A Case of Acute Intoxication from Sublingually Administering a Liquid Inhalation Product Containing a Marijuana Analogue

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(Received April 15, 2024; Accepted May 23, 2024)

A 20-year-old man was brought to the emergency room with chief complaints of dysarthria and vomiting after placing several drops of an inhalation liquid containing hexahydrocannabiphorol (HHCP) under his tongue. During ambulance transport, the patient had a post-vomiting convulsion that lasted approximately 1 minute. Upon arrival at the hospital, he was agitated, had dysarthria to the extent that he was in danger of falling from the stretcher, and was having visual hallucinations. Blood tests showed acidosis and a high lactic acid concentration. The patient was urgently admitted to the hospital with a diagnosis of acute poisoning and was started on supplemental intravenous fluids. The patient was able to communicate from the second day, started eating on the third day, finished receiving supplemental fluids on the fourth day, and was discharged from the hospital on the fifth day. HHCP was not illegal in Japan at the time and was distributed mainly through mail order. Clinical information on HHCP is lacking, but this case shows that the drug causes health problems. Although HHCP has been regulated by law in Japan since January 2024, clinicians and the general public should be aware that similar cases may occur in the future.

Key words: hexahydrocannabiphorol (HHCP), tetrahydrocannabinol (THC), cannabinoid, cannabis, drugs

INTRODUCTION

The number of arrests related to marijuana in Japan has rapidly increased in recent years, especially among young people under the age of 30, and has been increasing since 2014 [1, 2]. The number of marijuana-related arrests in Japan exceeded 5,000 for three consecutive years after 2020, with a peak of 5,482 in 2021 and a slightly lower number of 5,342 in 2022 [1, 2]. The reasons for this trend are thought to vary but may be associated with the lack of criminal awareness and lack of recognition of the illegality of marijuana, leading to the ingestion of candy, cookies, and chocolate containing marijuana ingredients and the inhalation of marijuana liquid through e-cigarettes. In fact, the most common reasons for marijuana use in Japan are "invited" and "curiosity" [1]. Regarding cannabis liquids, the illegal cannabis ingredient tetrahydrocannabinol (THC) has been modified to make it legal (semi-synthetic cannabinoids), and the legal cannabis ingredient cannabidiol (CBD) has been commercialized and is readily available on the internet and through other sources.

We experienced a case in which a patient was rushed to the emergency department with psychiatric and physical symptoms after sublingual administration of a liquid containing hexahydrocannabiphorol (HHCP). HHCP is currently illegal, but was legal at that time and was distributed by mail order. There have been no reports of acute poisoning with HHCP, and the risk is unknown; however, the clinical manifestations of HHCP poisoning may be similar to those of THC poisoning. Although HHCP became illegal in Japan in January 2024, similar cases of poisoning with semi-synthetic cannabinoids may occur in the future. We reported this case to alert the public to the dangers of HHCP and to provide information that will be helpful in later studies.

CASE

A 20-year-old man with no relevant medical history was brought to our hospital with dysarthria and vomiting. He had administered several drops of HHCP-containing inhalation liquid under his tongue (Fig. 1). Later, while riding in a car driven by his friend, he suddenly lost his ability to articulate and an ambulance was called. This was his first intake of HHCP. After contact with the ambulance service, he vomited food residues twice. During ambulance transport, he experienced post-vomiting convulsions that aborted spontaneously within approximately 1 minute. Upon arrival at hospital, he had a body temperature of 37.0°C, blood pressure of 150/70 mmHg, pulse rate of 108 beats/min, and respiratory rate of 16 breaths/min. Pulse oximetry revealed an oxygen saturation of 97% in room air. He was in an agitated state and could not speak clearly. Although he could follow some simple instructions, he repeatedly shouted unintelligibly as if

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Fig. 1 The product the patient is suspected to have ingested.

Table 1 Blood laboratory data on admission

Complete blood count		Biochemistry		Venous blood gas analysis	
WBC	8700 /μL	Alb	4.5 g/dL	pH	7.298
Hb	14.6 g/dL	T-Bil	0.4 IU/L	$PvCO_2$	57.7 mmHg
Plt	24.9 × 10^4/μL	AST	26 IU/L	PvO_2	35.3 mmHg
		ALT	18 IU/L	Base excess	0.3 mEq/L
Coagulation parameters		CK	235 IU/L	HCO_3^-	28.2 mEq/L
PT-INR	1.04	BUN	18 mg/dL	Anion gap	17.3 mEq/L
APTT	28 sec	Cre	0.99 mg/dL		
D-dimer	< 0.5 μg/mL	Na	141 mEq/L		
		K	3.7 mEq/L		
		Cl	102 mEq/L		
		CRP	0.13 mg/L		
		Lac	34 mg/dL		

WBC: white blood cell count; Hb: hemoglobin; Plt: platelet count; Alb: albumin; T-Bil: total bilirubin; AST: aspartate aminotransferase; ALT: alanine transaminase; CK: creatinine kinase; BUN: blood urea nitrogen; Cre: creatinine; Na: sodium; K: potassium; Cl: chloride; CRP: C-reactive protein; Lac: lactate; PT-INR: prothrombin time international normalized ratio; APTT: activated partial thromboplastin time; $PvCO_2$: partial pressure of carbon dioxide in venous blood; PvO_2: partial pressure of oxygen in venous blood

he were hallucinating, and he was unable to engage in conversation. The patient was in danger of falling off the stretcher because he was getting up suddenly and moving his limbs violently. Laboratory data showed a high lactate concentration of 34 mg/dL, and blood gas analysis showed acidosis with a pH of 7.298. There were no other notable findings (Table 1). All urinary drug tests were negative. An electrocardiogram (ECG) showed sinus tachycardia and no obvious ST changes. Chest radiography showed no abnormal findings.

The patient was urgently admitted with a diagnosis of acute HHCP poisoning. We started him on intravenous fluids comprising 100 ml/hr of Ringer's acetate and 40 ml/hr of maintenance fluid to promote external elimination of the drug. He continued to be agitated and to hallucinate on the second day, but was able to communicate by the second night (approximately 26 hours after admission). On the third day, oral intake was started and only maintenance fluids were administered. As he was coping well with the oral intake, we discontinued the intravenous infusions on day 4. The patient was discharged on day 5. During

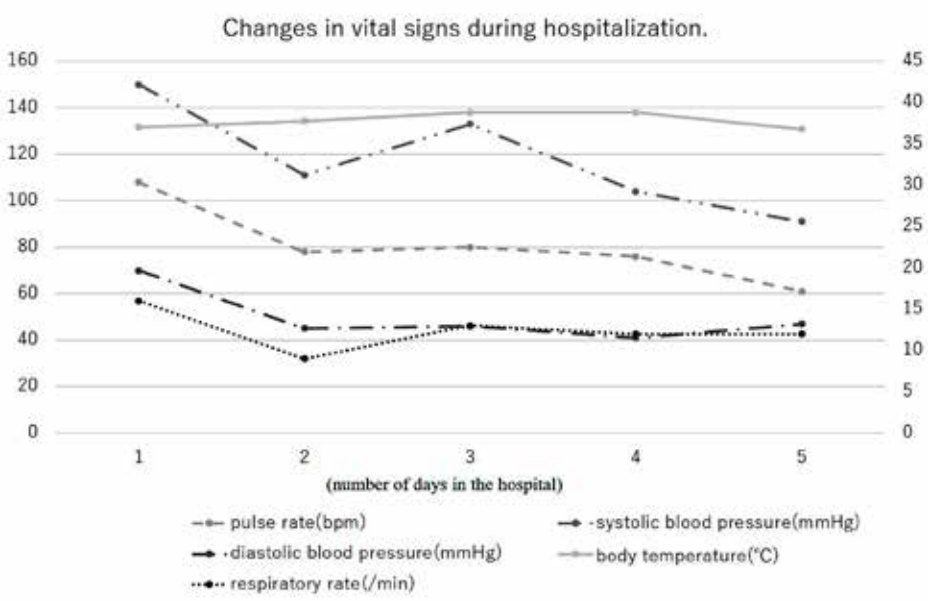

Fig. 2 Changes in vital signs during hospitalization. The first axis shows the pulse rate, systolic, diastolic blood pressure, while the second axis shows the body temperature and respiratory rate.

hospitalization, he never required oxygen and showed no significant changes on chest radiography. There were no blood pressure fluctuations or arrhythmias requiring medical intervention, and no ST-segment changes on the ECG. Fig. 2 shows the changes in his vital signs. His blood test results showed no evidence of infection, organ damage, or coagulopathy. His creatinine kinase concentration rose to 420 IU/L on the second day, but subsequently normalized. After he became able to converse, when we asked him about the incident, he told that he purchased the liquid for inhalation on the internet. He said that he administered the HHCP sublingually because he had heard that sublingual administration speeds up the onset of its effects.

DISCUSSION

As there is no literature on HHCP, we have discussed the effects of HHCP based on the pathogenesis of THC intoxication, the literature on synthetic cannabinoids (a group of compounds designed to study the effects of cannabinoid receptors), and the present case.

THC works by binding to cannabinoid receptors [3]. The two types of cannabinoid receptors are cannabinoid receptor 1, which exists mainly in the central nervous system, and cannabinoid receptor 2, which exists in peripheral tissues such as immune cells [3]. Orally administered cannabis has a lower bioavailability than inhaled cannabis due to degradation by gastric acid and the first-pass effect in the liver, whereas sublingual administration avoids the first-pass effect, resulting in better absorption [3]. The clinical findings of THC intoxication include feelings of “elation”, “pleasure”, and “relaxation”, as well as possible impairment of attention, concentration, short-term memory, and executive function [3]. Higher doses of THC may cause more severe symptoms such as hypotension, panic, anxiety, myoclonus, delirium, respiratory depression, and ataxia [3]. In addition, synthetic cannabinoids have a higher binding affinity for cannabinoid receptors than THC [4]. Cannabinoids (including THC) and synthetic cannabinoids are substrates for cytochrome P450 enzymes in the body, mainly in the liver, and are metabolized by the liver. The half-life of THC is estimated to be 20–57 hours, and although the exact half-life of synthetic cannabinoids is unknown, there are reports of symptom resolution within 24 hours [4, 5]. The treatment of THC poisoning comprises intravenous fluids and symptomatic treatment.

As HHCP has a similar structure to THC, it is expected to bind to cannabinoid receptors and exert its action like THC and to be metabolized by the liver. In the present case, in addition to physical symptoms such as vomiting, dysarthria, and convulsions, the patient had psychiatric symptoms such as restlessness, agitation, and hallucinations, similar to those that occur in patients who have overdosed on THC. Although the toxidrome caused by HHCP ingestion may be characterized by restlessness and convulsions, it is not clear whether this is an inherent effect of HHCP or an overdose. However, as the present patient administered the drug sublingually, it is possible that the blood concentration increased rapidly after transmucosal absorption. The symptom duration was approximately 26 hours in the present case, which suggests that HHCP may have a similar half-life and duration of action to THC and synthetic cannabinoids. Regarding the treatment of HHCP poisoning, there is no antagonist drug and it is reasonable to consider only infusion and symptomatic treatment rather than forced diuresis or dialysis, as in the case of THC poisoning. In the present case, the patient’s symptoms improved with the administration of intravenous fluids.

In the literature, there are 30 reported cases of subcutaneous ingestion of synthetic cannabinoids [6]. The frequently reported nervous system findings are coma, agitation, and convulsions; frequently reported cardiovascular findings are hypertensive emergencies, arrhythmias, myocardial infarction, and Takotsubo

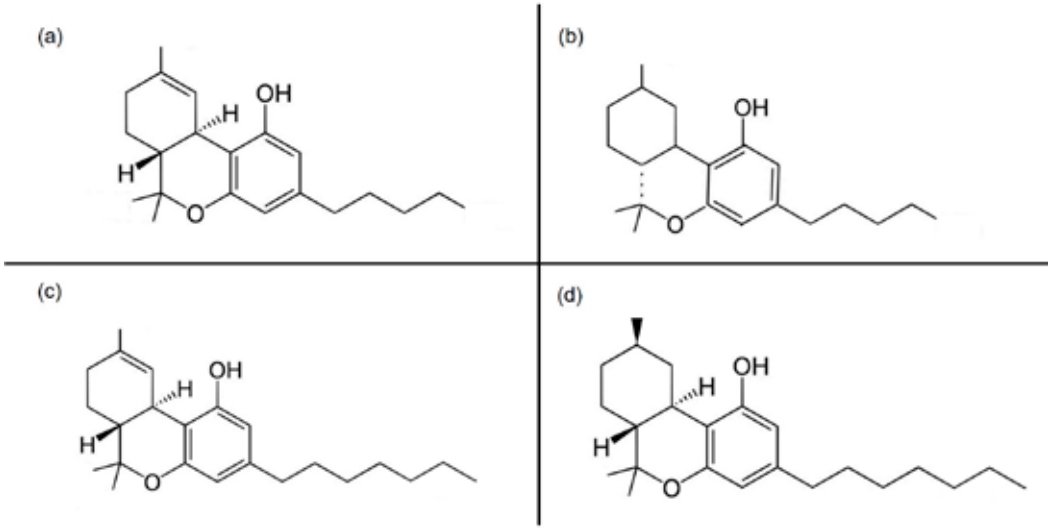

Fig. 3 Structural formulas of (a) THC, (b) hexahydrocannabinol, (c) tetrahydrocannabiphorol, (d) HHCP.

cardiomyopathy; and frequently reported pulmonary findings are type II respiratory failure, acute respiratory distress syndrome, and aspiration pneumonia [6]. There are also reports of renal dysfunction and rhabdomyolysis [6].

In the present case, the nervous system findings (agitation and convulsions) were similar to those reported in the literature. As for the cardiovascular findings, the ECG on admission showed sinus tachycardia and no obvious ST-segment changes, and a blood test was negative for troponin T. Furthermore, monitoring during hospitalization showed no obvious arrhythmias or findings suggestive of acute coronary syndromes, and no emergence of hypertensive emergencies. As for the pulmonary findings, although the patient had hypercapnia, which may have been due to seizure, there was no hypoxemia throughout the hospitalization, chest radiographic findings were normal, and blood tests showed no increased inflammation that may have been due to aspiration pneumonia. Additionally, the creatinine kinase concentration was only slightly increased on the second day and peaked thereafter, and there was no renal dysfunction. In summary, the present patient only had similar nervous system findings to the reported cases of subcutaneous injection of synthetic cannabinoids, with no signs of damage to other organs. The presence of acidosis, hypercapnia, and hyperlactatemia on blood tests was considered to be the result of seizures and associated respiratory depression during ambulance transport.

We will also address the social context of drugs, including marijuana. In Japan, marijuana is used as a fiber material, but is used as a drug overseas and has known psychoactive effects. Therefore, marijuana was designated as a narcotic drug in Japan, and its cultivation was totally prohibited. After that, in consideration of the production of hemp fiber, the cultivation of hemp in Japan was permitted only for the purpose of fiber and seed collection. Because the components of marijuana may be naturally inhaled during cultivation, the use of marijuana itself or the detection of THC in the body alone does not make it illegal under the current laws and regulations in Japan. However, the Ministry of Health is considering regulating the use of marijuana in light of the increasing number of marijuana-related arrests and the potential for drug crimes [7].

After the so-called "legal high" became popular in the 2000s, the structures of various illegal drugs were partially changed and products with the same effects but no legal restrictions were continually distributed [8]. Since 2013, drugs with similar structures have been collectively regulated in Japan through the "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices". However, as cannabis is regulated by the "Cannabis Control Act" rather than the "Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices", various semi-synthetic cannabinoids produced by hydrogenation and other modifications have been developed and sold over the internet in recent years to avoid the legal restrictions. To regulate these products, hexahydrocannabinol and tetrahydrocannabiphorol were designated as drugs from March 2022. However, a variety of THC analogues are continually being developed. The HHCP used in the present case has a similar structure to THC. In Japan, several THC-like ingredients and products containing them have been regulated by law since January 2024 due to potential health hazard, and HHCP was included in this regulation. However, it was not illegal at the time when we treated this patient (Fig. 3a–3d).

The pharmacological effects of HHCP are unknown. The product used in the present case contains 96% HHCP and no other cannabinoids. Therefore, the clinical findings are expected to reflect a rapid increase in blood concentrations of HHCP, but it is not known to what extent HHCP is inherently effective or to what extent it is potentiated by sublingual administration. However, HHCP has strong physical and psychological effects that required 5 days to subside in the present case. Therefore, the product cannot be called safe. When we searched the internet in May 2023 us-

ing the keywords "HHCP" and "liquid", we found that products containing liquid HHCP were easily available on well-known mail-order sites. There were also scattered posts on social networking sites spreading information about purchase sites (in May 2023). As HHCP has been illegal in Japan since January 2024, similar products claiming to be HHCP-free are now available. Thus, similar cases caused by the ingestion of semi-synthetic cannabinoids may continue to emerge. We believe that information on the characteristics of the semi-synthetic cannabinoid HHCP will lead to the treatment of patients suspected of ingesting similar ingredients, research into its pathophysiology, and the regulation of drugs containing it.

CONCLUSION

Although information on the psychiatric and physical symptoms of HHCP poisoning is lacking, our experience with the present case indicates that the product is not safe. Clinicians should be aware that similar cases of poisoning with semi-synthetic cannabinoids may occur in the future.

ACKNOWLEDGMENTS

We thank Kelly Zammit, BVSc, from Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

REFERENCES

1) Organized Crime Department, Government of Japan: Organized Crime Situation in 2022. https://www.npa.go.jp/sosikihanzai/R04sotaijousei/R4jousei.pdf (accessed 27th May 2023).
2) Cabinet Public Affairs Office, Government of Japan: Arrests for marijuana, especially among young people, have skyrocketed! The pitfalls of "invited" and "out of curiosity". https://www.gov-online.go.jp/useful/article/201806/3.html (accessed 27th May 2023).
3) Sarunya K, Dunyaporn T. An individuality of response to cannabinoids: challenges in safety and efficacy of cannabis products. Molecule 2023; 28: 2791.
4) Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, Huestis MA. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. Drug Alcohol Depend 2014; 144: 12–41.
5) Yoshito K. Cannabis (e.g., marijuana). In: Kamijo Yoshito ed. Clinical Toxicology, 1st ed. Tokyo: Igakushoin, 2009: 223.
6) Kourouni I, Mourad B, Khouli H, Shapiro JM, Mathew JP. Critical illness secondary to synthetic cannabinoid ingestion. JAMA Netw Open 2020; 3: e208516.
7) Subcommittee to Study Marijuana Regulation, Pharmaceuticals and Medical Devices System Subcommittee of the Health Sciences Council, Government of Japan: Summary of Discussion by the Subcommittee for the Study of Marijuana Regulations on the Regulation of Marijuana. https://www.mhlw.go.jp/content/11121000/001002508.pdf (accessed 27th May 2023).
8) Kikura-Hanajiri R, Uchiyama N, Kawamura M, Ogata J, Goda Y. Prevalence of new designer drugs and their legal status in Japan. Yakugaku Zasshi 2013; 133: 31–40. [in Japanese]