J. Med. Toxicol. (2015) 11:185–194
DOI 10.1007/s13181-014-0446-8

TOXICOLOGY INVESTIGATION

# Acute Methylenedioxypyrovalerone Toxicity

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Published online: 3 December 2014


**Abstract** The objective of this study was to characterize the acute clinical effects, laboratory findings, complications, and disposition of patients presenting to the hospital after abusing synthetic cathinone. We conducted a retrospective multicenter case series of patients with synthetic cathinone abuse by searching for the terms bath salts, MDPV, methylenedioxypyrovalerone, mephedrone, methcathinone, methylone, methedrone, and cathinone within the "agent" field of a national clinical toxicology database (ToxIC). The medical records of these patients were obtained and abstracted by investigators at each study site. Patients with confirmatory testing that identified a synthetic cathinone in either blood or urine were included in the series. Patients who had either an undetectable synthetic cathinone test or no confirmatory testing were excluded. A data abstraction sheet was used to obtain information on each patient. We entered data into an Excel spreadsheet and calculated descriptive statistics. We identified 23 patients with confirmed synthetic cathinone exposure—all were positive for methylenedioxyprovalerone (MDPV). Eighty-three percent were male and 74 % had recreational intent. The most common reported clinical effects were tachycardia (74 %), agitation (65 %), and sympathomimetic syndrome (65 %). Acidosis was the most common laboratory abnormality (43 %). Seventy-eight percent of patients were treated with

**Prior Presentations** Preliminary data were presented at the 2012 Annual Meeting of the NACCT, October 6, 2012, Las Vegas, NV, USA.

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benzodiazepines and 30 % were intubated. Ninety-six percent of patients were hospitalized and 87 % were admitted to the ICU. The majority (61 %) of patients was discharged home but 30 % required inpatient psychiatric care. There was one death in our series. The majority of patients presenting to the hospital after abusing MDPV have severe sympathomimetic findings requiring hospitalization. A number of these patients require inpatient psychiatric care after their acute presentation.

**Keywords** Toxicology · Poisons · Drug effects · Central nervous system stimulants · Street drugs · Designer drugs

## Introduction

Structurally similar to amphetamine, cathinone, derived from the plant *Catha edulis* is widely abused by people in the Horn of Africa and the Arabian Peninsula [1]. Synthetic cathinone abuse has been reported in multiple countries including Germany [2], the UK [3, 4], and Finland [5]. In the early 1990s, methcathinone was the first reported synthetic cathinone with widespread recreational abuse in the USA [6]. While there continues to be some sporadic abuse of methcathinone in the USA, the abuse of other synthetic cathinones, often sold as "bath salts" has become epidemic. Synthetic cathinones were initially easy to purchase because distributors marketed them as "bath salts" and sold them with labels that stated "not for human consumption." In 2011, legislation in the US was put in place in an attempt to reduce synthetic cathinone abuse, and these substances are currently classified as a schedule 1 drug. While there were few poison center calls prior to July 2010, by July 2011 poison centers were receiving greater than 20 calls per day regarding "bath salts" [7]. In the same year (2011), there were over 22,904 visits to the emergency department related to "bath salts" [8].

One of the synthetic cathinones that has been part of this recent surge in abuse in the US is methylenedioxypyrovalerone (MDPV) [9]. MDPV's mechanism of action has been deduced from animal and in vitro studies as well as the mechanism of action of other cathinones and amphetamines [10, 11]. MDPV is predominately a dopamine and norepinephrine reuptake inhibitor and to a lesser extent a serotonin reuptake inhibitor [12, 13]. MDPV use can result in severe clinical effects including psychosis, agitation, rhabdomyolysis, myocardial infarction, and death [14]. There are several case reports that describe hospitalized patients with detectable blood or urine MDPV concentrations [15–20] and several case reports and series that describe postmortem MDPV concentrations [14, 21–23]. There is a case series of two recreational MDPV users not in medical care with detectable MDPV concentrations [21]. A published study that utilizes the Poison Center data reports 11 patients with detectable MDPV serum concentrations, two patients with serum and urine MDPV concentrations, one patient with detectable urine MDPV concentration, and an individual with a postmortem urine and serum MDPV concentration [9]. An additional study that utilizes the Poison Center data reports two individuals with postmortem MDPV concentration [24]. We utilized a prospective multicenter clinical toxicology registry (the ToxIC Registry) [25] to determine the most common effects and outcomes of patients with confirmed MDPV exposure.

## Methods

This is a multicenter retrospective case series of patients presenting to medical care after a confirmed synthetic cathinone exposure. We identified cases using the ToxIC registry; [25] a registry of patients seen by medical toxicologists in the USA, Canada, and Israel. To enter patients into the ToxIC registry, clinicians use an online form to upload information related to six categories: demographics, encounter circumstances, agent, toxidrome, signs and symptoms, and treatment. Clinicians determine the substance that has caused the patient's toxicity and enter that information into the "agent" section. Synthetic cathinone cases were identified in the ToxIC registry by searching the "agent" section with the terms: bath salts, cathinone, MDPV, methylenedioxypyrovalerone, mephedrone, methcathinone, methylone, and methedrone. The search terms were chosen based on a review of the published literature regarding synthetic cathinones that were being sold as "bath salts" in the USA. The search terms "bath salts" and cathinone were included to obtain any subjects that did not have confirmatory testing available at the time that they were entered in the ToxIC registry. Between January 5, 2010–January 5, 2012, we identified 126 cases from 14 sites. Each site was contacted, and ten sites agreed to participate in the study. All ten participating sites were located in the USA. Each site obtained IRB approval. After IRB approval, every site was sent a list of ToxIC code numbers for patients that matched a "bath salt" search term. Primary investigators at each site abstracted data from the patient's medical records using a data collection form. The form consisted of nine sections: demographics, substance exposure, past medical history, clinical presentation, laboratory findings, medical complications, treatments, and disposition. Clinical presentation included the initial recorded vital signs and first recorded physical exam findings. Toxidromes were determined by recorded clinical exam findings and the interpretation of these findings by the abstracting medical toxicologist. Basic metabolic findings were the first obtained results within 4 h of presentation. Medical complications that occurred within 24 h of presentation were recorded. Treatments recorded were those given within 4 h of presentation. Vital signs and laboratory values were stratified as ranges. We defined confirmed cases as a patient with any of the following synthetic cathinones: MDPV, mephedrone, methcathinone, methylone,

or methedrone detected in the blood or urine. We defined a positive test as either the quantitative or qualitative detection of MDPV, mephedrone, methcathinone, methylone, or methedrone using either gas chromatography/mass spectrometry (GC/MS) or high-performance liquid chromatography/tandem mass spectrometry (HPLC/MS-MS). Patients were excluded if they did not undergo testing or if their testing did not detect a synthetic cathinone. Individual cases were entered into an Excel worksheet, and descriptive statistics were calculated.

## Results

From the ten participating sites, 54 patients were identified from the ToxIC database and 54 data forms were completed. Twenty-seven patients had no confirmatory testing, and four patients had negative synthetic cathinone tests. This resulted in 23 data forms from patients with confirmed synthetic cathinone exposure. All 23 confirmatory tests were positive for MDPV. Results summarizing the demographics, clinical effects, laboratory findings, complications, treatment, and disposition are in Table 1. Table 2 summarizes clinical findings in those patients with quantitative MDPV concentrations. Details regarding MDPV tests and additional analytical drug testing are in Table 3.

The majority of the patients in this series were younger males using MDPV recreationally. A substantial percentage (39.1 %) had a previous history that included a psychiatric diagnosis. The nine patients with prior psychiatric history had the following diagnoses: depression and alcoholism, bipolar and depression and anxiety and posttraumatic stress disorder, depression and bipolar and Asperger's syndrome, cocaine abuse, bipolar and borderline personality disorder, and polysubstance abuse, and three patients with depression. Of the known routes of exposure, the most common route was nasal insufflation, although there were patients who ingested, injected, or inhaled MDPV as well. In 19 of the patient charts, MDPV was initially referred to as a "bath salt," in one chart "8-ball," in one chart "white lightning," and in one chart "MDPV." Thirteen of our patients were transferred from outside medical facilities. Ten patients had no co-exposure by history, one of these patients did not have additional analytical drug testing and the other nine did have additional analytical drug testing (Table 3).

Within the first 4 h of presentation, 13 of the patients received lorazepam, four patients received lorazepam and midazolam, one patient received midazolam, and one patient received diazepam. The smallest total dose that a patient received was 1 mg of lorazepam. The patient who received diazepam was given a total dose of 15 mg. The largest total dose of benzodiazepines that a patient received was 8 mg of lorazepam and 5 mg of midazolam. All five patients who were treated with antipsychotics were also treated with benzodiazepines. Haloperidol, with doses from 2.5–5 mg, was the antipsychotic used in every patient except one, who received 20 mg of ziprasidone. Five patients were given a paralytic. Vecuronium or rocuronium were both used in two patients, and succinylcholine was given in one patient. All of the patients but one who received a paralytic were also given a benzodiazepine. One patient who was treated with a paralytic and was not treated with benzodiazepines received propofol and etodmidate. None of the patients treated with a paralytic were treated with an antipsychotic.

One patient died in our series—a 40-year-old male who was injecting and insufflating MDPV for recreational use. He had no past medical history and no co-exposures. He presented with hyperthermia, tachycardia, hypertension, and sympathomimetic syndrome. Laboratory findings were acidosis, hyperkalemia, and elevated creatinine (Table 2). In the first 4 h, the patient received lorazepam, epinephrine, atropine, lidocaine, flumazenil, naloxone, dopamine, and phenylephrine. The patient suffered a cardiac arrest, was intubated, and died after 2 days in an ICU [18].

## Discussion

The majority of patients with confirmed MDPV exposure presented with sympathomimetic and neuropsychiatric manifestations and a substantial percentage received inpatient medical care.

Similar to what others have reported, we found that the majority of our patients were young males using MDPV recreationally [9]. This is the demographic that has also been reported in early reports of other synthetic cathinones, such as mephedrone [26]. This finding is supported by other studies that have shown that young males are the most likely demographic to abuse illicit drugs [27]. The documented clinical symptoms from MDPV use were consistent with sympathomimetic effects with tachycardia being the most common finding. Blood pressure effects, however, were less evident; only 30 % had SBP >140 mmHg. These findings are consistent with other reports [28]. Tachycardia, hypertension, and agitation have also been reported with mephedrone abuse [26]. One of the most concerning manifestations of stimulant overdose is hyperthermia. In a previous study, patients presenting after substituted amphetamine use with a temperature of >104.9 °F had mortality rates of ~50 % [29]. While ours was a small case series, we did have one reported death and that occurred in a patient with a reported temperature of >104 °F.

Interestingly, three patients in our study presented with sedation. Sedation after "bath salt" use has previously been reported [24]. There are a few possibilities for this finding. One is that patients are presenting after catecholamines have

**Table 1** Characteristics of MDPV-confirmed patients ($n$=23)

| | | |
|---|---|---|
| Demographics | | |
| | Mean | Range |
| Age (years) | 31 | 16–49 |
| | *n* | Percentage |
| Male | 19 | 82.6 |
| Prior psychiatric history | 9 | 39 |
| Route of exposure | | |
| Ingestion | 3 | 13 |
| Insufflation | 8 | 34.8 |
| Injection | 2 | 8.7 |
| Inhalation | 2 | 8.7 |
| Other (unknown) | 8 | 34.8 |
| Intent | | |
| Recreational | 17 | 73.9 |
| Suicide | 5 | 21.7 |
| Unintentional | 0 | 0 |
| Unknown | 0 | 0 |
| Other | 1 | 4.3 |
| Clinical presentation | | |
| Initial vitals | *n* | Percentage |
| Temp (°F) | | |
| 96.1–100 | 16 | 69.6 |
| 100.1–102 | 5 | 21.7 |
| 102.1–104 | 1 | 4.3 |
| >104 | 1 | 4.3 |
| Unknown | 1 | 4.3 |
| HR (bpm) | | |
| <100 | 6 | 26.1 |
| 101–120 | 4 | 17.4 |
| 121–140 | 4 | 17.4 |
| >140 | 9 | 39.1 |
| SBP (mmHg) | | |
| 91–140 | 16 | 69.6 |
| 141–160 | 2 | 8.7 |
| 161–180 | 5 | 21.7 |
| DBP (mmHg) | | |
| 50–90 | 16 | 69.6 |
| 91–100 | 3 | 13 |
| >100 | 4 | 17.4 |
| Physical exam | | |
| Mydriasis | 5 | 21.7 |
| Clonus | 1 | 4.3 |
| Rigidity | 0 | 0 |
| Nystagmus | 0 | 0 |
| Mental status | | |
| Agitation | 15 | 65.2 |
| Somnolence | 3 | 13 |
| Psychosis | 2 | 8.7 |
| Delirium | 2 | 8.7 |
| Other | 1 | 4.3 |
| Toxidrome | | |
| Sympathomimetic | 15 | 65.2 |
| Sedative | 3 | 8.7 |
| Anticholinergic | 1 | 4.3 |
| Unknown | 5 | 17.4 |
| Laboratory (obtained within 4h of presentation) | | |
| Basic metabolic profile | *n* | Percentage |
| Glucose (mg/dL) | | |
| <80 | 1 | 4.3 |
| 80–150 | 19 | 82.6 |
| >150 | 3 | 13 |
| Sodium (mEq/L) | | |
| <125 | 1 | 4.3 |
| 125–134 | 3 | 13 |
| 135–145 | 16 | 69.6 |
| 146–155 | 2 | 8.7 |
| >155 | 1 | 4.3 |
| Potassium (mEq/L) | | |
| <3.0 | 1 | 4.3 |
| 3.0–3.4 | 5 | 21.7 |
| 3.5–5 | 15 | 65.2 |
| 5.1–6.5 | 1 | 4.3 |
| >6.5 | 1 | 4.3 |
| Bicarbonate (mmol/L) | | |
| <15 | 2 | 8.7 |
| 15–21 | 8 | 34.8 |
| 22–29 | 12 | 52.2 |
| Unknown | 1 | 4.3 |
| Creatinine (mg/dL) | | |
| 0.5–1.5 | 19 | 82.6 |
| 1.6–2.0 | 1 | 4.3 |
| 2.1–4.0 | 2 | 8.7 |
| >4.0 | 1 | 4.3 |
| | Median | Range |
| CPK (U/L) | 432.5 | 62–90,168 |
| Complications (within 24h of presentation) | *n* | Percentage |
| Myocardial infarction | 3 | 13 |
| Seizure | 0 | 0 |
| CVA | 0 | 0 |
| Intubation | 7 | 30.4 |
| Intubation reason | | |
| Agitation | 4 | 17.4 |
| Other | 2 | 8.7 |
| Multiple | 1 | 4.3 |
| Cardiac arrhythmia (other than sinus tachycardia) | | |
| None | 20 | 87 |
| Bradycardia | 2 | 8.7 |
| SVT | 1 | 4.3 |
| Treatments (within 4h of presentation) | *n* | Percentage |
| Benzodiazepines | 18 | 78.3 |
| Antipsychotics | 5 | 21.7 |
| Paralytics | 5 | 21.7 |
| Cooling | 1 | 4.3 |
| Disposition | | |
| | *n* | Percentage |
| Hospital admission | 22 | 95.7 |
| ICU admission | 20 | 87 |
| | Median | Range |
| Hospital LOS (days) | 2 | 0-20 |
| ICU LOS (days) | 1 | 1-12 |
| Final disposition | *n* | Percentage |
| Home | 14 | 60.9 |
| Psychiatric unit | 7 | 30.4 |
| Jail | 1 | 4.3 |
| Death | 1 | 4.3 |

been depleted; a phenomenon previously reported in cocaine users called "wash-out syndrome" [30]. Another possibility for sedation could be the co-exposure of a central nervous system depressant. All three patients in our study had additional substances detected on analytical drug screen. One patient did not have any sedating drugs detected and was only positive for caffeine. Another patient was positive for hydroxyzine, quetiapine, and lamotrigine, all of which could have contributed to sedation. This patient was also described as anticholinergic, which would be more likely secondary to the hydroxyzine and/or quetiapine ingestion than to MDPV. The third patient was positive for dextromethorphan, doxylamine, codeine, and morphine, all of which could contribute to sedation.

Acidosis, hypokalemia, and hyperglycemia were all observed in some of our patients. Collectively, these laboratory abnormalities are similar to what has been reported with adrenergic stimulation from other substances such as epinephrine [31] and methylxanthines [32]. In contrast to what would be expected with most stimulant drugs, one of our patients in this series developed hypoglycemia. The patient with hypoglycemia had no history of diabetes, no known co-exposures, and presented with psychosis but with no other signs or symptoms consistent with adrenergic stimulation. Along with hypoglycemia, the patient also had mild acidosis, an elevated creatinine phosphokinase (CPK), an elevated lactate, and a detectable urine acetone. The findings of hypoglycemia, urine ketones, and elevated lactate would be consistent with laboratory findings during a nutritionally deficient state. Hypoglycemia has also been reported in other cases of MDPV exposure [17, 33]. It is not known whether hypoglycemia is related to drug effect, a consequence of multiorgan failure, or the nutritional status of the patient. We observed both hypernatremia and hyponatremia in our patients. The lowest sodium in our series was <125 meq/L; this has also been previous reported with cathinone ingestion [34]. While a proposed mechanism of hyponatremia could be syndrome of inappropriate antidiuretic hormone secretion, the cause was never identified in our patient. The highest sodium in our series was >155 meq/L. It was not apparent in our study if this hypernatremia was due to dehydration or another cause. Interestingly, both the severe hypernatremic and hyponatremic patients also had rhabdomyolysis. Similar to other MDPV cases, some of our patients had laboratory evidence of renal injury [17]. Two patients with evidence of renal injury had normal CPKs on presentation. One patient with evidence of renal injury and normal CPK had a previous diagnosis of end-stage renal disease; the other patient had no previous medical history of renal disease. The patient with the most severe renal injury also presented with the highest CPK. MDPV may have direct renal toxicity or perhaps this is due to secondary causes such as rhabdomyolysis, ischemia, or dehydration. Two patients had CPKs of >5000 IU/L at presentation and an additional two developed rhabdomyolysis during hospitalization. Thirteen of the 23 patients had CPKs that were above 300 IU/L. Rhabdomyolysis has been previously reported after MDPV use [18].

Similar to what others have noted, MDPV does not cause a positive amphetamine result on analytical drug screens [35]. MDPV has been reported to cause a false positive phencyclidine (PCP) on a urine drug screen [36]. In our series, two patients tested positive for PCP on urine drug screen done by EIA but neither tested positive for PCP by GC/MS. In six patients with quantitative results, we did not find a correlation between the concentration of MDPV and patient outcome. This lack of correlation may be due to the timing of laboratory sampling in relation to use, underlying medical conditions, co-exposures, or other factors.

As in other reported cases, the majority of our patients (78 %) were treated with benzodiazepines and, in a few cases, antipsychotics [9]. Benzodiazepines are often the first-line therapy after stimulant toxicity, so their use as therapy after MPDV exposure is expected. The use of antipsychotics to control symptoms is not surprising considering the previous reports of psychosis after MDPV exposure and the reported neuropsychiatric symptoms in our patients. Ten of the 18 patients who received benzodiazepine were also treated with either an antipsychotic or paralytic. This may indicate that the

**Table 2** Clinical findings in patients with quantitative MDPV concentrations

| Patient no. | Urine (ng/mL) | Blood (ng/mL) | Clinical findings |
|---|---|---|---|
| 1 | 3100 | N/A[a] | Sympathomimetic, intubated secondary to agitation, 12 days of ICU hospitalization |
| 2 | 120 | 89 | Sympathomimetic, intubated secondary to agitation, rhabdomyolysis and myocardial infarction, 20 days of hospitalization |
| 3 | 1000 | N/A | Somnolence, 1 day of ICU hospitalization |
| 4 | 670 | 82 | Sympathomimetic, intubated after cardiac arrest, 2 days of ICU hospitalization, death |
| 5 | 2400 | 72 | Sympathomimetic, 2 days of hospitalization with 1 day in ICU |
| 6 | 509 | <10 | Sympathomimetic, SVT, 2 days of hospitalization with 1 day in ICU |

N/A[a] = not obtained

**Table 3** Analytical drug testing

| Patient | MDPV test information | MDPV result | Drug screen information | Drug screen result | Reported co-exposure by history | Medications given in first 4 h of hospitalization |
|---|---|---|---|---|---|---|
| 1 | Urine, HPLC-MS/MS, NMS Lab | 3100 ng/mL | Urine, GC/MS, comprehensive drug panel 1, AIT Laboratories | Lorazepam, acetaminophen, ibuprofen, lidocaine, midazolam, diphenhydramine, zolpidem, caffeine, nicotine | None | Diphenhydramine |
| 2 | Urine, GC/MS, Sonora Quest Lab | Positive | N/A | Not done | None | None |
| 3 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Nicotine, caffeine, ibuprofen, hydroxyzine, lamotrigine, quetiapine, polyethylene glycol | Quetiapine | Lorazepam, succinylcholine, fentanyl, thiamine |
| 4 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Nicotine, cotinine, caffeine | None | Midazolam, lorazepam, rocuronium, cefipime, vancomycin, fentanyl, propofol |
| 5 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Nicotine, cotinine, caffeine, polyethylene glycol | None | Midazolam, lorazepam |
| 6 | Urine, HPLC-MS/MS NMS Lab Blood, HPLC-MS/MS NMS Lab | 120 ng/mL, 89 ng/mL | Urine, GC/MS, Sonora Quest Lab | Caffeine, hydrocodone, benzodiazepine, propofol | None | Midazolam, vecuronium, acetaminophen |
| 7 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Acetone, cannabinoid, nicotine, cotinine | None | Lorazepam |
| 8 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Caffeine, nicotine, cotinine, dextromethorphan, doxylamine, codeine, morphine, trimethoprim | Alprazolam, quetiapine | Piperacillin-tazobactam, magnesium, naloxone |
| 9 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Acetone, cannabinoid, nicotine, cotinine | Synthetic cannabinoid | Lorazepam |
| 10 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Caffeine, propofol | Synthetic cannabinoid | Midazolam, lorazepam, vecuronium |
| 11 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Acetone, nicotine, caffeine | None | Diazepam, thiamine |
| 12 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Lidocaine, benzodiazepine, olanzapine | Alprazolam, olanzapine | Lorazepam, ziprasidone |
| 13 | Urine, GC/MS, Sonora Quest Lab | | Urine, GC/MS, Sonora Quest Lab | Caffeine, doxylamine, acetaminophen, nicotine, cotinine | Synthetic cannabinoid, caffeine | Lorazepam, acetaminophen |
| 14 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Acetone, quetiapine, citalopram, nicotine, cotinine, caffeine | Quetiapine, citalopram | None |
| 15 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Caffeine, cotinine, nicotine, polyethylene glycol | Synthetic cannabinoid | Lorazepam, haloperidol |
| 16 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Benzodiazepine | Alprazolam | Lorazepam, haloperidol |

**Table 3** (continued)

| Patient | MDPV test information | MDPV result | Drug screen information | Drug screen result | Reported co-exposure by history | Medications given in first 4 h of hospitalization |
|---|---|---|---|---|---|---|
| 17 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Benzodiazepine, meprobamate, caffeine, acetone, polyethylene glycol | None | Midazolam, lorazepam |
| 18 | Urine, GC/MS, Sonora Quest Lab | Positive | Urine, GC/MS, Sonora Quest Lab | Cannabinoids, acetone, nicotine, cotinine, propofol, acetaminophen, diphenhydramine, caffeine | Synthetic cannabinoid | Rocuronium, propofol, etomidate |
| 19 | Urine, HPLC-MS/MS, NMS Lab | 1000 ng/mL | Urine, GC/MS, NMS Lab | Caffeine | Synthetic cannabinoid | Lorazepam |
| 20 | Urine, HPLC-MS/MS, NMS Lab Blood, HPLC-MS/MS, NMS Lab | 670 ng/mL, 82 ng/mL | Urine, GC/MS, NMS Lab Blood, GC/MS, NMS Lab | Urine: opiates, acetaminophen, atropine, cotinine, lidocaine, trimethoprim, Blood: acetaminophen, caffeine, cotinine, lidocaine, trimethoprim | None | Lorazepam, clindamycin, epinephrine, atropine, lidocaine, flumazenil, naloxone, dopamine, phenylephrine |
| 21 | Urine, HPLC-MS/MS, NMS Lab Blood, HPLC-MS/MS, NMS Lab | 2400 ng/mL, 72 ng/mL | Urine, GC/MS, NMS Lab Blood, GC/MS, NMS Lab | Urine: benzocaine, caffeine, diphenhydramine, ropivicaine, theophylline, theobromine, blood: caffeine | Caffeine | Lorazepam, haloperidol |
| 22 | Urine, GC/MS, spectrum Health Regional Toxicology Lab | Positive | Urine, EIA, Spectrum Health Regional Toxicology Lab | Caffeine, nicotine, cannabinoids, phencyclidine *confirmation negative for phencyclidine | Cannabinoid | Lorazepam, haloperidol |
| 23 | Blood, HPLC-MS/MS, Atlantic Diagnostic Lab | 509 ng/mL | Urine, EIA, Harrisburg Hospital Lab | Benzodiazepine, opiate, phencyclidine *confirmation negative for phencyclidine | None | Lorazepam |

symptoms after MDPV exposure are difficult to control with benzodiazepines alone.

A variety of cardiac complications were noted after MPDV exposure. Three patients developed myocardial ischemia diagnosed by an elevation in troponin; none of these patients had ST segment elevation on EKGs. All three of these patients were positive for caffeine on analytical drug screening; no other stimulants were detected. One patient with elevated troponin had no previous medical history, one patient had a history of hypertension, and one patient had a history of end-stage renal disease, sickle cell anemia, hypertension, diabetes mellitus, and congestive heart failure. Two patients had QTc durations of >500 msec, and one patient had QRS duration of >100 msec. One of the patients with a prolonged QTc reported ingesting quetiapine, which is known to cause QTc prolongation; however, the comprehensive UDS did not detect quetiapine. The other patient with prolonged QTc did not have any known co-exposures, but the comprehensive UDS detected doxylamine and trimethoprim, both of which can prolong the QT interval. The patient with the wide QRS duration was also the patient who developed cardiac arrest and died. It cannot be concluded from our data whether MDPV has a propensity to cause changes to the QRS or QTc intervals. There was one patient in our series who developed supraventricular tachycardia (SVT). This patient did not have any known underlying cardiac pathology and did not report any co-exposures or test positive for any other stimulants on urine drug screen. Although SVT has been reported with other stimulants [37, 38], this is the first report of SVT associated with MDPV exposure.

None of the patients in this series developed seizures after MDPV exposure. To our knowledge, there is a single case report of a patient with confirmed MDPV exposure who had a reported seizure prior to hospitalization. The details of the seizure in this case report are not clear regarding who reported the seizure and how the seizure was substantiated. There are two review articles that focus on the "bath salt" MDPV and include a table that lists seizures as a complication from "bath salts". These two articles do not reference any specific cases of "bath salt"-associated seizures [35, 39]. There are case reports of patients with synthetic cathinone exposure other than MDPV who have had seizures, such as mephedrone [26, 40] and in one case ethcathinone and methylone [34]. A study that utilized the American Association of Poison Control Centers databases, found that 5.5 % of pediatric synthetic cathinone exposures were associated with seizures [41]. This study does not specify which synthetic cathinones are associated with the seizures, and the patients in this study do not have laboratory confirmation of exposure. It is possible that MDPV toxicity does not cause seizures or is less likely to cause seizures than other synthetic cathinones like mephedrone. However, it is also possible that seizures can occur after MDPV exposure but were not seen in a case series of our size.

All of the patients in this study except one were admitted to the hospital and most were admitted to the ICU. This likely reflects the severity of MDPV intoxication. Of those patients who were hospitalized, a substantial percentage (30.4 %) went on to receive inpatient psychiatric care. Four of the patients who were transferred to inpatient psychiatric facilities had a previous history of depression and had suicidal intent with their MDPV exposure. One patient had no known psychiatric history but did have suicidal intent. Two patients had no known psychiatric history and were abusing MDPV recreationally. It remains unclear if the suicidal intent and psychiatric disposition with MDPV use is secondary to underlying psychiatric condition; MDPV-induced psychiatric illness or a combination of both. Other case series have also reported serious psychiatric symptoms associated with synthetic cathinone use [9, 24]. The synthetic cathinone mephedrone has been associated with self-harm as well as high-risk behaviors [42].

Our study has several limitations. The search terms used to query the database were chosen based on previous literature; therefore, newer and less common synthetic cathinones were not searched for in this study. As with all retrospective chart reviews, we were limited to studying the documented effects and were reliant on the accuracy of the documentation. Since all the participating sites were large academic medical centers with medical toxicologists, the study also suffers from a referral bias leading to possible inclusion of a population with more severe illness. It is difficult to control for co-exposures and some of our patients may have had exposure to other substances besides MDPV that altered their clinical presentation and medical course. Twenty-two of the 23 patients in our study had analytical drug screens done to detect co-exposures. All 22 patients had at least one additional substance detected (Table 3). While co-exposure is a limitation, this is a phenomenon that has been reported in a previous case series of synthetic cathinone abuse [26]. It is possible that some of the patients we excluded had taken synthetic cathinones that were not detected by confirmatory tests. Some of the synthetic cathinone tests may not have had the ability to detect all substances that were abused as synthetic cathinones. It is also unclear how long MDPV is detectable in urine, and therefore some of the patients with a positive test may have had MDPV exposure unrelated to their acute presentation. Patients who had confirmatory MDPV testing done may be sicker than those that did not have confirmatory testing sent, adding selection bias for a population with more severe symptoms. Although all the MDPV testing was done by either GC/MS or by HPLC/MS-MS, not all of the testing was done in the same laboratory. The additional analytical drug testing was also performed using GC/MS in 20 of the 23 patients but was also done at several different laboratories.

Three of the patients included in this study have been previously reported as case reports. [18–20] This is similar to other studies that utilize a database, such as the national poison center database, which includes patients that may be reported as case reports in other literature sources.

## Conclusions

Patients using MDPV commonly present with sympathomimetic and neuropsychiatric symptoms. The clinical effects of MDPV are expected based on the proposed mechanism of action and the known effects of similar substances. One surprising finding was that none of our patients had seizures. This observation is in contrast to other synthetic cathinones like mephedrone, which has been associated with seizures. Patients who present with somnolence after MDPV abuse should be evaluated for co-exposure. Clinicians will need to rely on the patient history and clinical presentation to diagnose MDPV toxicity, as it is not detected by routine drug tests. Further research will continue to define the unique and similar characteristics of MDPV compared to other stimulants. The abuse of MDPV and other synthetic cathinones is an international problem that will continue to require collaboration to define and address.

**Conflict of Interest** None.

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