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TOXICOLOGY OBSERVATION

Cluster of Acute Toxicity from Ingestion of Synthetic Cannabinoid-Laced Brownies

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Abstract
Introduction Synthetic cannabinoid receptor agonists (SCRAs) are emerging designer drugs of abuse. Most reports on the health effects of these drugs are case reports. Unlike SCRAs, marijuana has classically been used via many routes of exposure including oral, such as in brownies. We report on 11 symptomatic patients who unknowingly ingested brownies laced with analytically confirmed SCRA and presented with mostly neuropsychiatric and cardiovascular symptoms.
Case Series All 11 patients were taken to the ED within 1 h of exposure with the onset of various symptoms. There were five males and six females, age range 20–57 years. Neuropsychiatric and cardiovascular symptoms predominated: memory impairment (91 %, 10/11) and inappropriate giggling (36 %, 4/11). All the patients had light-headedness, perioral and facial numbness and tingling sensation, dry mouth, difficulty focusing/blurring of vision, and sluggishness. No patient had depressed consciousness. Two patients had heart rates >100, and 4 of 11 (36 %) had BP >140/80. One patient had chest pain. All the symptoms were completely resolved 4 h following their onset except two patients who had ongoing weakness and fatigue. All patients had negative urine drugs of abuse immunoassays and ethanol, acetaminophen, and salicylate concentrations, as well as normal electrocardiograms (ECGS) and metabolic panels. The SCRA was confirmed to be AM-2201. All the patients were discharged from the ED in stable condition within 10 h of the exposure.
Conclusion Oral exposure of 11 patients to brownies laced with analytically confirmed SCRA resulted in neuropsychiatric and cardiovascular symptoms. This series reflects that like marijuana, oral exposures to SCRAs can lead to symptoms.

Keywords Synthetic cannabinoid receptor agonists · Cannabis · Acute toxicity · Tachycardia · Novel psychoactive substance

Introduction

New emerging designer recreational drugs continue to flood the market even as governments around the world are taking steps to control the availability and access to these drugs through legislation and scheduling. The rate of introduction of these drugs seems to outpace the capacity of the regulatory bodies to control access to them. Mostly these drugs are disguised as either nutritional supplement or as "incense blend," "not for human consumption," and sold in head shops, gas stations, and on the Internet [1–3].

Synthetic cannabinoid receptor agonists (SCRAs) are emerging designer recreational drugs. They were originally developed in the 1960s as tools to learn more about cannabinoid receptors and as potential pharmaceutical agents [2]. Today, they are also used for recreational purposes because of their desired psychoactive effects, ease of acquisition, relative legality, and inability to be detected in standard urine drug screens [4]. They are marketed as incense blends of herbs under different names such as "Spice" in Europe and "K2" in the USA [5]. These blends contain different SCRAs including the John William Huffman (JWH) series developed by John W. Huffman while working at Clemson University, HU series

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developed by Hebrew University, cyclohexylphenol (CP) series developed by Pfizer, and the newer SCRAs such as AM-2201 and ADB-PINACA, both also known as Black Mamba [4, 6]. The European Monitoring Center for Drugs and Drug Addiction (EMCDDA) reported in December 2009 the detection of SCRAs in Spice products; the same period when the first formal report of SCRAs trafficking in the USA was reported [1, 3, 7]. Because of their widespread use by young adults [8, 9], in 2011, five SCRAs including JWH-018, JWH-073, JWH-200, CP 47-497, and CP-47,497C8 were categorized as scheduled 1 drug under the Control Substance Act in the USA [3]. The number of newly available SCRAs is constantly expanding; many new SCRAs have been synthesized and introduced into the market following the scheduling of the five drugs prompting the DEA in November 2013, under its emergency scheduling authority, to include four additional SCRAs (PB-22, 5F-PB-22, AB-FUBINACA, and ADB-PINACA) [10].

Synthetic cannabinoid receptor agonists act on the same endogenous cannabinoid receptors as THC; however, studies have suggested that they may have different clinical effects [11–13]. Many case reports have reported on neurologic and cardiovascular toxicity of SCRAs [5, 14–16]. SCRAs are usually smoked as a blend of unknown herbs laced with single or mixture of synthetic cannabinoid receptor agonists [12]. Clinical effects among users vary; comparisons are difficult because of the lack of analytic confirmation. We report on 11 symptomatic patients who unknowingly ingested brownies laced with an analytically confirmed SCRA.

Case Series

Eleven staff (five males and six females; age range 20–57 years) in an inpatient unit of a large hospital had lunch together in a break room. One of the staff whose employment was later terminated based upon subsequent campus police investigations brought brownies that had been allegedly adulterated by her son. One brownie was eaten by each of the 11 staff. All patients were taken to the ED within 1 h of eating the brownies following the onset of various symptoms (Table 1). Because of the group illness, ED personnel assessed for a common source of exposure. The brownies were the only common food item ingested by all the staff. The toxicology service evaluated all 11 patients while they were in the ED, and they all denied history of drug use including SCRAs.

Neuropsychiatric symptoms predominated: memory impairment (91 %, 10/11) and inappropriate giggling (36 %, 4/11) (Table 1). There were no gastrointestinal or respiratory symptoms reported. All the symptoms were completely resolved 4 h following their onset except two patients who had ongoing weakness and fatigue that lasted for 10 h (Table 1).

All patients had negative routine urine drugs of abuse immunoassays, negative ethanol concentrations, and normal electrocardiograms (ECGs) and electrolytes. All the patients were discharged from the ED in stable condition within 10 h of the exposure.

The remaining brownie was analyzed by the Texas Department of Public Safety laboratory using gas chromatography mass-spectrometry (GC-MS) and was found to be positive for the synthetic cannabinoid receptor agonist AM-2201. Nothing else was detected.

Discussion

We have described the first case series of accidental intoxication by the synthetic cannabinoid receptor agonist AM-2201 by ingestion of adulterated brownies in a group of 11 individuals. In addition, this is the first case series to describe acute onset toxicity following inadvertent ingestion of brownies laced with synthetic cannabinoid receptor agonist AM-2201. The most frequently observed symptoms in this series were dry mouth, tingling sensation, memory impairment, lightheadedness, difficulty focusing, blurring of vision, and inappropriate giggling and laughing. Similar symptoms have been reported in patients who were exposed to marijuana [17, 18]. However, there were no gastrointestinal symptoms that would be expected with marijuana intoxication. More intense symptoms of SCRA intoxication including myocardial infarction, seizures, acute kidney injury, hyperthermia, and rhabdomyolysis following inhalational exposure have also been reported [5, 15, 16, 19, 20]. None of these severe symptoms were noted in our case series. The lack of severe symptoms may be related to a low dose of SCRAs within the brownies or to decreased bioavailability of the SCRAs after ingestion, although the concentration of AM-2201 within the brownies and its bioavailability after ingestion were not measured.

Synthetic cannabinoid receptor agonists were first recognized as novel psychoactive substances in Europe in early 2000s, and subsequently, the JWH-018, CP-47, 497, and HU-210 series were banned in Europe and Russia in 2010 [12, 21]. According to forensic laboratory reports, the initial appearance of SCRAs in the USA occurred in November 2008, where it was sold in head shops, gas stations, and on the Internet as “incense blend” [12, 22–24]. Most users are attracted to SCRAs because of its supposed similarity to marijuana, and unlike marijuana, it is not routinely detected in urine drug screen [6, 10]. Classically marijuana has been used via many routes of exposure including ingestion such as in brownies, whereas SCRAs are usually smoked. In our series, SCRA route of exposure was oral ingestion of the brownies.

Synthetic cannabinoid receptor agonists are thought to have cannabinoid-like effects, acting on the cannabinoid CB1 and CB2 receptors in the brain and immune system, respectively. CB1 receptors mediate the CNS effects of delta-9 THC, the active compound in *Cannabis sativa*, while

Table 1 Demographics and clinical features of 11 adults who unknowingly ingested brownies laced with SCRA AM-2201

Age (years)	Sex	Symptoms and signs (Y/N)						Symptom onset after eating brownie (min)	Symptom duration (h)
		Numbness and tingling sensation	Dry mouth	Difficulty focusing and blurring of vision	Light-headed	Memory impairment	Giggling		
38	M	Y	Y	Y	Y	Y	N	35	4
20	M	Y	Y	Y	Y	Y	Y	30	3
28	F	Y	Y	Y	Y	N	N	35	3
52	F	Y	Y	Y	Y	Y	N	60	4
35	F	Y	Y	Y	Y	Y	Y	25	4
41	F	Y	Y	Y	Y	Y	Y	30	4
56	M	Y	Y	Y	Y	Y	N	35	10
29	M	Y	Y	Y	Y	Y	N	25	2
56	F	Y	Y	Y	Y	Y	Y	60	4
57	F	Y	Y	Y	Y	Y	N	35	10
24	F	Y	Y	Y	Y	Y	N	45	2
total	11	11	11	11	11	10	4		

Y symptom, *N* no symptom

CB2 receptors mediate the immunomodulatory effects of the cannabinoids throughout the body [1, 3]. As a result, it is not surprising that some studies have described behavioral effect similar to those seen following consumption of marijuana in those exposed to SCRAs [11–13]. In April 2009, the CDC reported on a group of preschool teachers with nausea, dizziness, numbness, and tingling of fingertips after consumptions of brownies laced with marijuana, the same symptoms that were exhibited by patients in our case series following ingestion of brownies laced with SCRAs [18].

Forrester and others compared synthetic cannabinoid receptor agonists with marijuana exposures and found that hypertension, tachycardia, agitation, and hallucination were significantly more prominent with SCRA exposure. They concluded that SCRAs yield very different clinical effects than marijuana [11, 13]. THC is a weak partial agonist of the CB1 receptors, while most SCRAs in K2/Spice are full agonists with very high potency compared to delta-9 THC [3]; this may explain the intensity of the symptoms and signs seen in patients exposed to SCRAs. However, neuropsychiatric symptoms predominated in our case series, similar to the neurobehavioral effects observed with chronic cannabis use [25].

In our series, the onset of symptoms was between 25 and 45 min for nine of the 11 patients. In the remaining two patients, the onset of symptoms was 60 min after ingestion of the brownies. Also, the duration of symptoms was between 2 and 4 h in the majority of the patients. Fatigue and weakness persisted in two patients for up to 10 h following the exposure. A similar case series on inadvertent oral consumption of marijuana by five patients reported symptom onset of 30–180 min and symptom duration of 3–10 h [18]. In a double-blind crossover study following ingestion of 1.6 g of marijuana-laced brownies, Cone and others reported a peak behavioral effect of 2.5 to 3.5 h after consumption [17]. Although SCRAs have high potency at the CBI receptor compared to delta-9 THC [3, 26], the time to onset of symptoms and duration of action in our SCRAs series were similar to the marijuana series.

It is not surprising that the National Institute for Drug Abuse initial urine drug screen (UDS) panels were negative in our patients because SCRAs are not part of these UDS panels. Some users of SCRAs are attracted to the drug because it is not detected in standard UDS [4, 7]. It has been suggested that SCRAs should be considered and tested for in marijuana cases where no THC or metabolites were detected [2].

To our knowledge, this is the first case series of individuals becoming symptomatic following ingestion of brownies laced with the SCRA AM-2201. These patients were unaware of the contents of the brownies, but they all shared common clinical features, predominantly neuropsychiatric symptoms. These cases reflect that oral SCRAs can cause adverse effects. The limitation of this case series is that there was no screening of biological samples collected from individuals in this case series.

Conclusions

Clinicians need to consider oral exposure to SCRAs as potential etiology in patients presenting with unexplained symptoms.

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