and methylenedioxymethamphetamine (MDMA or "ecstasy").

Indicators of end-organ dysfunction were based on clinical findings, laboratory investigations and electrocardiogram (ECG) results. Hepatic injury was defined as a serum aspartate transaminase or alanine transaminase level greater than 1000 U/L.[10,11] Acute kidney injury was characterized by a rise in serum creatinine by at least 50% or at least 26.4 mmol/L from predicted baseline, or a urine output of less than 0.5 mL/kg per hour over 6 hours.[12] Rhabdomyolysis was defined as a creatine kinase level greater than 1000 U/L or more than 5 times the upper limit of normal.[13] Coagulopathy was defined as an international normalized ratio of 1.3 or higher. Cardiac ischemia was characterized by the presence of ST-segment depression or elevation or T-wave inversion on ECG, or a serum troponin T level level greater than 0.03 μg/L. Finally, sodium-channel blockade on ECG was characterized by a QRS duration greater than 120 ms and at least 1 of the following: a deep, slurred S wave in leads I and aVL; an R:S ratio greater than 0.7; or an R wave greater than 3 mm in lead aVR.[14-16]

Toxicologic analysis

Unless otherwise indicated, all Alberta cases were subject to testing for ethanol and related volatiles, plus comprehensive drug screening with a panel of enzyme-linked immunosorbent assays and broad-based gas chromatography with mass spectrometry. To quantify PMMA and related amphetamines, gas chromatography with mass spectrometry was used in selected ion-monitoring mode, after liquid–liquid extraction and derivatization with pentafluoroacetic anhydride. Matching deuterated internal standards were used for MDMA, methylenedioxyamphetamine, methamphetamine and amphetamine; MDMA-d_5 was used as the internal standard for PMMA and paramethoxyamphetamine. The lower limit of quantitation for PMMA and all other amphetamines was administratively set at 0.05 mg/L.

All cases in BC were tested for ethanol and related volatiles, plus comprehensive drug screening using liquid and broad-based gas chromatography with mass spectrometry. If urine was available, the TOX/See Drug Screen Test (Bio-Rad) was used. To quantify PMMA and related amphetamines, liquid chromatography with mass spectrometry (4000 QTRAP, AB Sciex) was used in selected ion-monitoring mode, after precipitation with acetonitrile without derivatization. Matching deuterated internal standards were used for MDMA, methylenedioxyamphetamine, methamphetamine and amphetamine; amphetamine-d_5 was used as the internal standard for PMMA and paramethoxyamphetamine. The lower limit of quantitation for PMMA and all other amphetamines was administratively set at 0.01 mg/L.

Statistical analysis

Microsoft Excel version 14.3.7 was used for data entry and analysis. We report median values with ranges for clinical features, toxicologic findings and postmortem autopsy findings.

Results

A total of 27 PMMA-associated deaths (20 in Alberta and 7 in BC) occurred in the 11-month period. Patient characteristics are summarized in Table 1. The median age was 24 (range

Table 1: Summary of 27 deaths associated with the use of paramethoxymethamphetamine (PMMA) in Alberta and British Columbia, June 2011 to April 2012

Case	Location and circumstances around presentation and death	Drug(s) believed to have been consumed	Postmortem findings
1	Took drugs at home; became unwell, friend called 911; died in ER	Ecstasy	Pulmonary edema, CAD
2	Took ecstasy alone; found 9 hours later; died in ER after unsuccessful resuscitation	Ecstasy	Rapid rigor mortis
3	Took pills alone, felt unwell and self-presented to ER; died in ICU	Ecstasy	Cerebral edema, pulmonary edema
4	Took ecstasy with friends; became unresponsive; transported to ER in private vehicle; died in ICU	Ecstasy	Cerebral edema, ascites, pleural effusion
5	At house party after taking drugs; became unresponsive; transported to hospital via EMS; died in ICU	Ecstasy	Rhabdomyolysis
6	Found unresponsive at house party; transported to hospital via EMS; had cardiac arrest, died in ICU	Ecstasy, alcohol	No autopsy
7	At house party; found unresponsive after last seen 1.5 hours earlier; transported to hospital via EMS, had cardiac arrest; died in ICU	Ecstasy	No autopsy
8	Found dead in bed at home	Unknown	Trivial soft-tissue abrasions
9	At house party with friends; became unwell; cardiac arrest after intubation with EMS; died in ICU	8 tabs of ecstasy	Lung congestion, patchy pneumonia
10	Watching live performance; became unwell; cardiac arrest with EMS; died in ER after unsuccessful resuscitation	1–2 g of MDMA, cocaine	Cardiomegaly, spleen congestion
11	At nightclub; became unwell; transported to ER in private vehicle; died in ICU	6 tablets of MDMA, hallucinogenic mushrooms, LSD	No autopsy
12	Found dead at home	Unknown	Pulmonary congestion, cerebral edema, mottled myocardium, cardiomegaly
13	Friend noticed patient acting abnormally; transported to hospital in private vehicle after seizure; died in ER	2 snorts of MDMA/ ecstasy powder	Congestion of heart, lungs and liver
14	Took drugs at house party; found unconscious outside at nearby property; died in ER after unsuccessful resuscitation	Unknown amount of white powder believed to be ecstasy	Congestion of heart, lungs, liver and spleen, cerebral edema
15	At a bar with friends; that night at home had a witnessed seizure, followed by cardiac arrest; pronounced dead upon EMS arrival	Unknown	Pulmonary edema, congestion of heart, liver and spleen, cerebral edema
16	Took 2 doses of ecstasy at bar; began acting strange upon return home with friends; had seizure en route to hospital with EMS, and cardiac arrest in ER; died in ER after unsuccessful resuscitation	2 pills of ecstasy	Pulmonary edema, kidney and spleen congestion, interstitial hemorrhage in heart
17	At home with friends drinking and taking drugs; found dead the next morning	Cocaine, MDMA, alcohol	Fatty liver, unremarkable post mortem
18	At a house party; felt unwell, called 911; cardiac arrest soon after EMS arrival; died in ER after unsuccessful resuscitation	Unknown white powder snorted	Rib and sternal fractures, pulmonary edema, advanced cirrhosis, enlarged spleen
19	Took MDMA powder the night before; felt unwell; found unresponsive the next afternoon; pronounced dead with EMS	1.5 g of MDMA rolled in paper and ingested	Cerebral and pulmonary edema
20	Took drugs throughout the night at home; had cardiac arrest; died in ER after unsuccessful resuscitation	MDMA, cocaine	Pulmonary congestion, cardiomegaly, nephrosclerosis
21	At party the night before with friends; found dead at home the next day	Ecstasy, cocaine	Edema and congestion of lungs, liver, spleen and kidneys
22	Last seen 3 days earlier; police/EMS attended; pronounced dead at the scene	Unknown	Pulmonary congestion
23	Partying with friends the night before; no history of drug use; found dead the next day	Unknown	Pulmonary edema
24	Last seen 3 days prior. Police/EMS attended, dead on scene.	Cocaine, alcohol	Congestion of lung, liver, spleen and kidneys
25	At house party; took multiple doses of MDMA through the night by snorting and ingestion; became confused and unresponsive; friends called 911; died in ER after unsuccessful resuscitation	0.5 g of MDMA	Pulmonary congestion
26	At party with friends; EMS called; cardiac arrest after intubation; resuscitated in ER, died in ICU	7 tabs of MDMA	No autopsy
27	At concert; took drugs and alcohol; pronounced dead at home with EMS	MDMA, cocaine, alcohol	No autopsy

Note: CAD = coronary artery disease, EMS = emergency medical services, ER = emergency department, ICU = intensive care unit, LSD = lysergic acid diethylamide, MDMA = methylenedioxymethamphetamine.

14–52) years, and 22 (81%) were male. Twelve (44%) had a reported history of illicit drug use. Ten (37%) were pronounced dead at the scene, 10 (37%) died in the emergency department, and 7 (26%) died after admission to the intensive care unit (ICU). The median time from exposure to hospital presentation was 6 (range 1.5–16.5) hours, and from exposure to death 17 (range 5–264) hours. In most cases, there was a delay in seeking medical care from the time a problem was identified by friends or family. The route of administration was unknown in most cases; among those for whom the route was known, most believed they were using ecstasy powder or pills.

The median first-recorded vital signs (and ranges) were: heart rate 160 (86–201) beats/min, blood pressure 89/43 (69/30–162/83) mm Hg, respiratory rate 40 (26–48) breaths/min, oxygen saturation 81% (68%–100%) and temperature 39.4°C (34–43.8°C). Sixteen (94%) of the 17 patients who died in hospital presented with clinical features consistent with serotonin syndrome. Three (11%) of the 27 patients experienced seizures. Among the 17 who died in hospital, there were multiple indicators of end-organ dysfunction (Figure 2). Evidence of cardiac sodium-channel blockade was present in 1 patient whose toxicologic analysis was negative for known sodium-channel blocking agents. The median recorded laboratory values are highlighted in Table 2. Interventions for the 17 patients transported to hospital are shown in Table 3.

Results of the toxicologic analyses are summarized in Table 4. Substances other than PMMA were detected in all patients, the most common being MDMA (n = 27), cocaine or its metabolite benzoylecgonine (n = 14) and methamphetamine (n = 12). The median antemortem and postmortem whole blood PMMA concentrations are reported in Table 5. Postmortem findings are summarized in Table 1.

Interpretation

We describe a large case series of 27 PMMA-associated deaths in 2 provinces over an 11-month period. Exposure to PMMA was characterized by multiorgan dysfunction, shock and serotonin syndrome, followed by cardiovascular collapse and death. Most of the patients died in hospital following a delay in presenting to the emergency department. Severe hyperthermia, hyperkalemia and hypoglycemia were present in most cases. Notable autopsy findings included pulmonary and cerebral edema. In addition to PMMA, multiple synthetic amphetamines were found in the toxicologic analysis in all patients.

The effect of PMMA is mediated primarily through the release of serotonin, and to a lesser extent dopamine, from presynaptic neurons.[18] PMMA is more similar in structure to MDMA than to amphetamine, yet influx into the brain is delayed compared with MDMA, which results in later onset of psychological effects.[19,20] PMMA has several active metabolites, including paramethoxyamphetamine and pholedrine.[21] It has a narrow margin of safety, with a two- to fourfold difference between the stimulant-producing and lethal doses observed in rats.[1] Hyperthermia from use of the drug is secondary to both serotonin syndrome and monoamine oxidase inhibition, and toxicity is increased in crowded conditions because of an accelerated rate of temperature change and longer duration of hyperthermia.[20] The delayed onset of desired effects may lead to frequent and early redosing, which increases the risk of life-threatening toxicity.

The clinical presentation we have described is consistent with previous published reports. The first reported PMMA-associated death occurred in Spain in 1993, followed by 3 deaths in Denmark in 2003, 1 in Germany in 2003, 8 in Taiwan in 2006, 24 in Israel from 2007 to 2008, and most recently 22 nonfatal and 12 fatal cases in Norway from 2010 to 2011.[2–7,18] There

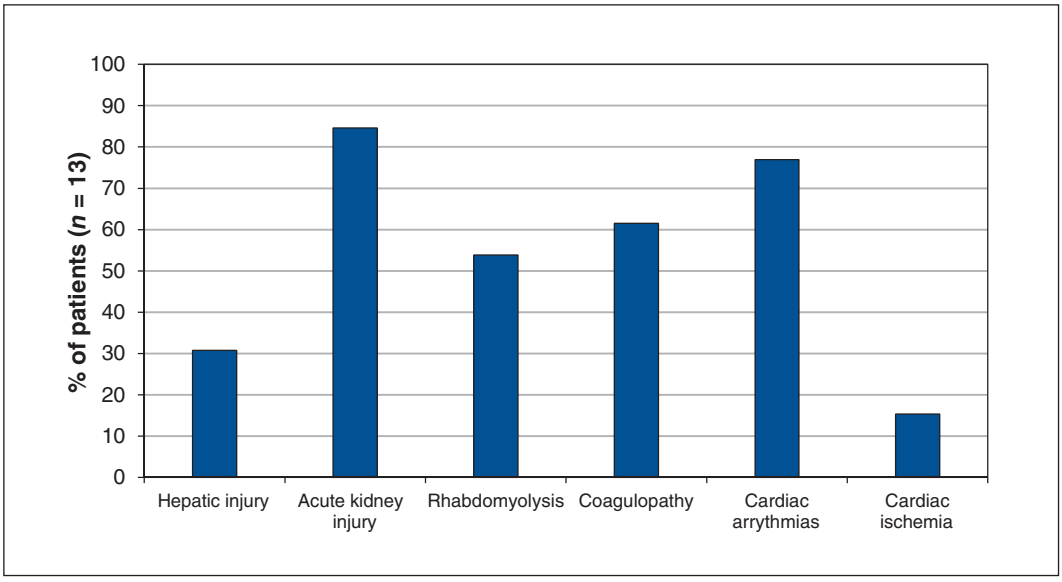

Figure 2: Antemortem end-organ dysfunction based on clinical findings and investigations of 13 of the 17 patients who died in hospital. Data were missing for 4 patients who were pronounced dead shortly after arrival in the emergency department [no antemortem investigations performed].

have, however, been PMMA-associated deaths since 2012 that have not appeared in the medical literature. Compared with our patients, a higher proportion of individuals in the previous reports died before reaching hospital, and there were fewer instances of exposure to additional synthetic amphetamines on toxicologic analysis. The PMMA concentrations in our series are similar to those previously reported.

The public health response to the PMMA-associated deaths in our series involved extensive collaboration among law enforcement, health services, emergency medical services, poison control centres, public health agencies, and the Office of the Chief Medical Examiner in Alberta and BC Coroners Service. In Alberta, a working group was created in early 2012, cochaired by senior public health, addictions and mental health leaders, and the medical director of the Poison and Drug Information Service. In BC, the BC Drug Overdose and Alert Partnership Committee, chaired by the BC Centre for Disease Control, facilitated the coordinated response between the various parties. The Alberta Poison and Drug Information Service, BC ambulance and the BC Drug and Poison Information Centre developed clinical management guidelines for MDMA and other sympathomimetic drugs of abuse, and the regional health authorities developed alerts for health care professionals (Appendix 1, available at www.cmajopen.ca/content/3/1/E83/suppl/DC1).

Through the use of media interviews, print materials, a "one-stop" PMMA website and social media (Facebook and Twitter), information was disseminated to the public, educators, universities and community agencies (Appendix 2, available at www.cmajopen.ca/content/3/1/E83/suppl/DC1).[22] Public health and law enforcement actively reached out to school and university populations, and targeted DanceSafe and online drug-user forums. The Office of the Provincial Health Officer along with the BC Coroners Service and law enforcement coordinated public announcements and media inquiries.

The reach of the collaborative messaging included coverage in regional and national newspapers and websites, and television coverage by national networks.[23–27] The American Association of Poison Control Centers released an alert on the deaths to all 55 poison centres in the United States. Multiple drug-user forums and blogs reported on the harmful effects of PMMA based on the advisories issued in Alberta and BC.[28–34] The messaging was included on a medical toxicology review blog "The Poison Review" as part of a series on PMMA.[35]

The coordinated public health response, and sharing of information among public health agencies, poison control centres, regional health services, the Office of the Chief Medical Examiner, the BC Coroners Service, and law enforcement in Alberta and BC played a role in the eventual decline in PMMA-associated deaths in both provinces. Although it cannot be shown that the public health response directly caused the decline in deaths, it did enable open communication among the key parties, which resulted in information dissemination and media attention. It is also difficult to identify which components of the public health response were most effective, because they were aimed at different populations. Other potential reasons for a decline in PMMA-associated deaths include the cessation of PMMA production by those manufacturing ecstasy, reduced dissemination of PMMA by drug dealers and the reduction of ecstasy consumption use by drug-using populations.[36] Finally, there may have been unintended consequences of the public health messaging, including a shift from the use of ecstasy to more dangerous drugs of abuse by at-risk teens, nightclub users and street-involved adults.[37]

The finding of multiple sympathomimetic drugs in the antemortem and postmortem specimens emphasizes the variability in the content of ecstasy powder and pills produced in clandestine laboratories.[38,39] In addition, the potential for exposure to numerous sympathomimetic drugs of abuse has implications when evaluating patients. Clinicians must anticipate multiple clinical effects from the increased release of dopamine, serotonin, norepinephrine and other neurotransmitters. Because the precise drug content of ecstasy is often unknown to the user, there is an increasing availability of drug-testing kits at mass gatherings such as raves and music festivals.[40] Future research is needed to examine whether these kits help the purchaser understand and appreciate the content before exposure.

Table 2: Results of antemortem laboratory investigations for patients transported to hospital (*n* = 13/17)*

Investigation	Level, median (range)	Normal range†
Peak potassium, mmol/L	7.0 (4.4–12.5)	3.5–5.1
Peak creatinine, mmol/L	214 (146–1127)	50–110
Peak AST, U/L	2944 (116–5124)	7–40
Peak creatinine kinase, U/L	8200 (1952–237 960)	38–215
Lowest recorded glucose, mmol/L	1.9 (0.4–17.1)	3.9–6.1

Note: AST = aspartate transaminase.
*Data missing for 4 patients; they were pronounced dead shortly after arrival to the emergency department (no antemortem investigations).
†Normal values were obtained from the Royal College of Physicians and Surgeons of Canada.[17]

Table 3: Therapies provided by emergency medical services or in hospital for patients transported to hospital (*n* = 9/17)*

Therapy	No. (%) of patients
Intubation	9 (100)
Paralysis	6 (67)
Sedation	5 (56)
Cooling	
Ice packs	4 (44)
Cooled intravenous fluid	2 (22)
Cyproheptadine	1 (11)
Cooling blanket	1 (11)
Cooling catheter	1 (11)

*Data missing for 8 patients.

Limitations

Our study has several limitations. First, we collected data retrospectively from medical records at the Office of the Chief Medical Examiner and BC Coroners Service rather than from hospital records. This resulted in missing data, especially therapies provided. Because of the geographic distribution of

Table 4: Results of toxicologic analysis

Case	Specimen type	Toxin, mg/L								Other findings*
		PMMA	PMA	MDMA	MDA	MAMP	AMP	Cocaine	BE	
1	Postmortem blood†	1.6	0.17	2.3	0.12	0.84	0.024	ND	ND	Lidocaine
2	Postmortem blood†	NSQ	NSQ	3.9	0.12	ND	ND	0.38	3.9	PMMA vitreous 0.69 mg/L; MDMA vitreous 1.4 mg/L; cannabinoids
3	Antemortem blood†	1.2	0.093	0.99	0.036	ND	ND	ND	0.32	
4	Antemortem blood†	1.6	0.098	0.52	0.021	ND	ND	ND	ND	Lorazepam
5	Postmortem blood†	1.8	ND	0.6	ND	ND	ND	ND	ND	Morphine, lidocaine, cannabinoids
6	Antemortem blood†	0.11	0.023	0.14	0.015	ND	ND	ND	ND	Midazolam, temazepam, rocuronium metabolite, acetaminophen
7	Antemortem blood†	URP	URP	0.32	ND	ND	ND	ND	ND	
8	Postmortem IVC blood	3.33	0.42	3.09	0.17	2.28	0.07	ND	ND	Dextromethorphan 0.66 mg/L, acetaminophen 18.2 mg/L, ketamine, oxycodone
9	Antemortem serum†	0.94	0.07	0.09	Trace	0.3	Trace	ND	ND	
	Postmortem IVC blood	0.14	Trace	Trace	Trace	0.11	Trace	ND	ND	
10	Antemortem blood†	2.28	0.1	0.31	Trace	0.75	Trace	ND	0.19	
	Postmortem femoral blood	4.41	0.25	0.6	Trace	1.47	Trace	Trace	0.26	
11	Antemortem blood†	0.44	0.08	Trace	Trace	0.18	Trace	TNP	TNP	Drug screen not performed (limited specimen)
12	Postmortem IVC blood	3.74	0.11	1.64	Trace	ND	ND	ND	ND	Ethanol 30 mg/100 mL
13	Antemortem blood†	1.25	0.07	0.11	Trace	0.35	Trace	ND	0.11	
	Postmortem IVC blood	2.67	0.18	0.26	Trace	0.8	Trace	ND	0.17	
14	Postmortem IVC blood	2.7	0.12	0.29	Trace	0.86	Trace	ND	ND	
	Postmortem central blood	4.35	0.18	0.43	Trace	1.28	0.05	ND	ND	
15	Postmortem IVC blood	2.97	0.08	0.32	Trace	ND	ND	0.04	0.3	Acetaminophen 10.6 mg/L, codeine 0.07 mg/L, atropine
16	Postmortem IVC blood	1.67	0.15	0.27	Trace	0.63	Trace	Trace	0.2	Oxycodone (trace), delta-9-tetrahydrocannabinol 2.3 ng/mL, carboxy- tetrahydrocannabinol 11.8 ng/mL
17	Postmortem IVC blood	4.88	0.22	1.12	0.04	1.78	0.06	0.08	0.84	Levamisole, phenacetin
18	Postmortem femoral blood	3.56	0.33	1.7	0.12	Trace	ND	ND	0.67	Benzylpiperazine
19	Postmortem central blood	0.65	0.06	2.58	0.06	ND	ND	ND	ND	Ethanol 10 mg/100 ml.
20	Postmortem femoral blood	15.7	0.75	0.65	Trace	ND	ND	ND	ND	Diphenhydramine
21	Postmortem femoral blood	6.19	0.51	0.26	Trace	ND	ND	ND	ND	Dextromethorphan
22	Postmortem iliac blood	5.36	1.08	0.6	0.05	1.45	0.1	Trace	0.11	Oxycodone 2.01 mg/L, ibuprofen
23	Postmortem femoral blood	6.34	0.23	0.34	Trace	ND	ND	Trace	1.16	Benzylpiperazine 1.65 mg/L, TFMPP 0.47 mg/L, ketamine, levamisole
24	Postmortem femoral blood	3.58	0.23	0.16	Trace	ND	ND	ND	ND	Benzylpiperazine 1.00 mg/L, TFMPP 0.15 mg/L
25	Antemortem blood†	1.6	0.1	0.14	Trace	0.47	Trace	Trace	1.09	Ketamine 0.71 mg/L, midazolam
26	Antemortem blood†	3.27	0.09	0.16	Trace	ND	ND	Trace	0.53	
	Postmortem iliac blood	3.83	0.14	0.19	Trace	ND	ND	Trace	0.55	
27	Postmortem iliac blood	2.17	0.08	1	Trace	ND	ND	0.05	0.46	Ethanol 10 mg/100 mL, naproxen

Note: AMP = amphetamine, BE = benzoylecgonine (metabolite of cocaine), IVC = inferior vena cava, MDA = methylenedioxyamphetamine, MAMP = methamphetamine, ND = none detected (below level of detection), NSQ = not sufficient quantities, PMA = paramethoxyamphetamine, TFMPP = trifluoromethylphenylpiperazine , trace = detected but below level of quantitation, TNP = test not performed, URP = urine positive for drug but insufficient antemortem blood available to permit quantitation.
*Unless otherwise specified, drugs in this column were not quantitated.
†Not otherwise specified.

deaths, it was not practical to access the medical records from each treating hospital. Second, although 16 of the patients were found to have serotonin syndrome, we are unable to comment on the presence of the syndrome in the 10 who were pronounced dead at the scene. Third, the presence of multiple synthetic amphetamines in all cases made it difficult to definitively identify PMMA as the drug responsible for death. However, the important role of PMMA in these deaths is emphasized by the known toxicity of the drug, and by the large number of deaths occurring in a short time frame. During the same 11-month period, there was only 1 methamphetamine-associated fatality and no deaths associated with either MDMA or amphetamine toxicity in Alberta (Dr. Graham Jones, Office of the Chief Medical Examiner, Edmonton, Alta.: personal communication, 2015). Although deaths from exposure to synthetic amphetamines other than PMMA periodically occur in Alberta and BC, the widespread availability and use of those drugs does not suggest that they are unique in terms of their lethality. What makes PMMA different is the cluster nature of related deaths, consistent with the extremely high toxicity of PMMA relative to other more common amphetamines. Furthermore, the concentration of PMMA in our case series was higher than that of other amphetamines in most cases and is similar to the concentration in previous studies describing PMMA-associated deaths.

Table 5: Antemortem and postmortem concentrations of PMMA in whole blood (*n* = 25/27)*

Blood sample	Concentration, mg/L, median (range)
Antemortem blood	1.43 (0.11–3.27)
Postmortem IVC and central blood	2.84 (0.14–4.88)
Postmortem femoral and iliac blood	4.41 (2.17–15.7)

Note: IVC = inferior vena cava, PMMA = paramethoxymethamphetamine.
*Insufficient blood sample for quantitation in case 2; antemortem urine test positive in case 7, but no postmortem blood test performed.

Conclusion

We describe 27 PMMA-associated deaths over an 11-month period in 2 provinces. Exposure to PMMA was characterized by serotonin syndrome, shock and multisystem organ failure. In addition to PMMA, multiple synthetic amphetamines were present on toxicologic analysis, which emphasizes the variability in the content of ecstasy powder and pills produced in clandestine laboratories. The potential for exposure to numerous sympathomimetic drugs of abuse has implications during the evaluation of patients. Clinicians must anticipate multiple clinical effects from the increased release of dopamine, serotonin, norepinephrine and other neurotransmitters.

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