



Semiha Orhan,
Kemal Yetiş Gülsoy,
Selvinaz Demirel,
Salih İnal,
Fusun Eroğlu

Rhabdomyolysis and Renal Insufficiency Due to Synthetic Cannabinoid Intoxication

Sentetik Kannabinoid İntoksikasyonuna Bağlı
Rabdomiyoliz ve Böbrek Yetmezliği

Received/Geliş Tarihi : 20.09.2016
Accepted/Kabul Tarihi : 21.12.2016

©Copyright 2017 by Turkish Society of Intensive Care
Turkish Journal of Intensive Care published by Galenos
Publishing House.

Semiha Orhan, Kemal Yetiş Gülsoy, Fusun Eroğlu
Süleyman Demirel University Faculty of Medicine,
Department of Anesthesiology and Reanimation,
Division of Critical Care, Isparta, Turkey

Selvinaz Demirel
Süleyman Demirel University Faculty of Medicine,
Department of Anesthesiology and Reanimation,
Isparta, Turkey

Salih İnal
Süleyman Demirel University Faculty of Medicine,
Department of Internal Medicine, Division of
Nephrology, Isparta, Turkey

Kemal Yetiş Gülsoy (✉),
Süleyman Demirel University Faculty of Medicine,
Department of Anesthesiology and Reanimation,
Division of Critical Care, Isparta, Turkey

E-mail : kemalgulsoy@gmail.com

Phone : +90 532 200 98 15

ORCID ID: orcid.org/0000-0002-3496-7004

ABSTRACT Bonsai is the street name of synthetic marijuana, which is a psychoactive substance. Since synthetic cannabinoids are easily accessible and cheap, their use is becoming widespread day by day. It can cause not only various clinical symptoms but also severe rhabdomyolysis. In this case, with severe rhabdomyolysis, we tried to discuss the treatment challenges of the patient examined in intensive care unit with the history of bonsai use.

Keywords: Synthetic cannabinoid, renal failure, rhabdomyolysis, plasma exchange therapy

ÖZ Bonzai psikoaktif bir madde olup, sentetik esrarın sokakta kullanılan ismidir. Sentetik kannabinoidler kolay ulaşılması ve ucuz olması nedeniyle kullanımı günden güne yaygınlaşmaktadır. Bonzai çeşitli klinik bulgularla görülebileceği gibi şiddetli rabdomiyolize de sebep olabilir. Biz yoğun bakım servisinde takip ettiğimiz bonzai kullanım öyküsü olan ciddi rabdomiyoliz ile seyreden olguda tedavi zorluklarını tartışmaya çalıştık.

Anahtar Kelimeler: Sentetik kannabinoid, renal yetmezlik, rabdomiyoliz, plazma değişim tedavisi

Introduction

Bonsai, which is the street name of synthetic marijuana is a psychoactive substance. Since synthetic cannabinoids (SC) are easily accessible and cheap, their use is becoming widespread day by day. Cannabinoids are lipid soluble and non-polar, and consist of 22 to 26 carbon structure/atoms (1). Also they easily evaporate when smoked. These SC effects are carried out through CB1 and CB2 receptors and the active ingredient is delta-9-tetrahydrocannabinol (THC).

While CB1 receptors are responsive from the psychoactive component of cannabinoids, the CB2 receptors control the release of cytokines and the migration of immune cells (2,3). The use of SC causes mental status changes, seizures, central nervous system depression, hallucinations, anxiety, and vivid dreams (4). In the literature, there have been cases that developed rhabdomyolysis depending on the use of SC. However, the number of cases that was monitored and treated with consecutive plasma exchange therapy (PET) and hemodialysis treatment are quite a few (5-7).

Case Report

An 19 year old male found unconscious by his girlfriend at home, and was brought to the emergency department. The patient had a history of alcohol and bonsai use and during his physical examination in the emergency department; Glasgow Coma Score was 13, heart rate was 128 beats/min, blood pressure was 150/110 mmHg, and fever was 37.2 °C. Besides, unconsciousness, agitation, non-pitting edema was observed in legs, rubescence, widespread body pain and facial trismus appearance were observable. The arterial blood gas analysis revealed pH: 7.35, PaO₂: 91.3 mmHg, PaO₂: 23.5 mmHg, BE: -11.8 mEq, HCO₃: 16.3 mEq. First blood chemistry results were creatine kinase (CK): 266760 U/L (normal value: 0-171), myoglobin: 2305, alanine aminotransferase (ALT) 562 U/L, aspartate aminotransferase (AST): 2491/L, lactate dehydrogenase (LDH): 8159 UL, blood urea nitrogen (BUN) 50 mg/dL, creatinine (Cr): 4.58 mg/dL, K⁺: 7.5 mmol/L, Phosphorus: 7 mg/dL, Na⁺⁺: 125 mmol/L, international normalized ratio: 1.46 PT: 17.6 sec, aPTT: 44.6. Since the drug panel THC in his blood and urine was positive, the patient was admitted to the intensive care unit for further treatment. Because of his high potassium, buffer to liquid was applied to the patient. The patient was taken to hemodialysis for two hours with the diagnosis of acute renal failure, since serum creatinine was 4.58 mg/dL and the hourly urine output was less than 10 mL/h. Because of prolonged coagulation tests two units of fresh frozen plasma (FFP) transfusion was made. On the second day of hospitalization, Cr level was 4.9 mg/dL, the patient was anuric, so hemodialysis was repeated for 3 hours, and as CK value was 365640 U/L, PET was performed with 2400 mL of plasma exchange because hemodialysis was considered to be insufficient. On the third day of hospitalization, Cr was 5.73 mg/dL, he was taken to haemodialysis with 2000 mL ultrafiltration (UF) for four hours. A dose of 0.1 mcg/kg/h dexmedetomidine infusion was given to the patient who had general body pain and agitation that resulted in aggression. On fourth day of hospitalization, CK was 338760 U/L, an increase of non-pitting edema was observed in bilateral lower extremities. For that reason, for the second time PET was performed with 4160 mL of plasma exchange and 3000 mL UF was removed. Over the time his hemodynamics was stable, 3500-4000 mL UF was removed - for three consecutive days- to the patient, who had breathing problem and whose chest X-ray had signs of fluid overload.

PET was performed third and fourth time by using 3000 mL of FFP with the value that the CK was 89040 U/L on the sixth day of hospitalization, and with the value that the CK was 44534 U/L on the eighth day of hospitalization respectively. During the intensive care, patient received oxygen support with a face mask, on the other hand mechanical ventilation support was not considered to be necessary. An improvement in renal function and an increase in the urine output were observed beginning from the twentieth day. Edema declined in both lower extremities. A total of 8 units red blood cell suspension and 2 units of FFP were transfused during follow-up. Samples for blood, sputum, and urine were sent for microbiologic investigation since he had fever during his follow-up on the fourth. Empiric piperacillin tazobactam therapy was started in a dose of 3x2.25 mg i.v. After 72 hours of the treatment, the patient's treatment was changed to teikoplanin 1x400 mg once in 72 hours, and it was replaced with meropenem 1x0.5 mg i.v. with diagnosis of pneumonia due to fever, consolidation on chest radiograph, and rough breath sounds on auscultation. Nutrition was initiated by the parenteral route, then continued through oral route. Plasmapheresis was performed on the second, fourth, sixth and eighth day of hospitalization. The patient, whose biochemical parameters regressed and agitations were controlled during his treatment, was transferred to the nephrology service. During his service follow-up, fever was not observed under the treatment of teicoplanin and meropenem. On the twenty-sixth day of hospitalization, serum Cr decreased to 1.1 mg/dL, and CK to 851 U/L level (laboratory findings listed at Table 1). The patient who had physical restraints was mobilized with appropriate physiotherapy support due to generalized rhabdomyolysis and muscle atrophy related to long term immobilization. The patient was discharged on the thirty-eight day of hospitalization.

Discussion

SCs were identified as a distinct psychoactive substance class in the early-warning system by the European Centre for Monitoring Drugs and Drug Addiction in 2008. It is produced by adding dried plant materials and chemical aroma in a solvent. These products, solvent and plant materials contain toxic compounds (8).

SCs are more effective than THC. Having full agonist activity, it may cause anxiety, agitation, seizures, catatonic

state and confusion by the effect of gamma-aminobutyric acid enzyme inhibition (9). It is noted that rhabdomyolysis, increased CK level, and consequently kidney failure may develop depending on increased activity (4).

In many cases, cannabinoid metabolites cannot be shown in the serum and urine samples since SC have a large number of isomers (4). Teske et al. (10), stated in their study that serum JMH-018N (methanone) level was at the highest with mass spectrometer within the fifth minute; it fell below to only 10 percent of the maximum after the third hour, and it could not be shown in the serum samples at and/or after twenty-four hours. Our case was not studied since he was admitted to hospital almost after twenty-four hours, and due to the fact that, in our hospital there was no test to show the SC metabolites in serum and urine samples.

SC use related rhabdomyolysis have been reported in the literature (5-7). Rhabdomyolysis is a life-threatening syndrome resulting from the breakdown of skeletal muscle, which causes the release of intracellular contents such as CK, LDH, myoglobin, potassium and phosphorus into the circulatory system.

In their case, Zhao et al. (6), started dialysis to the patient with two positive edema, and with a level of serum CK of 148000/L; potassium 6.9 mmol/L, and Cr 7.5 mg/dL on the third day of hospitalization. They made a total of 10 dialysis sessions. In the case published by Sherpa et al. (5), CK was increased to 302000 on the seventh day of hospitalization. Furthermore, SC metabolites were considered to contribute to the increase of CK. With the continuous renal replacement

therapy, it was observed that there was a decrease in the level of CK within two weeks.

Ronco (11) stated that conventional dialysis techniques have a limited capacity in removing myoglobin from the circulation due to the extracorporeal technical difficulties, molecular property, distribution in the body, solute transport mechanisms, and the membrane structure. It was commented that with high transfer coefficient, the PET in myoglobinemia was more efficient; on the other hand its restriction was the low volume change (11).

Because of the limited effect of removing myoglobin from the bloodstream with standard hemodialysis, PET was applied in addition to hemodialysis. With these treatments the CK levels were decreased by more than half (11). Swaroop et al. (12), suggested plasmapheresis in order to decrease the level of toxic muscle enzymes in patients who did not respond to i.v. fluid resuscitation and to medical therapy in the serious cases of rhabdomyolysis and acute renal failure. Paaske et al. (13), used PET successfully in acute compartment syndrome and acute renal failure that caused by rhabdomyolysis.

There were clouding of consciousness, agitation, and facial trismus in our case. Serum Cr was 5.16 mg/dL, serum potassium was 7.06 mmol/L, serum phosphate was 7 mg/dL, and the patient was anuric during his admission to hospital. Besides all these; there were generalized edema in the body, widespread body pain, myoglobin >3000, CK 266760/L, and rhabdomyolysis. Acute renal failure was thought to occur secondary to rhabdomyolysis. Since there

Table 1. Laboratory findings of the patient

Hospitalization day	BUN (mg/dL)	Creatinine (mg/dL)	ALT (U/L)	AST (U/L)	Potassium (mmol/L)	Phosphorus (mg/dL)	Creatine Kinase (U/L)	Myoglobine	INR
1.	50	4.58	562	2491	7.50	7	266760	2305	0.99
2.	52	5.16	404	1979	7.92	7	365640	>3000	1.16
3.	50	5.73	501	2303	6.63	7	266760	>3000	1.32
4.	50	5.45	418	1720	5.21	6	338760	>3000	1.24
5.	54	6.06	304	1654	4.86	5	223280	>3000	1.28
6.	41	4.95	350	1353	4.32	4	89040	3000	1.27
7.	45	4.57	377	967	5.08	4	42380	3000	1.49
8.	66	5.78	361	789	5.03	7	44534	>3000	1.26
10.	95	7.10	215	481	4.92	7	27929	>3000	1.32
12.	89	5.80	284	273	4.56	7	10164	>3000	1.32
14.	46	3.68	156	153	3.86	7	4595	>3000	1.28

BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, INR: International normalized ratio

was no possibility of continuous renal replacement therapy in our intensive care unit, the patient was taken to hemodialysis. Due to the serum CK, which reached to serious levels on the second day of hospitalization, hemodialysis was thought to be insufficient, so PET was added to the treatment. During the first PET, the plasma exchange was limited to 2400 mL because of hypotension, tachycardia, and sweating. As a result of an average 2500-4000 mL plasma exchange for a total of 4 times, the CK level of the patient was decreased to 27929 U/L. On the twenty-sixth day of hospitalization Cr was found to be 1.1 mg/dL and CK was found to be 851 U/L as a result of PET and hemodialysis treatments.

As a conclusion, since SC substance is easily accessible and cheap, the numbers of users increase rapidly. SC use should be considered only in those cases, which have symptoms of intoxication and when drug panels are negative, because of difficulties in detecting these substances in blood and urine samples. As occurred in our case, the use

of SC may cause serious life-threatening complications such as rhabdomyolysis. Because of the feature of myoglobin molecule, removing it from the circulation may be inadequate with conventional hemodialysis, it is thought that the addition of PET to the treatment may be useful.

Ethics

Informed Consent: It was taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.O., K.Y.G., Concept: S.O., Design: S.O., FE., Data Collection or Processing: S.O., K.Y.G., S.I., Analysis or Interpretation: S.O., Literature Search: K.Y.G., S.D., Writing: S.O., K.Y.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Fattore L, Fratta W. Beyond THC: The New Generation of Cannabinoid Designer Drugs. *Front Behav Neurosci* 2011;5:60.
- Ashton JC, Wright JL, McPartland JM, Tyndall JDA. Cannabinoid CB1 and CB2 receptor ligand specificity and the development of CB2-selective agonists. *Curr Med Chem* 2008;15:1428-43.
- Huffman JW, Marriott KC. Recent advances in the development of selective ligands for the cannabinoid CB(2) receptor. *Curr Top Med Chem* 2008;8:187-4.
- Harris CR, Brown A. Synthetic cannabinoid intoxication: a case series and review. *J Emerg Med* 2013;44:360-6.
- Sherpa D, Paudel BM, Subedi BH, Chow RD. Synthetic cannabinoids: the multi-organ failure and metabolic derangements associated with getting high. *J Community Hosp Intern Med* Perspect 2015;5:27540.
- Zhao A, Tan M, Maung A, Salifu M, Mallappallil M. Case Report Rhabdomyolysis and Acute Kidney Injury Requiring Dialysis as a Result of Concomitant Use of Atypical Neuroleptics and Synthetic Cannabinoids Case Reports in Nephrology Volume 2015, Article ID 235982, 4 pages.
- Ergül DF, Ekemen S, Yelken BB. Synthetic Cannabinoid 'Bonzai' Intoxication: Six Case Series. *Turk J Anaesth Reanim* 2015;43:347-51.
- EarlyWarning System. (2009). Available at: <http://www.emcdda.europa.eu/themes/new-drugs/early-warning> [accessed October 23, 2009].
- Laaris N, Good CH, Lupica CR. D9-tetrahydrocannabinol is a full agonist at CB1 receptors on GABA neuron axon terminals in the hippocampus. *Neuropharmacology* 2010;59:121-7.
- Teske J, Weller JP, Fieguth A, Rothämel T, Schulz Y, Tröger HD. Sensitive and rapid quantification of the cannabinoid receptor agonist naphthalen-1-yl-(1-pentylindol-3-yl)methanone (JWH-018) in human serum by liquid chromatography-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2010;878:2659-63.
- Ronco C. Commentary Extracorporeal therapies in acute rhabdomyolysis and myoglobin clearance. *Crit Care* 2005;9:141-2.
- Swaroop R, Zabaneh R. and Parimoo N. Case report Open Access Plasmapheresis in a patient with rhabdomyolysis: a case report. *Cases Journal* 2009;2:8138.
- Paaske WP, Bagl P, Lorentzen JE, Olgaard K. Plasma exchange after revascularization compartment syndrome with acute toxic nephropathy caused by rhabdomyolysis. *J Vasc Surg* 1988;7:757-8.