Synthetic Cannabinoid Receptor Agonists (SCRAs) Induced Seizure: A Case Report

Sentetik Kannabinoid Reseptör Agonisti Kullanımına Bağlı Nöbet: Olgu Sunumu

Merih Altıntaş[1], Murat Kuru[2]

ABSTRACT

With an ever-increasing prevalence, exposing new challenges to healthcare personnel, the use of synthetic cannabinoid receptor agonists (SCRAs) affects many systems. Clinical manifestations that may be caused by it become more predictable day by day thanks to increasing number of case reports on this issue. The use of these substances gives rise to serious side effects, which in turn affect psychiatric, neurological, cardiovascular, renal and pulmonary systems. Recently, there are a growing number of reports indicating that SCRAs would lead to seizures. It is considered that notably the patients referred to emergency rooms due to SCRA induced toxicity may be experiencing a series of life-threatening clinical presentations, one of which would probably be seizure, and which may sometimes require intensive care follow-up. This shows that all clinicians and the society should be highly aware of and get prepared for potential hazards to be triggered by use of SCRAs. This report makes mention of a case where a patient without any record of seizure in his medical history, who experienced his first epileptic seizure following SCRAs induced intoxication, and where the seizure was hardly terminated.

Key Words: Synthetic cannabinoid receptor agonist, cannabis, seizure.

ÖZET

Yaygınlığı her geçen gün artan ve sağlık çalışanlarını yeni problemler ile karşı karşıya bırakan sentetik kannabinoid reseptör agonistleri (SKRA) birçok sistemi etkilemektedir. Günden güne yeni bildirimler ile neden olabilecekleri klinik tablolar daha öngörülür olmaktadır. Bu maddelerin psikiyatrik, nörolojik, kardiyovasküler, renal ve pulmoner sistemi etkileyen ciddi yan etkileri mevcuttur. Son dönemlerde sentetik kannabinoid reseptör agonistlerinin nöbetlere neden olduğuna dair bildirimlerinin sayısı da artmaya başlamıştır. Özellikle acil servislere SKRA'lerinin neden olduğu toksisite nedeniyle getirilen hastalarda hayatı tehdit edebilecek bir seri klinik tablonun olabileceği ve bunlardan birinin de ciddi nöbetler olabileceği ve kimi zaman yoğun bakım takiplerinin gerekebileceği düşünülmektedir. Bu durum SKRA kullanımı sonrasında oluşabilecek potansiyel tehlikeler konusunda tüm klinisyenlerin ve toplumun haberdar ve hazırlıklı olması gerektiğini göstermektedir. Bu olgu sunumunda daha önce nöbet öyküsü olmayan, SKRA entoksikasyonu sonrası ilk epileptik nöbetini geçiren ve nöbetin güçlükle sonlandırıldığı bir olgudan bahsedilmektedir.

Anahtar Kelimeler: Sentetik kannabinoid reseptör agonisti, esrar, nöbet.

[1] Uzman Dr., Erenköy Ruh ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi, AMATEM Kliniği
[2] Asistan Dr., Erenköy Ruh ve Sinir Hastalıkları Eğitim ve Araştırma Hastanesi, Psikiyatri Kliniği

Address reprint requests to: Merih Altıntaş; Department of Psychiatry, Erenkoy Training and Research Hospital for Psychiatric and Neurological Disorders. Sinan Ercan cad. No: 29, Kazasker, Kadikoy, İstanbul - TURKEY

E-mail address: merihaltintas@yahoo.com

Phone: +90 (216) 302 59 59

Date of submission: June 14, 2016

Date of acceptance: August 20, 2016

INTRODUCTION

Synthetic cannabinoid receptor agonists (SCRAs) have recently become an important problem threatening public health. The number of reports on the intoxications following the use of these substances and resulting clinical manifestations has been increasing recently. Emergency rooms are now witnessing many cases of SCRA induced toxicity (1, 2, 3). All healthcare personnel face a state of clinical uncertainty due to heterogeneous structure and unclear content specification of these substances. Clinical manifestations that may be caused by SCRAs become more predictable day by day thanks to increasing number of the researches and case reports on this issue. However, emergence of new forms of SCRAs almost every passing day makes things much harder for clinicians. The use of these substances gives rise to serious side effects, which in turn affect psychiatric, neurological, cardiovascular, renal and pulmonary systems (4,5). There are also an increasing number of case reports and studies reporting that these substances would give rise to seizure, notably generalized tonic-clonic seizures (6). Another common characteristic of the seizures induced by SCRAs use is that they appear within a couple of hours following use of SCRAs (7). This report aims to present a case where a patient without any record of seizure in his medical history, who experienced his first epileptic seizure following SCRAs induced intoxication, and where the seizure was hardly terminated.

CASE

Presenting problem:

A 23-year-old male, single and high-school graduate patient was taken to emergency room by his relatives with complaints of staying in the bed in a sleepy mode for 24 hours without making contact with others. Suffering from use of SCRAs, the patient was observed to sweat too much, has an apparent anxiety, and difficulty in answering questions.

According to physical examination of the patient at emergency room, his blood pressure was 120/70mmHg, fever was 37.8°C and pulse rate was 130/min.

Mental state examination:

His mind was clouded with an impaired orientation. Also, a psychiatric examination of the patient revealed that his affection was irritable and troublesome, with a difficulty in becoming cooperative. His psychomotor activity was increasing from time to time, and excitation was observed. His ideations contained certain paranoid and persecuted hallucinations. His speech was quite slow and angry. As he started to toss and turn in the bed for no reason, the patient was fastened to the bed to ensure his security.

Medical History:

According to the information obtained from the patient's relatives, he first used cannabis for a couple of months, and then he began to use SCRAs. He has been using SCRAs for six years 4-5 gr /day via inhalation every day. He last intensively inhaled 24 hours ago, since then he stayed in bed in drowsiness, and he was not able to regain consciousness. Medical history of the patient made clear that he applied to AMATEM (Alcohol and Substance Addiction Treatment Center) a few times, but he continued to use substance. There was not any apparent medical or psychiatric disease pertaining to the pre-referral period. His family was stating that he had psychotic complaints whenever he used substance.

Follow up treatment:

2,5 mg haloperidol was administered parenterally with 1000 cc IV fluid. Blood samples were taken for complete blood count and biochemical analysis. Urinary test could not be performed as he was not able to provide urine. A subsequent urinary analysis indicated no substance in urine.

SCRA intoxication was thought to be the most probable one. It was planned to refer the patient urgently to another clinic having internal medicine department and intensive care unit. When making preparations for referral, the patient, under close monitoring, was observed to be experiencing

tonic-clonic spasms. With a cyanosed appearance, his oxygen saturation started to decrease. After administering 10 mg IV diazepam, the patient was referred to another clinic having intensive care unit via ambulance. Preliminary clinical rates examined at emergency room did show no specification other than leukocytosis. According to liver and kidney function tests, electrolyte, glucose and hemogram levels were within normal ranges.

It was then told that upon arrival at the clinic, the patient's tonic-clonic spasms intensified and he suffered epileptic seizure. Seizure could not be brought under control by 20 mg diazepam and 8 mg midazolam; thus he was curarized (0.6 mg/kg rocuronium bromide) and intubated with the diagnosis of status epilepticus. After this treatment, the seizure lasted and had no recurrence. He was followed up in intensive care unit for a while. To exclude the presence of an intracranial pathology, cranial computed tomography scan (CT) was found to be normal. Blood glucose level was also found to be 117 mg/dl. Hypoglycemia was excluded in the patient whose seizure etiology was investigated. The patient was monitorized and oxygen was given patient by face mask. The blood gases were measured and no significant pathology was noted. According to the results of subsequent biochemical tests, the following results were obtained creatine kinase>42670 U/L (N:30-200 U/L), ALT (alanine transaminase):1363 U/L (N:0-55 U/L), and AST (aspartate amino-transferase): 2671 U/L (N:5-34 U/L). The patient was kept under control in intensive care unit by internal medicine, anesthesia and psychiatry departments with the diagnosis of synthetic cannabinoid induced rhabdomyolysis and toxic hepatitis. After 7-8 days, his blood picture returned to normal with no observed epileptic seizure and no psychiatric complaint; accordingly he was discharged at his own request, with a recommendation of being followed up by Alcohol and Substance Addiction Treatment Center.

DISCUSSION

In the context of this case report, the patient was first evaluated at emergency room, according to which he was thought to have SCRAs induced intoxication; and immediately after such assessment, he was referred to an intensive care unit, and meanwhile he started to have myoclonic spasms and his general condition started to get worse. Then, the patient suffered a generalized tonic-clonic seizure.

The number of publications reporting synthetic cannabinoid induced toxicity is increasing day by day (8). Affecting many systems, synthetic cannabinoids are reported to be also giving rise to epileptic seizures (9). Synthetic cannabinoids may cause new-onset seizures and even coma in the individuals having no previous record in their medical history (10). Similarly, the patient in our case had no previous record of seizure in his medical history.

Even though the mechanism of potential proconvulsan impacts of SCRAs are unknown, it was asserted that they might be originating in the effects on CB1 (Cannabinoid 1) receptors (11). There are also some studies arguing that inhibition in GABA neurotransmission may be responsible for seizures (12). Absence of phytocannabinoids, as an anticonvulsant, in SCRA is considered to be one of the several reasons leading to convulsions (13). Hoyte et al. reported that 3.8% of the patients who applied to hospital after using SCRAs for a period 9 months had seizures according to national poison database (14). A 22-year-old male patient had a swiftly-generalized and self-terminating tonic-clonic convulsion after use of synthetic cannabinoid. Urinary analyses identified AM-2201. This is the first reported synthetic cannabinoid induced seizure in Europe, and also the first case showing the relationship between AM-2201 and convulsion (15).

There is another case report reporting that two patients with no prior neurological disease suffered their initial generalized tonic-clonic seizure after using SCRAs (11). Another patient who used one of SCRAs, JWH-018 with oral intake had supraventricular tachycardia and generalized seizure (16). Harris et al. reported that two of six patients referred to emergency room suffered seizure; however such seizures did not recur in those patients, whose follow-up period was almost 2.8 days (12).

Seizures were reported to be usually happening after use of SCRAs. Differently, a chronic SCRA user who suddenly stopped using substance was observed to have seizure within withdrawal

period (17). For this reason, medical history of the patients should be taken in detail, and it should be kept in mind that a patient who has suddenly stopped using SCRAs may suffer seizure, just like the case in SCRA intoxication. Schep et al. reported a case where the patient suffered seizure twice within 12 hours of SCRA intoxication (18).

One of the commonalities of these substances is that SCRAs are not detectable by conventional urine drug screening tests (1). Similarly, our patient' urinary analysis indicated no SC. However, it was known from his medical history that he had been using SCRAs, and his complaints appeared immediately after an intensive use of SCRAs.

There is another study confirming laboratory confirmed neurotoxicity; i.e., seizure of the patient and his housedog after digestion of a novel SCRA, so-called PB-22(QUPIC) (5). In parallel to our case, Tofighi et al. reported a 48-year-old male patient, who suffered loss of consciousness following use of SCRAs, experienced consecutive seizures, and recovered without having any neurological disability (10). Liver dysfunction of the patient in a short time is attention drawing. The number of publications increasingly reports hepotecellular damage caused by SCRAs related intoxications and high levels of liver enzymes.(19,20) And also a case of toxic hepatitis caused by the use of SCRAs was reported in our country (21). Therefore our case seems relevant with the literature.

Benzodiazepines turned out to be helpful in treatment of SCRAs induced seizures (19). However, in our case, the seizure could not be terminated via benzodiazepines leading to curarization and monitoring of the patient in intensive care unit for 3 days.

In the light of this case, it should be taken into account that manifestations after SCRAs intoxication may deteriorate the clinical picture in a short span of time, requiring immediate intervention. It should be kept in mind that notably the patients referred to emergency rooms due to SCRAs induced toxicity may be experiencing a series of life-threatening clinical presentations, one of which would probably be seizure. In this case, it is essential to keep these patients under close follow-up in a center having intensive care unit. All in all, we are of the opinion that all clinicians and the society should be highly aware of and get prepared for potential hazards to be triggered by use of SCRAs, which becomes more and more prevalent each passing day.

REFERENCES

1- Seely KA, Lapoint J, Moran JH, Fattore L. Spice drugs are more than harmless herbal blends: A review of the pharmacology and toxicology of synthetic cannabinoids. Prog Neuro-Psychopharmacol Biol Psychiatry 2012; 39: 234-243.

2- Hermanns-Clausen M, Kneisel S, Szabo B, Auwarter V. Acute toxicity due to the confirmed consumption of synthetic cannabinoids: Clinical and laboratory findings. Addiction 2013; 108: 534-544.

3- Bozkurt M. Sentetik kannabinoidler: Artık herkesin sorunu. Update in Psychiatry, Journal of Psychiatric Association of Turkey for Continuing Education/Continuing Professional Development 2014; 4: 165-177.

4- Brewer TL, Collins M. A review of clinical manifestations in adolescent and young adults after use of synthetic cannabinoids. JSPN 2014; 19: 119-126.

5- Gugelmann H, Gerona R, Li C, et al. 'Crazy Monkey' poisons man and dog: Human and canine seizures due to PB-22, a novel synthetic cannabinoid. Clin Toxicol (Phila) 2014; 52: 635-638.

6- Tait RJ, Caldicott D, Mountain D, et al. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clin Toxicol (Phila) 2016; 54: 1-13.

7- Louh IK, Freeman WD. A 'spicy' encephalopathy: Synthetic cannabinoids as cause of encephalopathy and seizure. Crit Care. 2014; 18: 553.

8- Wells DL, Ott CA. The "new" marijuana. Ann Pharmacother. 2011; 45: 414-417.

9- Pants S, Deshmukh A, Dholaria B, et al. Spicy seizure. AJMS 2012; 344: 67-68.

10- Tofighi B, Lee JD. Internet highs-seizures after consumption of synthetic cannabinoids purchased online. Journal Addic Med. 2012; 6: 240-241.

11- de Havenon A, Chin B, Thomas KC, Afra P. The secret "spice": An undetectable toxic cause of seizure. Neurohospitalist 2011; 1: 182-186.

12- Harris CR, Brown A. Synthetic cannabinoid intoxication: a case series and re-

view. J Emerg Med 2013; 44: 360-366.
13- Schneir AB, Baumbacher T. Convulsions associated with the use of a synthetic cannabinoid product. J Med Toxicol. 2012; 8: 62-64.
14- Hoyte CO, Jacob J, Monte AA, et al. A characterization of synthetic cannabinoid exposures reported to the National Poison Data System in 2010. Ann Emerg Med 2012; 60: 435-438.
15- McQuade D, Hudson S, Dargan PI, Wood DM. First Eoropean case of convulsions related to analytically confirmed use of the synthetic cannabinoid receptor agonist AM-2201. Eur J Clin Pharmacol 2013; 69: 373-376.
16- Lapoint J, James LP, Moran CL, et al. Severe toxicity following synthetic cannabinoid ingestion. Clin Toxicol (Phila) 2011; 49: 760-764.
17- Sampson CS, Bedy SM, Carlisle T .Withdrawal seizures seen in the setting of synthetic cannabinoid abuse. Am J Emerg Med 2015; 33: 1712.
18- Schep LJ, Slaughter RJ, Hudson S, et al. Delayed seizure-like activity following analytically confirmed use of previously nreported synthetic cannabinoid analogues. HET 2015; 34: 557-560.
19- Sheikh IA, Lukšič M, Ferstenberg R, Culpepper-Morgan JA. Spice/K2 synthetic marijuana-induced toxic hepatitis treated with N-acetylcysteine. Am J Case Rep 2014; 15: 584-588.
20- Altinisik U, Altinisik HB, Simsek T, Simsek E. Clinical characteristics of patients diagnosed with synthetic cannabinoid (Bonsai) intoxication in intensive care unit. J Turk Soc Intens Care 2015; 13: 117-121.
21- Sarıkaya M, Taser N. Bonzai kullanımına bağlı toksik hepatit. EP-17.5. Hepatoloji Okulu; Kocaeli, 2014.
22 Simmons J, Cookman L, Kang C, Skinner C. Three cases of "Spice" exposure. Clinical Toxicol (Phila) 2011; 49: 431-433.