Clinical Effects of Synthetic Cannabinoid Receptor Agonists Compared with Marijuana in Emergency Department Patients with Acute Drug Overdose

Milana Zaurova¹ · Robert S. Hoffman^{2,3} · David Vlahov⁴ · Alex F. Manini⁵

Received: 2 February 2016 / Revised: 7 May 2016 / Accepted: 14 May 2016 / Published online: 2 June 2016
© American College of Medical Toxicology 2016

Abstract

Introduction Synthetic cannabinoid receptor agonists (SCRAs) are heterogeneous compounds originally intended as probes of the endogenous cannabinoid system or as potential therapeutic agents. We assessed the clinical toxicity associated with recent SCRA use in a large cohort of drug overdose patients.

Methods This subgroup analysis of a large ($n=3739$) drug overdose cohort study involved consecutive ED patients at two urban teaching hospitals collected between 2009 and 2013. Clinical characteristics of patients with the exposure to SCRAs (SCRA subgroup) were compared with those from patients who smoked traditional cannabinoids (marijuana subgroup). Data included demographics, exposure details, vital signs, mental status, and basic chemistries gathered as part of routine clinical care. Study outcomes included altered mental status and cardiotoxicity.

Results Eighty-seven patients reported exposure to any cannabinoid, of whom 17 reported SCRAs (17 cases, 70 controls,

mean age 38.9 years, 77 % males, 31 % Hispanic). There were no significant differences between SCRA and marijuana with respect to demographics (age, gender, and race/ethnicity), exposure history (suicidality, misuse, and intent), vital signs, or serum chemistries. Mental status varied between SCRA and marijuana, with agitation significantly more likely in SCRA subgroup (OR=3.8, CI=1.2–11.9). Cardiotoxicity was more pronounced in the SCRA subgroup with dysrhythmia significantly more likely (OR=9.2, CI=1.0–108).

Conclusions In the first clinical study comparing the adverse effects of SCRA overdose vs. marijuana controls in an ED population, we found that SCRA overdoses had significantly pronounced neurotoxicity and cardiotoxicity compared with marijuana.

Keywords Cannabinoids · Cardiotoxicity · Overdose

Introduction

Over the last half century, a new class of recreational drugs has emerged, synthetic cannabinoid receptor agonists (SCRAs). Synthetic cannabinoid receptor agonists are a heterogeneous group of compounds that were originally developed as probes of the endogenous cannabinoid system or as potential therapeutic agents. Unfortunately, clandestine laboratories subsequently synthesized and marketed SCRAs as designer drugs of abuse [1]. Although originally designed in the 1960s as potential therapeutic agents [2], there has been a rapid increase over the most recent few decades in their recreational use and abuse in large part because of their relatively low cost, ambiguous legality, easy availability, and lack of cross reactivity with established urine drug tests for THC. These synthetic compounds are sprayed over plant material and then packaged

✉ Alex F. Manini
alex.manini@mssm.edu

¹ Emergency Medicine Residency, The Icahn School of Medicine at Mount Sinai, New York, NY, USA

² Division of Medical Toxicology, Ronald O. Perelman Department of Emergency Medicine, NYU School of Medicine, New York, NY, USA

³ New York City Poison Control Center, New York City Department of Health and Mental Hygiene, New York, NY, USA

⁴ School of Nursing, University of California, San Francisco, CA, USA

⁵ Division of Medical Toxicology, the Icahn School of Medicine at Mount Sinai, Elmhurst Hospital Center, One Gustave Levy Place, Box 1620, New York, NY 10029, USA

and distributed to the public [3]; they can be inhaled, ingested, or injected [4].

At present, there is a paucity of research describing the effects of SCRA ingestion. Several case reports, and fewer case series [5, 6], suggest effects of SCRA ingestion include vomiting, tachycardia, tremor, severe agitation [7], bradycardia [8], psychosis [9], and psychotic relapses [10]. There is even a case report describing tolerance and withdrawal phenomenon for a specific variant SCRA branded product named “Spice Gold” [11]. One regional Poison Control Center’s experience has also been published with respect to poisoning severity and tallying general clinical manifestations [12]. Two recent systematic reviews of available case reports found the most common SCRA effects reported as tachycardia, agitation, and nausea [13, 14].

Of late, there has been an overwhelming rise in the presentation of fatal SCRA ingestions to Emergency Departments (ED). We believe that there is a pressing need for better documentation and analysis of the toll SCRA is taking on our patients. We therefore assessed the clinical toxicity associated with recent SCRA use in a large cohort of drug overdose patients. Based on prior literature, we hypothesized significant associations with agitation [13, 14] and cardiotoxicity [7, 8, 13, 14] when compared to marijuana.

Methods

Study Design and Setting This was a subgroup analysis from a larger prospective cohort of consecutive ED adult patients with acute drug overdose at two large urban teaching hospitals collected between 2009 and 2013 [15, 16]. The current study examined the subgroup with self-reported exposure to SCRA (SCRA subgroup) compared with patients with self-reported exposure to regular marijuana (MARIJUANA subgroup). This study was conducted with approval from all involved sites’ institutional review boards with waiver of informed consent.

Study Population Patients with suspected drug overdose were screened by trained research assistants for inclusion. Patients were included who met both of the following criteria: (1) acute presentation (within 24 h of exposure) and (2) suspected overdose (i.e., illicit drug dose sufficient to cause symptoms or any prescription drug exposure greater than its therapeutic dose). Exclusion criteria for the present study were the following: alternative diagnosis (e.g., trauma or infection), chronic presentation (i.e., not meeting acute criteria above), exposures limited to dermal means only, age younger than 18 years, anaphylaxis, and prisoners.

Study Protocol Patients were identified by a trained research assistant who rounded during business hours to find acute

overdose cases and by cases that were called in to the poison center from either of the participating hospitals. While poison control center data were used for screening and inclusion, all other data, including outcomes, were abstracted from hospital medical records.

Data were collected from the charts by research assistants trained in medical abstraction and recorded using standardized data collection forms. Random sampling of 10 charts with 95 % agreement was done prior to initiation of mass data extraction. Data were abstracted to a de-identified electronic database with password protection.

Subjects were prospectively followed during their hospital stay through to hospital discharge with data that included electronic medical records, paper medical records, and consult records. Results (from electronic physician notes, laboratory records, radiology results, and discharge summaries) were prospectively available to the study investigators.

Data and Measurements Data included demographics (sex, age, and race), exposure details (timing of exposure, number of exposures, intent, and suicidality), toxin identification (detail from history and physical interview, serum drug concentrations if available), toxicology screens (urine ELISA panel and serum concentration, if available), initial ED vital signs, initial ED mental status, initial basic chemistries, and initial electrocardiograms (ECG) gathered as part of the routine clinical care. All patients in the marijuana subgroup had positive urine toxicology (marijuana metabolite THC-COOH).

Study outcomes included altered mental status (agitation, GCS) and cardiotoxicity (myocardial injury, dysrhythmia, and shock), as previously validated [15]. Myocardial injury was defined as any elevation of cardiac troponin I > 0.09 mg/dL. Dysrhythmia was defined as the occurrence of either ventricular tachycardia or fibrillation during the in-hospital stay. Shock was defined as hypotension requiring the administration of vasopressors.

Statistical Analysis Associations between SCRA clinical factors and the study outcomes were calculated using univariate analysis, with marijuana patients as the “control” group. We calculated 95 % confidence intervals using the estimated standard error method. Chi-squared (with two-tailed Fisher’s exact test when appropriate) and Mann–Whitney test were calculated for categorical and continuous variables, respectively, with one degree of freedom and 5 % alpha (two-tailed).

Results

Clinical Characteristics Study enrollment from the original cohort of 3739 patients is summarized in Fig. 1. The demographics characteristics of the 87 patients who reported exposure to any cannabinoid are outlined in Table 1. There were no

Fig. 1 Study enrollment

significant differences between groups with respect to demographics or intent of exposure (suicidality, recreational, and misuse).

Based on the initial basic chemistries gathered as part of the routine clinical care, there were no significant differences between SCRA vs. marijuana with respect to any of the following: sodium (139 vs. 140.7, mean difference = −1.7 mEq/L), glucose (138.9 vs. 110.8, mean difference = +28.1 mg/dL), potassium (3.9 vs. 3.8, mean difference = 0.1 mEq/L), chloride (102.8 vs. 103.5, mean difference = −0.7 mEq/L), bicarbonate (25.0 vs. 26.4, mean difference = −1.4 mEq/L), BUN (14.8 vs. 13.3, mean difference = +1.6 mg/dL), creatinine (1.03 vs.

1.02, mean difference = +0.01 mg/dL), or lactate (2.88 vs. 2.44, mean difference = +0.44 mEq/L).

Electrocardiographic data were available for 82 patients (15 SCRA and 67 marijuana). There were no significant associations with SCRA with respect to the following computer-generated parameters: Rate (100.0 vs. 88.6, mean difference = +11.4 bpm), QRS (90.0 vs. 88.4, mean difference = +1.6 ms), or QTc (448.3 vs. 441.4, mean difference = +6.9 ms).

Main Results Cardiovascular profiles of patients are summarized in Table 2. There were no differences between groups with respect to initial ED heart rate or blood pressure. Dysrhythmia was significantly associated with SCRA (OR = 9.2, CI = 1.01–108). There was no association between SCRA exposure and myocardial injury.

Neurological profiles of patients are summarized in Table 3. There were no differences between groups with respect to initial GCS, proportion of altered mental status, coma, or delirium. SCRA exposure was associated with higher rates of agitation (OR = 3.8, CI = 1.2–11.9).

Discussion

This is the first human study comparing the clinical effects of synthetic cannabinoid receptor agonists (SCRAs) vs. marijuana controls in an ED population of acute drug overdose. We found that SCRA overdose was significantly associated with more severe clinical toxicity than marijuana, including neurotoxicity and cardiotoxicity. These results should be used to

Table 1 Demographics of study population

Clinical characteristics	SCRA	Marijuana
Mean Age	37.5	39.3
Males	76.4 %	77.1 %
Race		
Black	9 (53 %)	28 (40 %)
White	5 (29 %)	35 (50 %)
Asian	1 (6 %)	1 (1 %)
Other	2 (12 %)	6 (9 %)
Hispanic*	4 (24 %)	22 (31 %)
Intent		
Suicide	4 (24 %)	12 (17 %)
Drug abuse	13 (76 %)	67 (96 %)
Unintentional	0	1 (1 %)
Co-ingestions		
Single drug	1 (6 %)	3 (4 %)
Multi-drug	16 (94 %)	67 (96 %)
Mean # exposures	3.2	3.0
Total	17	70

*Hispanic ethnicity was considered as separate from race (BWA0).

No substantial/significant differences between groups with respect to demographics, or intent of exposure.

Abbreviations: SCRA synthetic cannabinoid receptor agonist

Table 2 Cardiovascular profiles of patients

Characteristic	SCRA	Marijuana
Heart rate (mean bpm)	102.0	94.4
SBP (mean mmHg)	146.0	135.4
DBP (mean mmHg)	84.3	77.6
Cardiotoxicity**	4 (23.5 %)	3 (4.3 %)
Dysrhythmia*	2 (11.8 %)	1 (1.4 %)
VT	1 (5.9 %)	1 (1.4 %)
VF	1 (5.9 %)	0
TdP	0	0
Shock	0	0
Myocardial injury	2 (11.8 %)	3 (4.3 %)
Total	17	70

Initial/triage ED vital signs are listed. Cardiotoxicity defined as in-hospital occurrence of any of the following: dysrhythmia, shock, and myocardial injury

Abbreviations: bpm beats per minute, DBP diastolic blood pressure, mmHg millimeters mercury, SBP systolic blood pressure, SCRA synthetic cannabinoid receptor agonist, TdP Torsades des pointes, VT ventricular tachycardia, VF ventricular fibrillation

* $p < 0.05$; ** $p < 0.01$

Table 3 Neurological profiles of patients

Characteristic	SCRA	Marijuana
GCS (median, IQR)	14.5, 14–15	15.0, 14–15
Altered mental status (any)	9 (52.9 %)	34 (48.6 %)
Coma	1 (5.8 %)	2 (2.9 %)
Agitation*	7 (41.2 %)	11 (15.7 %)
Delirium	0 (0 %)	5 (7.1 %)
Total	17	70

Initial ED mental status is listed

Abbreviations: GCS Glasgow coma scale, IQR interquartile range, SCRA synthetic cannabinoid receptor agonist

* $p < 0.05$

inform treating healthcare providers in attempts to prevent adverse clinical outcomes following SCRA overdoses, especially given that SCRA abuse and overdose will likely become more common in the years to come.

Our findings of agitation and cardiac dysrhythmia suggest an atypical sympathomimetic SCRA toxidrome. Interestingly, sympathomimetic effects were previously described in case reports of SCRA ingestion. In two cases published by Schneir et al in 2010, both patients reported feeling “anxious” and one was found to be tachycardic on arrival to the ED [7]. These patients felt the need to activate Emergency Response Services after smoking an SCRA called “Banana Cream Nuke.” It appears what concerned these patients was that they felt disoriented, “as if [they] didn’t know where [they] were.” The authors submitted the packets for analysis and identified compounds JWH-018 and JWH-073. Similarly, case reports from several authors indicate significant variability in the content of these packets; this presents a challenge in studying the clinical effects of SCRA as a class [17]. Further, it is unclear whether these patients had any underlying mental illness or addiction to other drugs of abuse. Effects of various different SCRA compounds on patients with pre-existing psychiatric comorbidity is even more challenging to study.

Case reports of SCRA use have reported psychiatric presentations including agitation [7] and psychosis [18], and the present study’s association of SCRA use with agitation adds credence to these case report findings. To add complexity to the interpretation of these findings, there are likely many users of SCRA who have underlying mental illness. A study from New Zealand conducted semi-structured interviews with 15 mentally ill patients who had used and SCRA containing substance called “Aroma” [9]. Results found that 100 % of the sample described psychoactive effects after ingesting Aroma; 69 % reported having psychotic symptoms; 15 % reported feeling anxious. Five patients endorsed symptoms of psychotic relapse within 24 h of smoking Aroma, which lasted anywhere from hours to several weeks. This qualitative study sheds light on an important issue regarding the possibility of

novel and deleterious effects of SCRA on mentally-ill individuals. Further studies of psychiatric effects of SCRA abuse are warranted to determine whether SCRA abuse may cause psychiatric sequelae independent of prior psychiatric medical conditions [19].

Our findings of cardiotoxicity associated with SCRA use add to a growing body of evidence in this regard. Scattered reports suggest that there is a potential association between traditional cannabis use and cardiotoxicity, as summarized in a recent report from the Euro-DEN group [20]. One possible mechanism of myocardial depression and conduction abnormalities due to cannabinoid receptor agonism includes blockade of Na⁺ channel and inhibition of Na⁺/Ca²⁺ exchanger in cardiac myocytes [21–23]. Many case reports of SCRA toxicity describe patients presenting with tachycardia [24], and even junctional bradycardia [8], after SCRA exposure. Young et al. describe a 17-year-old man who presented to the ED with pounding chest pain, pressure, dyspnea on exertion, and hallucinations 10 min after smoking K9 (SCRA) [8]. He endured a lengthy hospital stay with continued chest pain unresponsive to nitroglycerin. This patient, however, had co-ingested Oxyelite (a diet pill containing caffeine) along with smoking the K9. Thus, it is unclear if the resultant cardiotoxicity was in part due to the combination of the SCRA and the “diet pill”. In addition to these reports, other cases have noted myocardial infarction [25], QT prolongation [26], and sudden cardiac death [27] following SCRA exposure. Therefore, the associations of the present study with cardiotoxicity are both consistent with, and add to, the current understanding of SCRA-related cardiotoxicity.

This is the first controlled study comparing the clinical effects of SCRA vs. marijuana in an ED population of acute drug overdose. Questions raised by the current study require subsequent validation, most importantly the association with dysrhythmia. Since the seizure prevalence and non-lethal dysrhythmias (e.g., supraventricular tachycardias) were unanswerable by this study, future studies should address these as well. Finally, future clinical trials investigating the optimal treatment and management regimens for SCRA overdose are warranted.

Limitations This subgroup analysis has some possible limitations, including self-reported SCRA data (i.e., no GCMS confirmation of SCRA), which may represent misclassification bias; however, all patients in the SCRA subgroup had self-reported and clinician-documented exposure to SCRA; therefore, this is unlikely a true limitation. Furthermore, all patients in the marijuana subgroup had positive urine toxicology screens. Some potential toxicities, most notably seizures and psychosis, could not be assessed given their absence from the original data collection instrument. Because multi-drug exposures were included, effects may be incorrectly ascribed to marijuana or SCRA and may in fact represent effects from

other exposures; however, given the biological plausibility of the clinical findings, this also is unlikely a true limitation. It is possible that trained research assistant availability was a limitation for nights and weekends; however, charts were reviewed and screened for the prior night and weekend regularly so this is unlikely a true limitation. And finally, small numbers over a number of years may introduce limitations about the current validity, reliability, and transferability of these data; however, our findings represent an important first controlled study in understanding differences between SCRA and marijuana toxicity.

Conclusions

In the first clinical study comparing the adverse effects of SCRA overdose vs. marijuana controls in an ED population, we found that SCRA overdose was significantly associated with more severe clinical toxicity than marijuana. Adverse effects included significant associations with neurotoxicity and severe cardiotoxicity. Future studies should assess the optimal treatment modalities to prevent adverse clinical outcomes following SCRA overdoses.

Acknowledgments None.

Sources of funding This study was supported in part by grant K23DA026476 from the National Institute on Drug Abuse (PI: AFM). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute on Drug Abuse or the National Institutes of Health.

Compliance with ethical standards

Conflicts of interest None.

Previous presentations Presented in abstract form at the XXXV International Congress, European Association of Poisons Centres and Clinical Toxicologists, St. Julian's, Malta, 2015.

References

1. Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, Huestis MA. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug Alcohol Depend.* 2014;1(144):12–41.
2. Guindon J, Hohmann AG. The endocannabinoid system and pain. *CNS Neurol Disord Drug Targets.* 2009;8(6):403–21.
3. Vardakou I, Pistos C, Spiliopoulou C. Spice drugs as a new trend: mode of action, identification and legislation. *Toxicol Lett.* 2010;197(3):157–62.
4. Rosenbaum CD, Carreiro SP, Babu KM. Here today, gone tomorrow ... back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones (bath salts), kratom, *Salvia divinorum*, methoxetamine, and piperazines. *J Med Toxicol.* 2012;8:15–32.
5. Hermanns-Clausen M, Kithinji J, Spehl M, Angerer V, Franz F, Eyer F, et al. Adverse effects after the use of JWH-210 - a case series from the EU Spice II plus project. *Drug Test Anal.* 2016; Jan 15.
6. Hermanns-Clausen M, Kneisel S, Szabo B, Auwärter V. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: clinical and laboratory findings. *Addiction.* 2013;108(3):534–44.
7. Schneir AB, Cullen J, Ly BT. “Spice” girls: synthetic cannabinoid intoxication. *J Emerg Med.* 2011;40:296–9.
8. Young AC, Schwarz E, Medina G, Obafemi A, Feng SY, Kane C, et al. Cardiotoxicity associated with the synthetic cannabinoid, K9, with laboratory confirmation. *Am J Emerg Med.* 2012;1320:e5–7.
9. Every-Palmer S. Warning: legal synthetic cannabinoid-receptor agonists such as JWH 018 may precipitate psychosis in vulnerable individuals. *Addiction.* 2010;105:1859–60.
10. Müller H, Sperling W, Köhrmann M, Huttner HB, Kornhuber J, Maler JM. The synthetic cannabinoid Spice as a trigger for an acute exacerbation of cannabis induced recurrent psychotic episodes. *Schizophr Res.* 2010;118:309–10.
11. Zimmermann US, Winkelmann PR, Pilhatsch M, Nees JA, Spanagel R, Schulz K. Withdrawal phenomena and dependence syndrome after the consumption of “Spice Gold”. *Dtsch Arztebl Int.* 2009;106:464–7.
12. Forrester MB, Kleinschmidt K, Schwarz E, Young A. Synthetic cannabinoid and marijuana exposures reported to poison centers. *Hum Exp Toxicol.* 2012;31(10):1006–11.
13. Tait RJ, Caldicott D, Mountain D, Hill SL, Lenton S. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clin Toxicol (Phila).* 2016;54(1):1–13.
14. Gunderson EW, Haughey HM, Ait-Daoud N, Joshi AS, Hart CL. “Spice” and “K2” herbal highs: a case series and systematic review of the clinical effects and biopsychosocial implications of synthetic cannabinoid use in humans. *Am J Addict.* 2012;21(4):320–6.
15. Manini AF, Nelson LS, Stimmel B, Vlahov D, Hoffman RS. Incidence of adverse cardiovascular events in adults following drug overdose. *Acad Emerg Med.* 2012;19(7):843–9.
16. Manini AF, Hoffman RS, Stimmel B, Vlahov D. Clinical risk factors for in hospital adverse cardiovascular events after acute drug overdose. *Acad Emerg Med.* 2015;22(5):499–507.
17. Winstock A, Mitcheson L, Ramsey J, Marsden J. Mephedrone: use, subjective effects and health risks. *Addiction.* 2011;106(11):1991–6.
18. Oluwabusi O, Lobach L, Akhtar U, Youngman B, Ambrosini PJ. Synthetic cannabinoid induced psychosis: two adolescent cases. *J Child Adolesc Psychopharmacol.* 2012;22:393–5.
19. Peglow S, Buchner III J, Briscoe G. Synthetic cannabinoid induced psychosis in a previously nonpsychotic patient. *Am J Addict.* 2012;21:287–8.
20. Dines AM, Wood DM, Galicia M, Yates CM, Heyerdahl F, Hovda KE, et al. Euro-DEN research group, dargan PI. Presentations to the emergency department following cannabis use—a multi-centre case series from ten European countries. *J Med Toxicol.* 2015;11(4):415–21.
21. Al Kury LT, Voitychuk OI, Ali RM, et al. Effects of endogenous cannabinoid anandamide on excitation-contraction coupling in rat ventricular myocytes. *Cell Calcium.* 2014;55:104–18.
22. Al Kury LT, Voitychuk OI, Yang KH, et al. Effects of the endogenous cannabinoid anandamide on voltage-dependent sodium and calcium channels in rat ventricular myocytes. *Br J Pharmacol.* 2014;171:3485–98.
23. Al Kury LT, Yang KH, Thayyullathil FT, et al. Effects of endogenous cannabinoid anandamide on cardiac Na(+)/Ca(2)(+) exchanger. *Cell Calcium.* 2014;55:231–7.

24. Lapoint J, James LP, Moran CL, Nelson LS, Hoffman RS, Moran JH. Severe toxicity following synthetic cannabinoid ingestion. *Clin Toxicol (Phila)*. 2011;49(8):760–4.
25. Mir A, Obafemi A, Young A, Kane C. Myocardial infarction associated with use of the synthetic cannabinoid K2. *Pediatrics*. 2011;128:e1622–7.
26. Von Der Haar J, Talebi S, Ghobadi F, Singh S, Chirugi R, Rajeswari P, et al. Synthetic cannabinoids and their effects on the cardiovascular system. *J Emerg Med*. 2016;50(2): 258–62.
27. Ibrahim S, Al-Saffar F, Wannenburg T. A unique case of cardiac arrest following K2 abuse. *Case Rep Cardiology*. 2014;2014.