Prevalence of Rhabdomyolysis in Sympathomimetic Toxicity: a Comparison of Stimulants

Ayrn D. O'Connor · Angie Padilla-Jones ·
Richard D. Gerkin · Michael Levine

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Abstract Synthetic cathinones have emerged as popular drugs of abuse and produce sympathomimetic toxicity. It is unknown if rhabdomyolysis occurs more frequently following the use of synthetic cathinones compared to other stimulants. This retrospective study sought to determine the prevalence of rhabdomyolysis in patients with sympathomimetic toxicity and compare rates among patients using specific agents. Patients greater than 14 years of age with sympathomimetic toxicity and detection of a stimulant agent in urine via gas chromatography-mass spectroscopy (GC-MS) were included. Patients were excluded if clinical sympathomimetic toxicity was not present, a serum creatine kinase (CK) was not measured, or urine GC-MS was not performed. Rhabdomyolysis and severe rhabdomyolysis were defined as CK>1000 and 10,000 IU/L, respectively. Prevalence of rhabdomyolysis and

severe rhabdomyolysis were reported. Logistic regression was performed to determine the relative effect in single-agent exposures of a synthetic cathinone compared to other sympathomimetics on rhabdomyolysis. A secondary outcome, a composite endpoint defined as need for mechanical ventilation, renal replacement therapy, development of compartment syndrome, or death, was also analyzed. One hundred two subjects met inclusion criteria; median age (IQR) was 32 (25–42) years with a range of 14–65 years; 74 % were male. Rhabdomyolysis occurred in 42 % (43/102) of subjects. Patients whose sympathomimetic toxicity could be ascribed to a single agent were considered for further statistical analysis and placed into four groups: methamphetamine ($n=55$), synthetic cathinone ($n=19$), cocaine ($n=9$), and other sympathomimetic ($n=6$). In 89 subjects with single stimulant exposure, the prevalence of rhabdomyolysis was as follows: synthetic cathinone, 12/19 (63 %); methamphetamine, 22/55 (40 %); cocaine, 3/9 (33 %); and other single agent, 0/6 (0 %). The occurrence of severe rhabdomyolysis (CK>10,000 IU/L) for each of the four groups was synthetic cathinone with 5/19 (26 %), methamphetamine with 2/55 (3.6 %), cocaine with 1/9 (11 %), and other with 0/6 (0 %). Median maximal CK (range) by groups was as follows: synthetic cathinone, 2638 (62–350,000+) IU/L; methamphetamine, 665 (61–50,233) IU/L; cocaine, 276 (87–25,614) IU/L; and other, 142 (51–816) IU/L. A statistically significant difference ($p=0.004$) was found when comparing maximal CK among the four groups. Exposure to a synthetic cathinone compared with other sympathomimetics was associated with increased risk of developing rhabdomyolysis and severe rhabdomyolysis with odds ratios of 3.09 and 7.98, respectively. In this cohort of patients with sympathomimetic toxicity, 42 % developed rhabdomyolysis. Synthetic cathinones were associated with an increased risk of rhabdomyolysis and severe rhabdomyolysis compared with other stimulants.

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A. D. O'Connor (✉)

Department of Medical Toxicology, Banner Good Samaritan Medical Center; Department of Internal Medicine, and Center for Toxicology and Pharmacology Education and Research, University of Arizona College of Medicine-Phoenix, Phoenix, AZ, USA
e-mail: Aym.OConnor@bannerhealth.com

A. Padilla-Jones

Banner Research Institute, Banner Good Samaritan Medical Center, Phoenix, AZ, USA

R. D. Gerkin

Department of Medical Toxicology, Banner Good Samaritan Medical Center; Department of Emergency Medicine, and Center for Toxicology and Pharmacology Education and Research, University of Arizona College of Medicine-Phoenix, Phoenix, AZ, USA

M. Levine

Department of Emergency Medicine, Section of Medical Toxicology, University of Southern California, Los Angeles, CA, USA

M. Levine

Department of Medical Toxicology, Banner Good Samaritan Medical Center, Phoenix, AZ, USA

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Introduction

The emergence of synthetic cathinones as popular drugs of abuse has been notable. They first gained notoriety in the USA in 2010, although they were popular on the international illicit drug market several years prior. They were commonly referred to as “bath salts” which encompasses a myriad of agents belonging to the class phenylethylamines. The mechanism of action of synthetic cathinones is similar to that of amphetamine or methamphetamine, but little is known about their specific pharmacokinetic properties. Clinically, intoxication from these agents produces a characteristic sympathomimetic toxidrome with salient features such as agitation, delirium, pressured speech, hypertension, tachycardia, and hyperthermia [1]. Previously reported and expected complications of sympathomimetic toxicity from synthetic cathinones include seizures, metabolic acidosis, rhabdomyolysis, acute kidney injury, hepatic injury, disseminated intravascular coagulation, and death [2, 3].

In 2010, our medical toxicology service at an academic tertiary care referral center in a major metropolitan area began seeing an increase in cases of sympathomimetic toxicity from synthetic cathinones. The earliest identified agents included mephedrone and methylenedioxypyrovalerone (MDPV) but with establishment of schedule I status by the Drug Enforcement Agency (DEA), other agents such as α -pyrrolidinovalerophenone (α -PVP) emerged [4]. It appeared a significant number of patients with sympathomimetic toxicity from synthetic cathinones developed rhabdomyolysis, and rhabdomyolysis was frequently severe. This observation, along with the evolving ability of our institution’s laboratory to detect and identify specific synthetic cathinones, resulted in the present study in which the authors hypothesize that synthetic cathinones confer an increased risk for rhabdomyolysis and possibly severe rhabdomyolysis.

Methods

This study was approved by the institutional review board. It is a retrospective chart review of consecutive patients treated by medical toxicologists at a single tertiary care medical center over a 3 year and 1 month span (January 1, 2010, to January 30, 2013) for sympathomimetic toxicity. This study sought to determine the prevalence of rhabdomyolysis in patients with sympathomimetic toxicity and compare rates among patients using specific agents. Cases were identified via review of a patient log book, which is a record of all patient encounters by medical toxicologists at this referral center. Inclusion criteria were patient age >14 years, clinical evidence of sympathomimetic toxicity, and the presence of stimulant agent confirmed via comprehensive urine drug screen (CUDS) using gas chromatography-mass spectroscopy (GC-MS). Patients were

excluded if a serum CK was not measured, CUDS was not performed, or if despite detection of a stimulant on CUDS patients did not have clinical evidence of sympathomimetic toxicity.

Data Collection and Processing Data abstracted from the medical records included descriptive information (age, sex, reason for ingestion), initial and maximal serum creatinine kinase concentration, initial and maximal serum creatinine concentration, results of the CUDS, neurologic status, initial mean arterial pressure, maximal temperature, and the presence of any complications.

Data were abstracted onto pre-designed data abstraction forms by two reviewers (ML, APJ) and subsequently entered into a spreadsheet (Excel 2007; Microsoft Corp, Redmond, WA) by one investigator (ML). Prior to performing data abstraction, each reviewer received standardized training in systematic chart review. Each of the two reviewers was given five “practice” charts prior to ensure uniform data abstraction. Following data abstraction, a kappa statistic was performed on 10 % of the charts to assess for inter-rater reliability.

Definitions The following definitions were made a priori: rhabdomyolysis, CK>1000 IU/L; severe rhabdomyolysis, CK>10,000 IU/L; and acute kidney injury (AKI), creatinine >1.6 mg/dL. Neurologic status was categorized as either awake, agitated/hallucinating, or CNS depressed/comatose. Sympathomimetic toxicity was considered present when physician documentation explicitly stated that the patient had sympathomimetic toxicity in the impression/decision-making section. The “other” class of stimulants was a pre-defined list of eight sympathomimetic agents (methylphenidate/dexmethylphenidate, ephedrine/pseudoephedrine, phen-termine, atomoxetine, dextroamphetamine, lisdex- amfetamine, armodafinil, sibutramine).

Statistics Descriptive statistics were utilized to determine the primary outcome of prevalence of rhabdomyolysis overall and the prevalence of rhabdomyolysis in patients exposed to specific agents. Secondary outcomes included acute kidney injury, mechanical ventilation, compartment syndrome, and death. Median maximal creatinine kinase with overall range for each stimulant is provided. Statistics were performed on single-agent exposures only. Four groups were identified and included synthetic cathinone, methamphetamine, cocaine, and other. In order to be included in the methamphetamine group, amphetamine also had to be identified on CUDS. If CUDS detected more than one synthetic cathinone but no other stimulants were identified, then patients were included in the single-agent exposure synthetic cathinone group. A comparison among single-agent exposures using a Kruskal-Wallis test was performed. In constructing logistic regression models, the three non-cathinone groups were combined to increase power

and to promote interpretation of the odds ratios obtained. Univariate or multivariate (when applicable) logistic regression was performed to adjust for potential confounding variables which included sex, age, initial mean arterial pressure (MAP), neurologic status, maximal temperature, and reason for exposure (suicide vs. non-suicide attempt) for both rhabdomyolysis and severe rhabdomyolysis in single-agent exposures. Univariate logistic regression was used to evaluate patients with single-agent exposure reaching the composite endpoint defined as those requiring renal replacement therapy (CVVHD or HD), endotracheal intubation with mechanical ventilation, or those who developed compartment syndrome or died. The composite endpoint was created to identify a population of patients with severe manifestations or complications resulting from their sympathomimetic toxicity.

Results

An initial review of the patient care log identified 153 potential cases in which patients were exposed to a stimulant agent. Fifty-one patients were excluded, yielding a final population of 102 patients. See Fig. 1 for details regarding reasons for exclusion. The inter-rater reliability analysis revealed a 100 % agreement for all the categorical variables measured. This resulted in a kappa score of 1.00 for all comparisons. Median age (IQR) was 32 (25–42) years with range of 14–65 years; 74 % were male. Rhabdomyolysis occurred in 42 % (43/102) of subjects. Eighty-nine patients whose sympathomimetic toxicity could be ascribed to a single agent were considered for further statistical analysis and divided into four groups: methamphetamine ($n=55$), synthetic cathinone ($n=19$), cocaine ($n=9$), and other sympathomimetic ($n=6$). The other sympathomimetic agents identified were methylphenidate (3),

pseudoephedrine (1), and phentermine (2). In patients with synthetic cathinone exposure, MDPV was the identified agent in 12 patients and α -PVP in 7 patients, one of whom also had pentylone and pentedrone detected on CUDS. Sympathomimetic toxicity resulting from a combination of agents was found in 13 patients: methamphetamine and cocaine ($n=11$), methamphetamine and synthetic cathinone ($n=1$), and methamphetamine and other stimulant ($n=1$). Further statistical analysis was not performed on this cohort of patients.

In 89 subjects with single-stimulant exposure, the prevalence of rhabdomyolysis was as follows: synthetic cathinone, 12/19 (63 %); methamphetamine, 22/55 (40 %); cocaine, 3/9 (33 %); and other single agent, 0/6 (0 %). The prevalence of severe rhabdomyolysis for each of the four groups was synthetic cathinone 5/19 (26 %), methamphetamine 2/55 (3.6 %), cocaine 1/9 (11 %), and other 0/6 (0 %). Median values for maximal CK (range) by group were as follows: synthetic cathinone, 2638 (62–350,000+) IU/L; methamphetamine, 665 (61–50,233) IU/L; cocaine, 276 (87–25,614) IU/L; and other, 142 (51–816) IU/L (summarized in Table 1). Additional clinical findings including temperature, heart rate, mean arterial pressure, and maximal creatinine are summarized in Table 2.

A statistically significant difference ($p=0.004$) was found when comparing maximal CK between the four groups of patients exposed to a single agent. Logistic regression was used to assess for confounders. Increasing age was statistically significantly associated with increased risk of rhabdomyolysis while other variables (sex, initial mean arterial pressure, worse neurologic status, maximal temperature, and reason for exposure (suicide vs non-suicide attempt)) were not. With adjustment for age, there was an average increase in the risk of developing rhabdomyolysis (odds ratio=3.63) for synthetic cathinone compared to non-cathinone exposure ($p=0.021$; 95 % confidence interval (CI) 1.21–10.9).

When using univariate logistic regression and looking at the endpoint of severe rhabdomyolysis (CK>10,000 IU/L), an odds ratio of 7.98 was found for synthetic cathinone compared to non-cathinone exposure ($p=0.008$; 95 % CI 1.71–37.3). There was no apparent association between age and development of severe rhabdomyolysis, and no other confounders were identified when evaluating sex, mean arterial pressure, and neurologic status.

Other complications that occurred in this cohort of 102 patients included acute kidney injury in 22 % (23/102) with 3 requiring renal replacement therapy, mechanical ventilation required in 20 % (21/102), development of compartment syndrome in 3 % (3/102), and death in 1 patient. Eighteen patients (20.2 %) in the single-stimulant exposure group met the composite endpoint. Upon performing univariate logistic regression, an odds ratio of 3.13 was found ($p=0.048$; 95 % CI 1.01–9.71), with the cathinone-exposed group having an increased risk for the development of the composite endpoint.

Fig. 1 Selection of the final study population

Table 1 Summary of findings regarding single-agent exposures

Single-agent exposure (<i>n</i>)	Max CK IU/L median (range)	Rhabdomyolysis (CK>1000 IU/L)	Severe rhabdomyolysis (CK>10,000 IU/L)
Synthetic cathinones (19)	2638 (62–350,000+)	12/19 (63 %)	5/19 (26 %)
Methamphetamine (55)	665 (61–50,233)	22/55 (40 %)	2/55 (3.6 %)
Cocaine (9)	276 (87–25,614)	3/9 (33 %)	1/9 (11 %)
Other (6)	142 (51–816)	0/6 (0 %)	0/6 (0 %)

Discussion

Cathinones have been available for centuries in African and Middle Eastern cultures in which people chew the leaves of the *Catha edulis* plant for its stimulant properties. Various derivatives of cathinone were identified in the 1920s and some investigated for medical use in the treatment of depression, obesity, and “chronic fatigue” [1]. Methcathinone was synthesized in clandestine laboratories and utilized as a drug of abuse in Russia in the 1980s and in the USA in the 1990s [1, 4]. In 2008, various international illicit drug markets experienced a surge in synthetic cathinone abuse. This trend reached the USA in 2010 when mephedrone and MDPV were identified [4]. Mephedrone is a β -ketonated amphetamine, and MDPV is a pyrrolidine derivative of beta-ketonated methylenedioxypheethylamine [5]. Synthetic cathinones belong to the broader class phenethylamines; for simplicity, this text refers to these various phenethylamines as “synthetic cathinones” which conveys the presence of a ketone group on the beta carbon [5].

With the arrival and escalation of synthetic cathinone abuse, there was a heightened awareness and investigation on the part of law enforcement. Mephedrone, MDPV, and methylone were identified and eventually given schedule I status by the DEA. After the emergency scheduling of these agents by the DEA, a second wave of synthetic cathinones occurred. Shanks et al. noted the emergence of α -PVP, butylone, and 6-aminopropylbenzofuran post-federal ban [6, 7]. Consequently, on February 27, 2014, the DEA temporarily made α -PVP schedule I, along with nine other agents.

Mirroring what was being seen on a national scale, the Banner Poison and Drug Information Center experienced an increase in calls regarding synthetic cathinones with 247 calls

in 2011, compared to only 2 calls in 2010. This coincided with a notable increase in patients being admitted to our medical toxicology service with classic manifestations of sympathomimetic toxidrome but without cocaine or methamphetamine detected on comprehensive drug testing, prompting the current investigation.

In this cohort of patients with sympathomimetic toxicity, the development of rhabdomyolysis was a common occurrence. The pathophysiology of stimulant-induced rhabdomyolysis is multifaceted and involves several pathways which culminate in increased metabolic demands in excess of the supply of nutrients and oxygen. This may be due to skeletal muscle overuse seen in patients with excited delirium or repetitive behaviors, extreme vasoconstriction, hyperthermia, and/or impaired adenosine triphosphate production (ATP) from impaired cellular respiration. Also, compression injury may result in myonecrosis in patients with depressed level of consciousness or coma from their stimulant intoxication. This may occur following seizure activity with prolonged post-ictal state or after intracerebral vascular catastrophe.

In this study, rhabdomyolysis resulting from exposure to synthetic cathinones was associated with a higher median maximal CK. Patients exposed to synthetic cathinones were more likely to develop rhabdomyolysis and severe rhabdomyolysis compared to the non-cathinone-exposed group. The precise reason for the increased risk of rhabdomyolysis following cathinone exposure is unclear. The underlying pathophysiology of rhabdomyolysis from synthetic cathinones is expected to be similar to that occurring from other stimulants. Consequently, potential explanations for the increased risk of rhabdomyolysis and severe rhabdomyolysis in patients exposed to synthetic cathinones include user unfamiliarity with potency and pharmacokinetics of the cathinones resulting in

Table 2 Clinical findings by drug type (median (range))

	Temp (max) °C	HR (init) bpm	MAP (init) mmHg	Creatinine (max) mg/dL
Synthetic cathinones (19)	37.9 (36.5–42.1)	135 (74–191)	98 (49–132)	1.28 (0.67–8.24)
Methamphetamine (55)	37.4 (36.5–42.5)	109 (73–166)	102 (54–141)	1.02 (0.56–6.82)
Cocaine (9)	37.5 (35.3–38.8)	106 (72–145)	89 (41–116)	0.96 (0.66–3.00)
Other (6)	37.2 (36.8–37.5)	120 (100–160)	99 (81–116)	0.79 (.63–0.93)

excessive dosing and subsequent increased toxicity. For example, agents that have delayed onset of action may prompt the user to repeat or increase the dose trying to achieve the desired effect. Additionally, some agents may have prolonged duration of action resulting in increased toxicity. Some synthetic cathinones may cause increased neuropsychiatric symptoms resulting in more severe or prolonged agitated delirium or they may cause repetitive behaviors. These effects would contribute to skeletal muscle overuse and increased metabolic demand in the setting of profound vasoconstriction or hypoperfusion. Conversely, if an agent does not penetrate the blood-brain barrier well and has limited central nervous system effects, exaggerated peripheral effects may prevail, leading to severe vasoconstriction and limited heat dissipation contributing to hyperthermia and further skeletal muscle cell breakdown.

In this cohort, MDPV and α -PVP were the two synthetic cathinones identified in single-agent exposures. Both MDPV and α -PVP are structurally related α -pyrrolidinophenones, differing by a methylenedioxy moiety. Although there have been some studies in animal models and in vitro studies with human microsomes performed to evaluate their metabolism, little is known about their specific pharmacokinetics [8, 9]. MDPV is reported to have an onset of action of 15 to 30 min, although this is dependent on route of exposure [6]. It is felt to be more potent than mephedrone, and doses of 3 to 5 mg can produce psychoactive effects, although 10 to 15 mg is typically used [10]. Its duration of action is estimated to be 6 to 8 h, although some cite effects lasting 48 h [5, 10]. Some authors report a compulsion to redose MDPV to avoid the harsh, extremely unpleasant effects associated with resolution of intoxication [10]. This relative increased potency, delayed onset of action, and compulsion to redose may explain the increased prevalence of rhabdomyolysis seen in patients exposed to MDPV. MDPV was identified in most of the patients in the synthetic cathinone group in this study, specifically 12 of the 19 (63 %). Even less information regarding the pharmacokinetic properties of α -PVP is available. And specific data regarding onset and duration of action in humans is not available.

Because the development of any single adverse event was predicted to be relatively uncommon, a composite endpoint was created a priori. This endpoint was chosen because it was felt to represent the most serious complications likely to be encountered. The composite endpoint allowed for comparison among single-agent exposures to determine if one was more commonly associated with severe toxicity. Using univariate logistic regression, patients exposed to cathinones were compared to those exposed to non-cathinone stimulants, which was the combination of methamphetamine, cocaine, and other single-agent exposures. This comparison revealed patients in the cathinone group were 3.1 times more likely to reach the composite endpoint than those in the non-cathinone group,

implying that more severe toxicity occurred in the cathinone group.

This study demonstrates that patients with sympathomimetic toxicity due to synthetic cathinones are at a higher risk of developing rhabdomyolysis and severe rhabdomyolysis and may be at risk for more severe complications when compared to other stimulant agents. Clinicians should be aware of this increased risk and direct diagnostic evaluation and therapy accordingly. Therapy for stimulant-induced rhabdomyolysis includes aggressive intravenous fluid resuscitation and rapid correction of hyperthermia in addition to titration of benzodiazepines to control manifestations of sympathomimetic toxicity in order to reduce muscle activity and metabolic demand. Alkalinization therapy is a reasonable consideration, but the primary goal of therapy should be to achieve a urine output >2 mL/kg/h.

Limitations

Limitations of this study include those inherent to a retrospective chart review, such as missing or incomplete data or introduction of unintended bias. There are several specific concerns that warrant discussion. The first being that the study population included patients admitted to an adult tertiary care facility; consequently, only patients >14 years of age were considered for inclusion. This means that these findings should not be extrapolated to other patient populations. An additional limitation is that patients were excluded from the study if a stimulant was not found on CUDS despite clinical manifestations of sympathomimetic toxicity and/or supporting history of exposure. However, this would likely preferentially eliminate synthetic cathinones or other novel stimulants as methamphetamine and cocaine are easily detected on CUDS, making our results a conservative assessment. Eighteen patients were eliminated because a CUDS was not obtained, yet most of these had immunoassays for drugs of abuse that were positive for cocaine or methamphetamine. It is possible that the combination of these two factors resulted in a balanced and accurately reflective cohort.

During this study period, our laboratory could detect 12 synthetic cathinones: butylone, flephedrone, 5,6-methylenedioxy-2-aminoindane (MDAI), MDPV, mephedrone, 3,4-methylenedioxy-pyrrolidinobutylphenone (MDPBP), 4-methylethcathinone (4-MEC), naphyrone, pentedrone, pentylone, and meta-1 and meta-2 α -pyrrolidinovalerophenone (α -PVP). Clearly, there are numerous other illicit psychoactive substances we may have missed. Consequently, the CUDS may not have detected a stimulant when present, and patients identified as having single-agent exposures may have been exposed to other novel agents contributing to their clinical outcomes.

Additionally, nine patients were eliminated from the original cohort due to lack of clinical features of sympathomimetic toxicity documented in the medical record. It is possible that these patients had mild effects consistent with sympathomimetic toxicity that was not adequately documented prompting their elimination from the study cohort, creating selection bias toward a more severely intoxicated population.

Another potential limitation involves the presence of caffeine on CUDS. The majority of patients, 66 % (67/102), had caffeine detected on CUDS. This is a common finding in all patients that have CUDS which is routinely performed on patients admitted to the medical toxicology service and may reflect typical dietary consumption. However, in a patient population with sympathomimetic toxicity, it cannot be reliably distinguished whether caffeine contributed to the clinical manifestations of sympathomimetic toxicity or not. Furthermore, there are several reports of novel psychoactive substances, specifically those claiming to be synthetic cathinones, that were analyzed and found to contain significant concentrations of caffeine with some containing only caffeine [11–13].

Lastly, it should be highlighted that the total number of patients reaching composite endpoint was low and the 95 % confidence interval approached 1, indicating that further study is warranted before drawing definitive conclusions regarding quantification of risk.

Conclusion

One can conclude that in this cohort of patients with sympathomimetic toxicity, rhabdomyolysis was a common occurrence. Rhabdomyolysis and severe rhabdomyolysis occurred more commonly in patients with sympathomimetic toxicity from exposure to synthetic cathinones than from other agents. Clinicians should anticipate this complication, monitor for rhabdomyolysis, and institute appropriate therapy early in the patient's clinical course.

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Conflict of Interest All authors have nothing to disclose.

Author Contributions ML and ADO conceived the study, drafted study protocol, designed the data abstraction sheet, and obtained IRB

approval. ML and APJ conducted the chart review and data abstraction. ML and AOC supervised and ensured accuracy of the data collection. ML was responsible for entry of data into electronic database. RDG provided statistical advice on study design and analyzed the data. AOC drafted the manuscript, and all authors contributed substantially to its revision. AOC takes responsibility for the paper as a whole.

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