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CLINICAL CASE STUDIES

Synthetic Cannabinoid Intoxication Presenting as Malignant Catatonia: a Case Report

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Abstract The use of synthetic cannabinoids (SCs) has been steadily increasing in recent years and represents a new class of substances of abuse. Despite they elicit cannabimimetic effects similar to Δ9-tetrahydrocannabinol (THC), they have stronger affinities to the endocannabinoid system and cause greater psychiatric and medical effects. Case reports of catatonia following SC use have been sporadically described in the literature, but the underlying mechanisms behind these symptoms are unclear. In this article, we present a case of a patient who presented in a state of malignant catatonia following SC use, and we discuss the possible underlying mechanisms behind this association.

Keywords Synthetic cannabinoids · Catatonia · Movement disorders

The use of synthetic cannabinoids (SCs) has been steadily increasing in recent years and represents a new class of substances of abuse (Bulbena-Cabre et al. 2013). They first appeared in the 1960s in research laboratories that explored potential medical uses of the endocannabinoid system. These new classes of substances elicit cannabimimetic effects similar to Δ9-tetrahydrocannabinol (THC); however, while THC acts as partial agonist of the cannabinoid receptors (CB1 and CB2), SCs have higher affinity and act as full agonists of

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those receptors (Castaneto et al. 2014). In fact, SCs have 2–100 times more potent pharmacological effects and significantly greater physiological and psychoactive effects compared to regular THC (Castaneto et al. 2014).

The psychiatric manifestations of the SC intoxication are variable and include agitation, altered mental status, paranoid behavior, psychosis, and seizures among others (Bulbena-Cabre et al. 2013; Castaneto et al. 2014). Additionally, it has been proven through analysis of the herbal mixture components that these products do not contain what the package discloses (Hassen et al. 2015). Nausea, pallor, hyperventilation, diaphoresis, headache, numbness, seizures, muscle twitching, and autonomic hyperactivity have also been described as side effects of SCs (Gunderson et al. 2012). Additionally, Winstock et al. estimated that the risk of requiring emergency medical treatment is between 14 and 30 times greater following the use of SCs compared with traditional THC (Winstock et al. 2015). Case reports of catatonia following SC use have been sporadically described in the literature (Haro et al. 2014; Khan et al. 2016; Leibu et al. 2013; Smith and Roberts 2014), but the exact underlying mechanisms of this association remain unclear.

In this article, we present a case of SC intoxication that presented in a state of malignant catatonia, and we discuss the possible underlying mechanisms behind this symptomatology.

Case Presentation

Mr. X was a 50-year-old male with no significant medical or psychiatric history. He was brought to the medical emergency room (ER) via ambulance after he was found unresponsive, rigid, and stuporous in a park. On arrival, his heart rate was 134 bpm, blood pressure 132/72 mmHg, respiratory rate of 24′, and temperature 103.5 °F. Physical examination was significant for posturism, mutism, and rigidity and he did not respond to stimuli. The routine urine toxicology screen was negative for illicit substances including cocaine, benzodiazepine, phencyclidine (PCP), THC, and opiates, and the blood alcohol level was 0 mg/dL. A sample of urine was also sent to an external laboratory to perform a liquid chromatograph with mass spectrograph to rule out SC intoxication. The urinalysis, complete blood test, basic metabolic profile, liver function tests, and thyroid-stimulating hormone were within normal limits except for mild leukocytosis $11.6 \times 103/mm^3$ (reference range $4.0–10.0 \times 103/mm^3$) and elevated creatinine phosphokinase which was 240 U/L (reference range 5–130 U/L). His chest radiography (CXR), head computerized tomography (CT) scan, and electroencephalogram (EEG) were negative for any acute abnormalities. While in the ER, he received intravenous hydration with 2 L of 0.9% sodium chloride saline solution and also a total of 4 mg IV midazolam. He was admitted to the medical ward for observation where he was treated with further hydration (3 L of 0.9% sodium chloride saline) and a total of 2 mg of IV lorazepam and 8 mg of IM lorazepam to treat his catatonic symptoms. He also received a total of 50 mg of IV dexamethasone during his inpatient admission while meningitis was being ruled out by subsequent cerebrospinal fluid (CSF) cultures. The patient began to improve on his second day of admission, and by day 5, the catatonic symptoms resolved and his mental status examination was unremarkable showing no acute psychiatric symptoms. He then admitted to smoking SCs prior to coming to the hospital although he was unable to provide specific details about the "k2" type.

The differential diagnosis included neuroleptic malignant syndrome (NMS), but it was unlikely due to the lack of neuroleptic use and the positive response to the lorazepam challenge.

Other possible diagnoses that were considered included non-convulsive status epilepticus that was ruled out after the normal head CT and EEG and CNS infection, but the blood and CSF cultures had no growth on his third day of admission ruling out an infectious etiology.

He was discharged home after 7 days on no medications, and a referral to an outpatient substance abuse program was provided. Approximately 4 weeks after his discharge, the results of the qualitative synthetic cannabinoid analysis were negative for the following SC compounds: JWH-018 and metabolites, JWH-073 and metabolites, JWH-122 and metabolites, JWH-200 and metabolites, JWH-250 and metabolites, JWH-398 and metabolites, RCS-4 metabolites, AM-2201 metabolites, UR-144 metabolites, and XLR-11 metabolites.

Discussion

In this paper, we present the case of a patient with no significant past medical or psychiatric history who presented to the hospital with malignant catatonia after using SCs. The published evidence linking catatonia to SC use presents similar cases of young adults with no significant medical problems (Haro et al. 2014; Khan et al. 2016; Leibu et al. 2013; Smith and Roberts 2014), which emphasizes the severe health consequences of using SCs. Most of these papers highlight the importance of not only educating physicians and healthcare workers but also reaching out to communities, schools, shelters, and group homes to raise awareness about synthetic cannabis health risks.

SC intoxication is a clinical diagnosis and relies mainly on patient's history or self-reports of SC use and the clinical presentation (Bulbena-Cabre et al. 2013). They are non-detectable by routine drug screening tests, and in fact, this is one of the main reported motivations for its use (Gunderson et al. 2014). During the past few years, research has focused on identifying different techniques to detect SCs in biological specimens (Seely et al. 2012). In this case, we used a liquid chromatography that came back negative for ten subtypes of SCs and their metabolites, but the composition of SCs constantly changes to escape from FDA regulations and it is estimated that there are over 140 different SC compounds. Therefore, a negative liquid chromatography cannot rule out SC intoxication.

This patient presented with catatonic-like symptoms, unstable vital signs, and leukocytosis following SC use, and the symptoms resolved with hydration and benzodiazepines, which is suggestive of SC-induced malignant catatonia. Malignant catatonia is a subgroup of catatonia that presents with motor deficiencies and severe level of metabolic decompensation and is usually accompanied by autonomic instability.

Catatonia was initially described by Kahlbaum in the nineteenth century as a psychomotor syndrome with motor, affective, and behavioral symptoms; however, later nosology had classified catatonia into a motor deficiency in schizophrenia (Wilcox and Reid Duffy 2015). Recently, the new Diagnostic and Statistical Manual (DSM¬5) of the American Psychiatric Association (2013) documented a modern specification of the catatonic syndrome and reports that catatonia can be found in a variety of disorders and is not specific to schizophrenia (Association). The literature describes the pathophysiology of catatonia as an increase of glutamate (the main excitatory neurotransmitter) and loss of inhibitory signals in some key brain areas involved in movement as a result of decreased activity of D2 and G-aminobutyric acid GABA neurons (Soltanianzadeh et al. 2016; Wilcox and Reid Duffy 2015).

The endocannabinoid receptors are particularly abundant in basal ganglia structures (e.g., caudate-putamen, globus pallidus, substantia nigra) compared to those in other brain regions

(Bisogno et al. 1999). In fact, the CB1 receptors are located in striatal neurons projecting to the substantia nigra pars reticulate/internal globus pallidus and the external globus pallidus, both key motor areas (Bisogno et al. 1999). Both groups of neurons use GABA as a neurotransmitter, although they also express selective phenotypical markers (e.g., encephalin and D2 receptors in striatopallidal neurons and dynorphin/substance P and D1 receptors in striatonigral neurons) (Fernández-Ruiz 2009). Research showed that substances that activate the cannabinoid signaling (e.g., direct receptor agonists such as k2 or spice) have powerful effects on the control of the movement areas, mostly of inhibitory nature (Crawley et al. 1993; Sañudo-Peña et al. 2000). In light of these results, the endocannabinoid system is being studied as a treatment for motor dysfunction diseases such as Parkinson's disease or Huntington Chorea among others (Fernández-Ruiz 2009).

Additionally, several studies have shown that SCs also have important effects on the cardiovascular system (Mukhopadhyay et al. 2008; Pacher et al. 2005), which may explain the autonomic instability seen in this patient. Those studies showed that the cardiovascular effects of SCs are complex and may involve modulation of autonomic outflow in the central and peripheral nervous systems as well as direct effects on the myocardium and vasculature, which may represent a promising target for cardiovascular diseases.

However, it is important to note that several thousands of compounds that are not always chemically related are being considered SCs, and thus, a very wide range of medical consequences can be seen. Medical but also psychiatric emergency staff should be aware of these dangerous effects, which appear as a life-threatening condition together with typical catatonic features.

Conclusion

In this case, the patient displayed catatonia and significant autonomic instability after smoking SCs. These findings would be consistent with the hypothesis that SCs are strong full agonists of the endocannabinoid system causing severe movement and cardiovascular abnormalities among other symptoms. Physicians and healthcare professionals should be familiar and vigilant about this unusual but lethal side effect, and more efforts should be made to educate the community and the high-risk populations. Research should further study the composition and safety of SCs and expand the knowledge on the potential side effects of these substances.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval This is a retrospective case report study; for this type of study, formal consent is not required. Patient identification information has been de-identified.

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