Synthetic Cannabinoid 'Bonzai' Intoxication: Six Case Series

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In the language of the streets, 'bonzai', known as '1-naphthalenyl of methanol', also known as JWH-18 group, is a drug belonging to the group of synthetic cannabinoids. At the beginning of 2004, it started to be sold on the internet and it is seen that private markets. It has structurally similar chemical characteristics as delta 9-tetrahydrocannabinol (THC), the active substance in marijuana. In 2013, in a study conducted by the European Monitoring Centre of Drugs and Drug Addiction (EMCDDA), 102 varieties of synthetic cannabinoids were identified; however, more than 200 substances have been reported since 1997. In this study, we report the difficulties in the clinical course, treatment and management of six patients that had a use history of bonzai although it was not detected in blood in a short period of time in the intensive care unit.

Keywords: Cannabinoids, intoxication, delirium, acute renal failure, compartment syndrome

Introduction

'1-naphthalenyl of methanol' known as 'Bonzai' in the street language, with its other name JWH-18 group, is a drug included in the synthetic cannabinoid group. The sale of this drug over the internet and in special markets started from the beginning of 2004 (1). It displays a similar structural feature chemically with 9-tetrahydrocannabinol (THC), which is the active ingredient of marijuana. Although 102 different kinds of synthetic cannabinoid substances were reported to the early warning system of European Monitoring Centre of Drugs And Drug Addiction (EMCDDA) until December 2013, more than 200 substances have been reported since 1997 (1, 2). In the presentation of our cases, it was aimed to discuss the clinical courses, treatment management and the difficulties in the diagnosis of six patients who were followed up in the intensive care unit and whose blood tests were negative despite the presence of the history of bonzai use.

Case Presentations

Case 1

A 27-year-old male patient who developed clouded consciousness after drinking alcohol with bonzai use was brought to our hospital's emergency unit by his friends. It was learned that he was confused and agitated at admission and his heart rate (HR) was 135 beat min⁻¹ and blood pressure (BP) was 80/50 mmHg. In his blood gas analysis, pH was 7.25, PaO₂ was 155 mmHg, PaCO₂ was 27.8 mmHg, BE was -13.6 mEq and HCO₃ was 14.2 mEq. In the biochemistry analysis, creatine kinase (CK) was 139.890 U L⁻¹ (normal value, 30–200 U L⁻¹), alanine aminotransferase (ALT) was 250 U L⁻¹, aspartate aminotransferase (AST) was 1350 U L⁻¹, lactate dehydrogenase (LDH) was 8100 U L⁻¹, blood urea nitrogen (BUN) was 45 mg dL⁻¹, creatinine was 2.28 mg dL⁻¹, K was 4.9 mEqL⁻¹, INR was 1.7, PT was 20 and aPTT was 52.3. Considering these values, the patient was hospitalized in our intensive care unit for the purpose of further follow up and treatment.

Because there was no hypoxia in the blood gas analysis of the patient, he continued to take oxygen with the mask. The drug panel (marijuana, LCD, heroin, cocaine, bonzai, amphetamine, methamphetamine, oxycodone, methadone, tricyclic antidepressant, barbiturate) and ethanol levels in the blood and urine of the patient gave no result. Both the orbita surroundings and conjunctiva were hyperaemic and oedematous. Papillae oedema was not detected in the patient consulted to the ophthalmologist because of haemorrhage in his eyes. Follow up and symptomatic treatment were recommended to the patient

having no vision loss. He had non-pitting oedema beginning firstly in the right arm and extending from both arms to the shoulders.

Because radial and ulnar pulses of the patient with increased diameter, which was detected in the measurements performed on the first day of follow-ups due to non-pitting oedema, could not be taken, the development of bilateral compartment syndrome was found and emergent bedside fasciotomy was performed in the department of plastic surgery. Metro-nidazole 2x500 mg and cefazolin 3x1 g were initiated after fasciotomy. Despite this, *Acinetobacter baumannii* grew in the culture taken from the wound site on the 5th day after fasci-otomy. Antibiotherapy of the patient was switched, and met-ronidazole 2x500 mg and cholistin 2x150 mg were adminis-tered. The patient underwent wound site debridement twice. Because of a circulatory disorder in both arms, 0.5 ng kg⁻¹ of iloprost (Ilomedin®, Bayer Schering Pharma AG, Germany) therapy was initiated for 1 week in accordance with the rec-ommendations of the department of cardiovascular surgery.

Considering the possibility of having consumed smuggled alcohol based on the information received from the patient's relatives and then from the patient, methanol levels were eval-uated. However, it was not detected in the blood because he was brought to the hospital 6 h after the intake. Because the presence of metabolic acidosis with high anion gap suggest- ed methanol intoxication, intermittent haemodialysis (IHD) treatment was initiated under emergency conditions on the first day of hospitalization and 100 mL st⁻¹ dose of 10% eth-anol was started after 4-h dialysis.

Blood ethanol levels were maintained below 100 mg dL⁻¹ during follow-ups. Thiamine (100 mg) (Behaptal®, Osel, Is- tanbul, Turkey), K-vitamin ampule 2x1, 200 mL s⁻¹ isoton-ic, 100 mL s⁻¹ Ringer's lactate and 100 mL s⁻¹ 5% dextrose

were administered in addition to the treatment. The patient who reached the CK value of 243920 U L⁻¹ after dialysis was planned to be given selective plasma exchange therapy (SPET-Evaclio™ Kawasumi Laboratories, Inc, USA). Then, CK values of the patient decreased to around 62000 U L⁻¹, and his haemostasis values increased. Therefore, 3-unit fresh frozen plasma (FFP) and 2-unit erythrocyte suspension (ES) replacements were performed. SPET was administered three more times to the patient whose CK level displayed a fluctu-ating course every other day (Table 1). Despite hydration and diuresis treatment, on the 7th day of hospitalization, creati- nine and BUN levels of the patient elevated up to 4.7 mg dL⁻¹ and 72 mg dL⁻¹, respectively. The patient whose urine output decreased, BUN and creatinine levels increased and chest radiography revealed findings consistent with fluid loading during the first week was administered with IHD 2500 mL ultrafiltration (UF) for 4 h in the presence of stable haemo- dynamics and continuous renal replacement therapy (CRRT) (The Prismaflex® system, Gambro, Lakewood, CO, USA) in the absence of stable haemodynamics every other day. On the 30th day of the follow-up period, BUN and creatinine levels returned to normal. During follow-ups, a total of 8 units of ES and 8 units of FFP were replaced. After his ALT level in- creased to 3500 U L⁻¹, it showed a falling tendency. Because ALT levels decreased below 5 U L⁻¹ in the next follow-ups, he was consulted by the department of gastroenterology and recommended to be followed up because of the possibility of liver failure. In his follow-up examinations performed every other day, his ALT values were measured as zero twice. The bedside ultrasonography revealed that the liver was of normal size and echogenic. His haemostasis parameters were high, near the upper limit, but then returned to normal. On the 30th day of hospitalization, an increase was observed in ALT and AST values. During his hospitalization in the intensive care unit, he was given oxygen support with a mask; no me-

Table 1. Biochemical values of the first case

Day of hospitalization	AST (U L ⁻¹)	ALT (U L ⁻¹)	LDH (IU L ⁻¹)	CK (U L ⁻¹)	Creatinine (mg dL ⁻¹)	BUN (mg dL ⁻¹)	aPTT	INR
1 st day	1350	250	24000	139.890	2.28	16.5	14.8	1.29
2 nd day								
First measurement	3598	810	14830	243.920	1.34	13.1	54.8	1.59
Second measurement	1780	450	6376	62.652	1.6	16.3	90	1.95
3 rd day	1651	370	3147	43.220	2.86	30.94	74.9	1.43
8 th day	158	1	928	1668	3.46	29.86	44.4	1.01
9 th day	74	3	724	440	5.63	90.2	64.25	1.12
20 th day	50	0			4.03	57.45		
22 nd day	27	2	523	65	5.10	95.0	39.9	1.15
25 th day	32	26	821	618	0.53	23.66	35.9	1.05
38 th day					0.86	20.49	31.2	1.12
AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CK: creatinine kinase; BUN: blood urea nitrogen; aPTT: activated partial thromboplastin time; INR: international normalized ratio								

chanical ventilation support was needed. From the 25th day of his hospitalization, improvement was observed in his renal functions, which were impaired until then. The patient was administered with parenteral nutrition support on the first days of his hospitalization. Then, on the 5th day, enteral nutrition with oral solutions was administered via the nasogastric route first and then continued orally. On the 38th day of hospitalization, he was cured and transferred to the department of plastic surgery for grafting. Follow-up continued to be conducted by the clinic of plastic surgery. Because he was cooperative, oriented and without any sequela, he was discharged from the hospital.

Case 2

A 24-year-old male patient presented to the emergency unit with the complaint of mental fog that occurred after using bonzai. In the initial measurement of the blood gas values of the patient at the emergency unit, pH was 7.01, BE was -15, HCO₃ was 8 and CK was 159544 U L⁻¹. AST and ALT values were 3872 U L⁻¹ and 1445 U L⁻¹, respectively. The body temperature of the patient, who was hyperaemic, was measured to be 38.1°C. His urea and creatinine values were 28.9 and 3.12 mg dL⁻¹, respectively, and he was underwent forced diuresis and fluid treatment. The urea and creatinine values of the patient increased at the second hour, and he was given IHD. After 4-h dialysis, his CK value was measured as 147707 U L⁻¹ and he underwent SPET, assuming that IHD treatment was insufficient. Although fluctuation was observed in CK values at the end of the first day, the value regressed to 65170 U L⁻¹. With a decrease in the urine output, IHD and CRRT therapies were intermittently given in correlation with haemodynamics. Because the patient experienced pain in the left gluteal area and leg, the development of compartment syndrome was suspected; therefore, intramuscular compartment pressures were measured from the femoral region. When re-measurement was performed, the pressure values were found to be over 50 mmHg. Therefore, he urgently underwent fasciotomy with the diagnosis of compartment syndrome on the 2nd day of his hospitaliza-

tion. His antibiotic therapy was expanded and re-adjusted. On the first 3 days, the patient underwent SPET three times, IHD three times, and CRRT once. On the 1st day after fasciotomy, abdominal tenderness, fever and defence developed. With the suspicion of acute abdomen, an emergency operation was planned for exploratory laparotomy by the general surgery department. During the operation, diffuse necrosis and oedema were detected. After debridement, the surgery ended. Then, the patient, who had urinary retention, was administered with positive inotrope support because his TA values were low. Subsequently, CRRT was administered. The patient developed decreased saturation and hypoxia, and he was intubated on the 4th day of his hospitalization. Because his platelet values decreased below 30000 mm³ after fasciotomy, 2 units of aphaeresis platelet suspension were given. With a decrease in Hg value to 6 g/dL⁻¹, 3 units of ES were replaced. The patient died of multiple organ failure associated with sepsis on the 6th day of his hospitalization.

Case 3

A 21 year-old male patient, who was intubated by 112 emergency service because of respiratory arrest, was brought to the emergency unit. When he was admitted, he was intubated, unconscious GKS, 3; pupillary, miotic, hypotensive and bradycardic. The patient had blood gas pH of 6.61; his PaO₂ was 45, PaCO₂ was 25, BE was -31 and HCO₃ was 5. The patient, who was administered with sodium bicarbonate infusion, was put on a mechanical ventilator. It was detected that the patient, receiving treatment because of drug dependence according to the relative's and then the patient's statements, consumed alcohol and took bonzai with antipsychotic drugs. Bonzai or another drug was not detected in the drug panel. Because his spontaneous respiration returned and blood gas values improved on the 2nd day of his hospitalization, he was extubated. His AST, ALT and CK values were found to be high at the upper limit. On the 3rd day of hospitalization, CK values increased from 364 U L⁻¹ to 6500 U L⁻¹. On the 4th day of the patient who was followed as immobile due to enzyme tests, SPET was performed twice every other day because CK val-

Table 2. Biochemical values of the second case

Day of hospitalization	AST (U L ⁻¹)	ALT (U L ⁻¹)	LDH (IU L ⁻¹)	CK (U L ⁻¹)	Creatinine (mg dL ⁻¹)	BUN (mg dL ⁻¹)	aPTT	INR	PH
1 st day									
First measurement	3872	1445	11940	159544	3.12	28.9	32.1	1.21	7.01
Second measurement	2884	966	5591	65170	1.87	20.6			
2 nd day									
First measurement	1698	446	3061	108210	3.18	30.7	Maximum	1.5	7.32
Second measurement	704	157	4575	48668	2.68	24.5			
3 rd day	1269	339	7200	97000	3.35	28.9	251	1.4	7.31
5 th day	863	244	6800	82840	2.15	25.6			
6 th day	481	51	748	10129	4.43	44.4	98.3	2.24	7.0
AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CK: creatinine kinase; BUN: blood urea nitrogen; aPTT: activated partial thromboplastin time; INR: international normalized ratio; pH: power of hydrogen									

Table 3. Biochemical values of the third case

Day of hospitalization	AST (U L ⁻¹)	ALT (U L ⁻¹)	LDH (IU L ⁻¹)	CK (U L ⁻¹)	Creatinine (mg dL ⁻¹)	BUN (mg dL ⁻¹)	aPTT	INR	PH
1 st day	21	16	606	342	0.66	9.05	21.3	1.37	6.61
3 rd day									
First measurement	61	23	618	364	0.68	5.8	25.8	1.05	7.40
Second measurement			1146	6500	0.70	7			
Third measurement			921	8901	2.86	30.94			
4 th day	151	50	1560	15560	0.76	9.05	117.5	1.17	7.28
5 th day	77	31	731	8490	0.7	6.79			7.38
7 th day	48	18	320	2224	0.61	6.1	41.8	1.07	
9 th day	82	72	465	1528	0.76	10.3			7.47
AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CK: creatinine kinase; BUN: blood urea nitrogen; aPTT: activated partial thromboplastin time; INR: international normalized ratio; pH: power of hydrogen									

ues increased to 15560 U L⁻¹. Infusion was initiated with 0.1 µg kg⁻¹ st⁻¹ dexmedetomidine (Precedex®, Hospira Inc., Lake Forest, IL, USA) in the patient with a general body pain and agitation during this period. When his CK values decreased to normal values during the follow-ups, he was discharged as cured and was recommended to visit the outpatient clinics of psychiatry and nephrology for controls (Table 3).

Case 4

A 28-year-old male patient with the clinical picture of delirium was brought to the emergency unit by the ambulance of 112 emergency service. It was learned that the patient, who had a diagnosis of bipolar personality disorder, had a history of taking bonzai with alcohol half and hour before his admission. The drug panel and blood gas values of the patient were found to be normal. In biochemical evaluation, his CK value was 250 U L⁻¹, ALT was 55 U L⁻¹ and AST was 34 U L⁻¹. Because of increased somnolence in the emergency unit, he was hospitalized in the intensive care unit. Because of the aggressive degree of his agitations, infusion was initiated with 0.2 µg kg⁻¹ dexmedetomidine (Precedex®, Hospira Inc., Lake Forest, IL, USA). His CK values increased up to 800 U L⁻¹ on the 3rd day of hospitalization and he was applied diuresis and hydration. The patient, who had no additional problem during his follow-ups, was discharged from the hospital on the 8th day of hospitalization by recommending control visits to the outpatient clinic of psychiatry.

Case 5

A 28-year-old male patient applied to the emergency unit with the complaints of impaired consciousness, palpitation, fever and shivering on the day after taking ecstasy and bonzai. After he was hospitalized in the intensive care unit, he was observed to be agitated and non-cooperative, and he experienced shivering and flushing on his face. His HR was 130 beats min⁻¹, and his ECG revealed supraventricular tachycardia. His body temperature was 38.5°C, and he complained of a general body pain. Because of hyperthermia, the patient underwent diuresis and hydration with cold isotonic. Biochem-

istry values were as follows: ALT was 65 U L⁻¹ and CK was 200 U L⁻¹. CK values reached to the peak level of 1850 U L⁻¹ on the 3rd day. His biochemical parameters regressed during follow-ups, and his agitations were kept under control. He was discharged as cured with the recommendations of the department of psychiatry on the 5th day of his hospitalization.

Case 6

A female patient, who was the wife of the former case, was admitted to the emergency unit with her husband. She had a history of taking bonzai. She was conscious and cooperative, but she had a dominant feeling of 'thanatophobia'. In her biochemistry parameters, no clinical finding was detected, except her high CK values at the upper limit. Because a decrease was observed in CK values on the 2nd day in the patient, who was followed as immobile, she was discharged from the hospital with the recommendations of the psychiatry clinic.

Discussion

Huffman et al. (3) synthesised compounds including naphthoylindoles, naphthoylpyrrole and cannabinoid receptor activity, and this became the main compound of new substances, including synthetic cannabinoid over time. Then, synthetic cannabinoids were begun to be called as 'JWH substances' with reference to the initials of John W. Huffman. These substances, including synthetic cannabinoid, are often named as 'Spice' in Europe, 'K2' and 'Genie' in USA and 'Bonzai' or 'Jamaica/Gold' in Turkey.

The cases in this study were presented in chronological order. Although various drug intoxications were followed in the intensive care unit until confronting with the first case, a clinical picture at this level was experienced for the first time and successively. Across the country, the use of bonzai was first seen in late 2005, and its use has increased day by day. In the pharmacology laboratory in our faculty, drug monitoring is performed by the cloned enzyme donor immunoassay (CE-DIA) method. Despite the presence of the history of bonzai

usage in all cases presented above, bonzai could not be detected in urine and blood samples. The most important problem related to the analysis and definition of such next generation drugs is the presence of a large number and type of isomers and their derivatives. Another difficulty is the problems encountered during updating licensed libraries of devices used in forensic laboratories. When a substance not included in these libraries is found, it is controlled with existing standard substances (4). This situation causes difficulty in the detection of next generation bonzai types.

Cannabinoid receptor (CB1) affinities and activities of bonzai are higher than the derivatives of tetrahydrocannabinol (THC). Accordingly, its effect, size and frequency and severity of negative effects are higher than THC. Its effects begin more rapidly, and they can last longer or shorter. Compared with THC, the negative effects seen more commonly are convulsions, anxiety, aggression, muscle rigidity and confusion (4). The cause of deep agitations, anxiety, epileptic seizures and convulsion was stated to be GABA enzyme inhibition with agonist activity (5). Cases with acute renal failure, acute vision loss and Wernicke’s syndrome associated with synthetic cannabinoids were reported (6, 7). In the 2010 report of the United Nations, it was stated that it was difficult to determine a specific effect of synthetic cannabinoids because they had a large number and type of compounds (6). In addition, it was detected that it had a cumulative effect in repeating uses because of its lipophilic structure (3, 8).

Considering all cases that we followed, increased CK values are remarkable. Increased CK values associated with rhabdomyolysis was observed in three cases, two of which were serious. It is suggested that ABY can develop in association with muscle rigidity resulting from the direct effect of synthetic cannabinoids, or it can develop because of the chemical substances that are mixed together. It has been observed in visual media that many substances such as pesticides, fluorescent powder, water speedwell and industrial chemicals can be mixed with synthetic cannabinoid. Because its levels in blood and urine cannot be detected, its exact effect in any case is unknown, which is a serious problem for diagnosis and treatment (6, 8, 9). Although intravenous lipid therapy was reported to be effective because of its lipophilic chemical structure (10), a known specific antidote or treatment is not available, apart from the abovementioned symptomatic treatments. It can be stated that SPET, which was performed for increased CK values in the first three cases, provided more efficient and rapid treatment than IHD and CRRT methods.

Conclusion

The use of bonzai is increasing day by day because of its features, including its easy accessibility, low cost and its non-detection in medical analyses. As demonstrated in this case series, serious life-threatening situations connected with the use of synthetic cannabinoids can occur. Their high distribution volume and accumulation associated with their lipophilic

structure can cause prolonged and excessive effects. Moreover, because of the existence of increasing isomers and their derivatives, the detection of these substances in urine and blood samples can be more difficult.

For the patients admitted to the emergency unit with the signs of intoxication, but whose drug panel is found to be negative, the use of synthetic cannabinoids should be remembered, and symptomatic treatment should be initiated early. Considering that the findings can present in late period, the duration of monitoring should be extended. The necessity for updating pharmacology laboratories as soon as possible to prevent possible deaths is confronted as an obligation for the development of national health politics.

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