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Original Contribution

Suspected synthetic cannabinoid receptor agonist intoxication: Does analysis of samples reflect the presence of suspected agents?

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ABSTRACT

Background: There has been a surge in synthetic cannabinoid receptor agonist (SCRA) exposures reported in recent years. The constituents of SCRA preparations are constantly evolving and rarely confirmed. We sought to characterize the constituents of reported SCRA exposures presenting to the emergency department (ED).

Methods: Patients who presented to two academic EDs in Washington, DC with reported or suspected SCRA exposure from July 2015–July 2016 were enrolled at the discretion of the treating provider. Blood and/or urine samples were obtained as part of routine clinical care and sent to the DC medical examiner's office for identification of known SCRAs with liquid chromatography-mass spectrometry-mass spectrometry. Standard toxicology screens were additionally performed to determine the presence of other drugs of abuse.

Results: 128 samples were analyzed. Seventy-one (55.5%) were positive for an SCRA. The most common SCRAs detected were AB-fubinaca (28, 39.4%), ADB-fubinaca (15, 21.1%), AB-chminaca 3-methyl-butanoic acid (15, 21.1%), ADB-chminaca (14, 19.7%), and 5-flouro-PB-22 (8, 11.3%). Fifty-seven (44.5%) samples were negative for an SCRA, of which 28 (21.9%) were positive for another substance, most commonly delta-9-tetrahydrocannabinol and phencyclidine. An additional 29 (22.7%) patients had both negative SCRA and toxicology screens.

Conclusions: Of patients presenting with reported SCRA intoxication, 55.5% had detectable SCRAs on analytical testing. These results suggest that in a considerable proportion of cases, clinicians are misattributing the effects of other drugs or medical conditions to SCRA use. The individual SCRAs detected in our study differed from compounds detected in earlier studies, suggesting there has been a change in constituents.

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1. Introduction

In recent years, the recreational use of synthetic cannabinoid receptor agonists (SCRAs), colloquially referred to as "K2" or "Spice", has grown considerably [1]. These compounds were originally synthesized starting in the late 1970s to investigate the endocannabinoid family of receptors and elucidate potential therapeutic targets [2,3]. Beginning in the early 2000s, a number of laboratories in the US, Europe, and Japan, started developing and combining novel SCRAs in an effort to create psychoactive "herbal mixtures" which have of late been marketed as legal alternatives to marijuana [1]. The use of these products has since become popular due to their easy availability, legal ambiguity, inability to be detected by current drug screens, and the potent high that is experienced when they are used [4].

Given the wide range of symptoms associated with acute SCRA intoxication, many of which are potentially dangerous, SCRAs pose a unique challenge to emergency medicine clinicians in the identification and management of patients [5]. Primarily via case reports, a variety of presentations have been reported in the literature from benign, self-limiting alterations in mood and perception to more dangerous complications including prolonged seizures, rhabdomyolysis, acute kidney injury, and myocardial infarction [6-9]. Recent reports speculate that greater than 28,000 patients per year

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present to US emergency departments for complications associated with the use of SCRAs [10,11]. Trecki, Gerona, and Schwartz reported in 2015 that at least 40 fatalities have been attributed to complications associated with acute SCRA intoxication [12].

Among the inherent challenges in identifying and treating SCRA intoxication is the wide variety of active compounds that fall into this class. The first generation of SCRA products was composed largely of the cyclophenols including CP47–497 and CP55–940, the dibenzoypyran HU-210 and members of the extensive JWH family [5,13]. CP47–497 was first developed by Pfizer in the 1980s as a CB1 receptor agonist touted for its potential efficacy as an analgesic [14,15]. HU-210, also an agonist of the CB1 receptor, was discovered by Raphael Mechoulam at the Hebrew University in 1988 and noted to be an up 800 times more potent activator of the CB1 receptor than natural tetrahydrocannabinol [16,17]. The JWH family of SCRAs, which is comprised of over 450 members, include prominent agents such as JWH-18, JWH-073, JWH-398, and JWH-250. These agents, which are potent activators of both CB1 and CB2 receptors were originally synthesized by John Huffman at Clemson University in the 1990s and early 2000s [18-20]. Each of these compounds have been found in varying concentrations in many modern formulations of SCRA products [21,22].

In the face of mounting evidence that these compounds have significant toxic effects, the US Drug Enforcement Agency has passed legislation to schedule currently known SCRAs including CP47–497, HU-210, and members of the JWH family as Schedule I controlled substances [23,24]. Furthermore, methods to detect the presence of SCRAs in blood and urine including screening immunoassays, have been developed to assist in the management of patients with suspected SCRA use. Despite these measures, manufacturers of SCRA products have continued to synthesize new compounds in order to evade regulatory efforts and sustain the market for their products. As the components of these products change it is vital to identify the constituents of the current status quo so they may be incorporated into current regulatory schemata as well as protocols for detection and management. The objective of our study was to characterize and confirm the constituents of reported or suspected SCRA exposures presenting to two academic emergency departments (EDs) in Washington, DC.

2. Methods

Patients who presented to two academic EDs in Washington, DC with reported SCRA exposure from July 2015–July 2016 were enrolled at the discretion of the treating provider. Patients were considered eligible if they were age 18 years or older and either admitted to SCRA use, there was bystander report of SCRA use, or if the patients possessed SCRA products at the time of admission in the proper clinical context.

Blood and/or urine samples were obtained during routine care for the patient's intoxication or presenting complaint. Samples were only obtained if the patient was ordered a blood or urine sample as part of routine clinical care. Bedside nurses would obtain 1 or 2 tubes of blood or urine for analysis at their discretion. Samples were then sent to the DC medical examiner's office for toxicology screening and testing for SCRAs. Samples were de-identified as we were unable to obtain informed consent from intoxicated patients. We did not obtain additional clinical data from chart review as this would also require informed consent. The study protocol was reviewed and approved by the MedStar Health Research Institute's Institutional Review Board.

Laboratory identification of known SCRAs with routine liquid chromatography-mass spectrometry-mass spectrometry (LC/MS/MS) was performed at the medical examiner's office. Individual SCRAs were identified as well as other routine drugs of abuse on toxicology screen. Ethanol concentrations were not routinely obtained unless clinically indicated because they were not part of the medical examiner's office surveillance efforts and to avoid unnecessary cost to the patient.

3. Results

A total of 132 unique cases were submitted for analysis; 4 had samples that were inadequate or pending at the study conclusion and were excluded from the study. There were 159 blood samples collected from 114 patients and 71 urine samples collected from 68 patients. From 45 patients, both blood and urine samples were collected. Of the 128 unique cases included in the study 71 (55.5%) were positive for an SCRA. Forty (31.3%) of these were positive for an SCRA alone and 31 (24.2%) for an SCRA and another substance. Eighteen (25.4%) were positive for more than one SCRA. Of those, 12 were positive for 2 SCRAs, 4 were positive for 3 SCRAs, and 2 were positive for 4.

The most common SCRA detected was AB-fubinaca (28, 39.4%). Other common SCRAs detected were ADB-fubinaca (15, 21.1%), AB-chminaca 3-methyl-butanoic acid (15, 21.1%), ADB-chminaca (14, 19.7%), and 5-flouro-PB-22 (8, 11.3%) (Table 1). Of the 31 cases that tested positive for an SCRA and another substance, delta-9-tetrahydrocannabinol (THC) and phencyclidine (PCP) were the most common substances identified (Table 2). Fifty-seven patients (44.5%) were negative for an SCRA of which, 28 (21.9%) were positive for another substance, the most common being THC and PCP. (Table 3) Twenty-nine (22.7%) patients were negative for SCRAs and on toxicology screen.

4. Discussion

In this study we found that patients who were labeled as being intoxicated by an SCRA tested positive for an SCRA in only 55.5% of cases, indicating that patients were incorrectly identified almost half of the time. Nearly 22% of patients falsely identified as SCRA intoxications tested positive for another drug on toxicology screen. These misidentifications could be accounted for by an interplay between the similar presentations of SCRA intoxication and intoxication with the other identified agents. It could also represent clinician bias affected by recent increases in patients presenting to EDs with acute SCRA intoxication. Commonly reported negative effects of SCRA intoxication include nausea, vomiting, anxiety, paranoia, palpitations, seizures, and psychosis [6,8,26]. It is important to note that many of these adverse effects have been historically associated with the use of cocaine, PCP, marijuana, and amphetamines, which were detected in a considerable proportion of the patients identified both correctly and incorrectly as being intoxicated with SCRAs

Table 1
synthetic cannabinoid receptor agonists (SCRAs) detected.

SCRA	Patients with SCRA detected number (percent)
AB-fubinaca	28 (39.4%)
ADB-fubinaca	15 (21.1%)
AB-chminaca-3-methyl-butanoic acid	15 (21.1%)
ADB-chminaca	14 (19.7%)
5-fluoro-PB-22	8 (11.3%)
AB-chminaca	6 (8.4%)
AB-PINACA-N-pentanoic acid	4 (5.6%)
UR 144-N-pentanoic acid	3 (4.2%)
FUB-AMB	2 (2.8%)
FUB-BP-22	1 (1.4%)

*Eighteen patients had more than one SCRA detected in their samples, therefore the sum of patients with the listed SCRAs detected in their samples exceeds the total number of patients in which one or more SCRAs were detected.

Table 2
Substances detected in patients positive on both synthetic cannabinoid receptor agonist and toxicology assays.

Substances detected	Number of patients
THC	11
PCP + THC	5
PCP	3
Benzodiazepine	3
Cocaine	3
Morphine	1
Codeine	1
THC + PCP + Morphine	1
THC + PCP + Cocaine	1
THC + Cocaine + Benzodiazepine	1
PCP + Codeine + Morphine + Benzodiazepine	1

THC = delta-9-tetrahydrocannabinol.
PCP = phencyclidine.

[27-29]. These results suggest that in some cases clinicians are misattributing these symptoms to SCRA use when they may be better attributed to the use of other drugs. It is important to note that a remaining 22% of patients tested negative for SCRAs and other drugs. It is possible that the clinical presentation of these patients resulted from acute alcohol intoxication, medical conditions, trauma or other substances, including novel SCRAs, that were not detectable by current screening assays.

The most frequently encountered synthetic cannabinoid identified by our study was AB-fubinaca (28, 39.4%). AB-fubinaca is an agonist of both CB1 and CB2 receptors [29]. The compound was originally synthesized for use as an analgesic by Pfizer in 2009 but was never released for commercial use [30]. A report from Japan in 2012 first implicated AB-fubinaca as an active ingredient in a variety of SCRA products and studies from 2015 and 2016 suggest an association between the use of products containing this compounds and a number of suicides, hospitalizations, and deaths [12,31,32]. AB-fubinaca is currently deemed a controlled substance in Germany and China and was designated a Schedule I substance in the US in January 2014 [33-35].

Members of the CHMINICA family, AB chminica 3 methylbutanoic acid and ADB-chminica were additionally found in nearly 21% of patients with suspected SCRA intoxication. These compounds are indazole-based SCRAs with affinities for CB1 and CB2 receptors [36]. A number of studies have linked these SCRAs to adverse events including psychosis, seizures and death [12,37]. Both compounds are currently designated schedule I by the US Drug Enforcement Agency. [38]. Finally, the indole derivative 5-Flouro-PB-22 was found in 11.3% of tested samples. This compound, a full agonist of CB1 and CB2 receptors has also been associated with adverse effects including seizures and death and is currently designated as Schedule I by the USDEA [12,25,38,39].

Table 3
Substances detected in patients who tested negative for an synthetic cannabinoid receptor agonist.

Substances detected	Number of patients
THC	7
PCP, THC	5
PCP	4
Cocaine	3
Benzodiazepine, Cocaine, PCP	2
Morphine	1
Morphine, Codeine	1
THC, Cocaine	1
PCP, Cocaine	1
THC, Morphine, Cocaine	1
THC, Amphetamine, Methamphetamine	1
Ephedrine, Amphetamine, Methamphetamine	1

THC = delta-9-tetrahydrocannabinol.
PCP = phencyclidine.

The results of our study indicate a potential shift in the constituents of contemporary SCRA products. Previous analyses of commercially available SCRA mixtures primarily detected classical cannabinoids such as HU-210, the nonclassical cyclohexylphenols such as CP 47–497, and most commonly the aminoalkylindoles, a class dominated by members of the JWH family of SCRAs [29,40-43]. In contrast, the assays employed by our study detected none of these classic compounds in samples taken from our patient population suggesting that manufacturers of contemporary SCRA products have discontinued incorporating these former compounds possibly in an attempt to evade regulation.

The current study was limited by a number of factors. Because the laboratory data were de-identified from individual patient records we were unable to examine and describe the clinical effects of individual SCRAs. Additionally, our findings were limited by the assays available at the time of the study; therefore, it is plausible that the samples taken may have contained additional SCRAs which were not detectable. Our study took place in two urban academic EDs in Washington, DC and our results may not be generalizable to other populations or different regions. Our findings could be subject to selection bias as more severe presentations would be more likely to have had blood and/or urine specimens obtained by the treating physician. As mentioned previously, providers may have erroneously attributed intoxications to SCRAs due to bias or recent trends. We also did not routinely obtain ethanol concentrations, which may have accounted for or contributed to a number of the reported presentations. Finally, we did not pursue informed consent of patients when they were sober, which would have permitted us to collect clinical data.

5. Conclusion

The results of our study suggest that ED providers may be overattributing a large portion of clinical presentations to SCRA use. Many of these patients may be presenting due to serious health problems, which could require further investigation, treatment, and follow up. Despite reported or suspected SCRA use, clinicians should not forgo a thorough evaluation of other possible etiologies for presenting symptoms understanding that many severe medical issues or exposures can resemble acute SCRA intoxication. Additionally, the individual SCRAs detected in our study were different than compounds detected in earlier studies, suggesting that there has been a change in constituents, possibly to avoid regulation, or due to regional differences. Additional prospective research is needed to determine the clinical outcomes and implications of these findings.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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