

CASE REPORT

Safety of cannabidiol products as a social issue: A case series

Yukari Maki  | Asuka Tsuchiya | Rie Yamamoto | Takeshi Saito | Seiji Morita |
Yoshihide Nakagawa

Department of Emergency and Critical
Care Medicine, Tokai University School of
Medicine, Isehara, Kanagawa, Japan

Correspondence

Asuka Tsuchiya, Department of Emergency
and Critical Care Medicine, Tokai University
School of Medicine, 143, Shimokasuya,
Isehara, Kanagawa 2591193, Japan.
Email: tsuchiya.asuka@tokai.ac.jp

Abstract

Background: Cannabidiol (CBD) products have increased in popularity in Japan in recent years, particularly among young people. Some CBD products contain tetrahydrocannabinol (THC), the main ingredient of cannabis, and its analogs, which are illegal in Japan and have become a social issue. This report discusses the safety of CBD products.

Case Presentation: Five patients with symptoms of CBD ingestion, including nausea, presented to our hospital. Three of the products these patients ingested contained THC. Metabolites of THC were detected in the blood and urine of all three patients, although there were some discrepancies in the urine drug screening test (DS10[®]). These examination results differed even when the same product was consumed.

Conclusion: CBD products are unsafe and may unintentionally contain THC. It is also important to understand that CBD can turn into THC, and the effective time needed to conduct urine drug screening.

KEY WORDS

cannabidiol, cannabinoid, cannabinoid analogs, illegal drug, tetrahydrocannabinol

BACKGROUND

The medicinal plant *Asa* (*Cannabis sativa* L.) contains over 500 compounds, including cannabinoids and terpenes. Among these, 104 bioactive substances are known to be cannabinoids. The most well-known cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC, the main ingredient in cannabis, is extracted from the ears, leaves, and roots of the cannabis plant. This compound can cause elation, excitement, and hallucinations when consumed, with side effects such as nausea and headaches. CBD, which has no psychoactive effects, is extracted from the stems and seeds of the plant and is not addictive. CBD is said to have a relaxing effect when ingested and is used as a treatment for epilepsy in some countries. Although THC is illegal in Japan, CBD is not illegal and is considered safe to use. In recent years, the availability of CBD products, such as gummy candies and the liquid in e-cigarettes, has increased

in Japan. These products can be easily and rapidly ingested and are particularly popular among young people. Some CBD products that claim to be legal contain THC ingredients or analogs, posing a risk to consumers of unknowingly ingesting illegal substances. This report discusses the safety of CBD products by summarizing clinical symptoms and laboratory findings from patients who ingested CBD products and were transported to our hospital.

CASE PRESENTATION

Five patients who ingested CBD products presented to our hospital via ambulance between January and December of 2023. We had not treated any such cases before 2022.

Table 1 shows the patient characteristics, vital signs, urinary drug screening (DS10[®]), and THC metabolites found in the patient's blood and urine samples.

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TABLE 1 Patient characteristics, vital signs, urinary drug screening (DS10[®]), and tetrahydrocannabinol (THC) metabolites in blood and urine samples.

Case number	1	2	3	4	5
Age (years)/Sex	28/Female	20/Male	18/Male	30/Female	36/Male
Occupation	Office worker	Office worker	Student	Office worker	Office worker
Comorbidities	None	None	None	None	None
Consciousness					
Japan Coma Scale	2	3	1	1	1
Glasgow Coma Scale					
Eye opening	3	4	4	4	4
Verbal response	5	3	5	5	5
Best motor response	6	6	6	6	6
Symptom time (h)	1	1	1	1	1
Vital					
Body temperature (°C)	35.3	37	36.5	36.7	37.7
Bloodpressure (mmHg)	120/66	150/70	150/100	100/74	140/80
Respiratory rate (/min)	18	16	25	21	23
Heart rate (/min)	82	108	107	93	85
Pupil (R/L) (mm)	4/4	5/5	3/3	3.5/3.5	4/4
Pupil reflex	+/+	+/+	+/+	+/+	+/+
Lactate (mg/dL)	30	34	18	10	14
DS10 [®]	All negative	All negative	THC+	All negative	THC+
Serum sample; THC-COOH (ng/mL)					
Day 1	Not collected	5.5	9.2	Not detected	10.8
Day 2		5.2	3.8		
Day 3		3.9	2.5		
Day 4		4.2			
Urine sample: THC-COOH (ng/mL)					
Day 1	Not collected	Not collected	7	Not detected	6.3

Case 1

A 28-year-old woman ingested three CBD gummies she purchased online. She developed nausea, vomiting, and mobility difficulties approximately 1 h later and requested an ambulance. Upon arrival at the hospital, her vital signs were normal. The results of a DS10[®] test were negative. The patient was rehydrated, her symptoms improved, and she was discharged. The ingested gummies were found to contain THC components (Figure 1).

Case 2

A 20-year-old man became unresponsive while traveling in the car of a friend, who then called for emergency assistance. He stated that he had inhaled vapor from a CBD liquid e-cigarette 1 h before the car ride. He vomited several times in the ambulance and continued to vomit upon arrival at the hospital. On arrival, his vital signs were normal, except for high blood pressure and an elevated pulse rate. The CBD

liquid he ingested was found to contain a THC component (Figure 1), although the results of a DS10[®] test were negative. THC-COOH, a metabolite of THC, was detected in serum samples from the patient. He was hospitalized for 4 days and discharged with improved symptoms.

Case 3

An 18-year-old man hit a guardrail and fell while riding a motorbike. He experienced bleeding from the head and requested an ambulance. His memory of the fall was vague. He had inhaled vapor from a CBD liquid e-cigarette with a friend approximately 6 h before the accident and developed symptoms of nausea while riding the motorbike. His vital signs were within normal ranges, except for elevated blood pressure and pulse rate. The ingested product contained a THC component (Figure 1), and a DS10[®] test was positive for THC. We also identified THC-COOH in the patient's serum and urine. He was hospitalized for 3 days, his symptoms improved, and he was discharged.

Case number	1	2	3
Type	gummy	e-cigarette	e-cigarette
Components	Starch syrup (manufactured in Japan), sugar, Cola syrup (fructose-butane liquid sugar, syrup, other), gelatine, HHCP, CBG, Vegetable fats, Cornstarch/acidifier, bicarbonate of soda, flavouring, Colouring (caramel colour)	HHCP, H4CBD, terpenes	THCV, CBD, CBDV, CBG, terpenes



FIGURE 1 Types and components of cannabidiol products ingested in Cases 1–3.

Case 4

A 30-year-old woman inhaled vapor from a CBD oil e-cigarette with her friends. After approximately 1 h, she became agitated, and her friends called for emergency help. On arrival at the hospital, she complained of dry mouth and mood discomfort. Her vital signs were normal. She did not bring the CBD oil and was not sure about the product. A DS10[®] test was negative. After hydration and follow-up, her symptoms improved, and she was discharged.

Case 5

A 36-year-old man had inhaled vapor from the same e-cigarettes as Case 4. Approximately 1 h later, he became short of breath and requested emergency medical assistance. On arrival, his vital signs were normal except for a slightly elevated body temperature of 37.7°C. He had not ingested CBD

oil, and the product was unknown. A DS10[®] test was positive for THC. Serum and urine samples revealed THC-COOH. Hospitalization was recommended; however, the patient refused hospitalization and was discharged with hydration.

DISCUSSION

This report described the characteristics of patients who had consumed CBD products and the properties of these products. In Cases 1–3, the subjects consumed products that also contained THC analogs (Figure 2). Cases 1 and 2 contained a compound called hexahydrocannabinol (HHC), which is produced from THC and shares the same structure.¹ In addition to CBD, Cases 1 and 3 had also consumed tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), and cannabigerol (CBG). These are different compounds, but cannabinoids with a structural formula similar to THC.² Therefore, Cases 1–3 experienced THC-like effects.

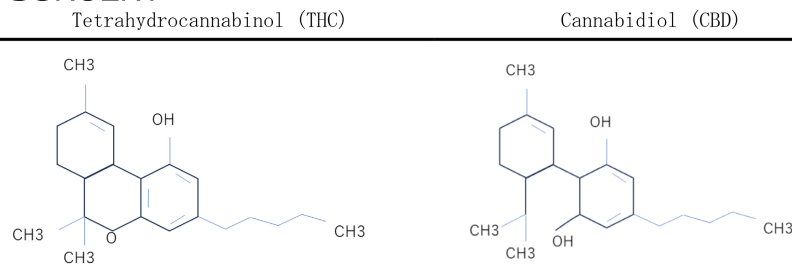


FIGURE 2 Structural formulas of tetrahydrocannabinol and cannabidiol.

Papers reporting overseas consistently report the safety of cannabidiol preparations, with no clear side effects documented.^{3–5} None of these papers have reported symptoms characteristic of those observed in Japanese patients. However, in our study, patients reported symptoms such as headache, nausea, and mood discomfort after consuming cannabidiol products, contrary to findings from overseas. This discrepancy suggests that Japanese individuals may be more susceptible to side effects, given the rapid increase in complaints of adverse reactions to recently popularized cannabidiol products in Japan, emerging as a social concern. Additionally, it is plausible that side effects could be attributed to the presence of THC in some cannabidiol products, suggesting that not all side effects can be solely attributed to cannabidiol products.

Even pure CBD can be converted or metabolized to THC. Case 5 was exposed to THC-free products that claimed to contain pure CBD but also experienced THC-like side effects such as nausea and mood discomfort. THC metabolites were also detected in the patient's serum and urine samples. This suggests that CBD underwent chemical transformation to THC inside or outside the patient's body. An *in vivo* animal study did not detect any THC metabolites in the blood or stomach contents of mini-pigs treated with CBD⁶; therefore, it is highly unlikely that pure CBD is converted into THC in the human body. However, CBD has a similar structural formula to THC (Figure 2), and heating CBD under acidic conditions can produce THC outside the body.⁷ The possibility of converting CBD into THC has been supported by several studies; however, uncertainties remain regarding this reaction. Therefore, the possibility of CBD being converted into THC under certain conditions does not guarantee the safety of pure CBD products. Clinicians should be aware of the possibility of THC being detected when examining patients who have ingested e-cigarette-type products containing CBD.

In clinical practice, as THC identification poses challenges, THC-COOH, a metabolite of THC, can serve as an alternative marker to confirm THC uptake by the body. Mass spectrometry and chromatography methods are predominantly utilized for THC-COOH identification and quantification. Mass spectrometry techniques encompass gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry. For quantification, a standard solution of THC-COOH is prepared, and a standard curve is generated using this solution. Subsequently, the amount of THC-COOH in the unknown sample can be determined through calculation.

In addition, the timing of DS10[®] testing is also significant. Following ingestion, THC is metabolized in the body (e.g., in the liver) and excreted in the urine or blood as the THC metabolite THC-COOH. Quantification or qualification of THC-COOH via DS10[®] is therefore necessary to confirm THC use. The THC-COOH peak on DS10[®] can be observed after approximately 4 h.⁸ In our cases, symptoms appeared approximately 1 h following consumption, and all tests were performed almost simultaneously. In Case 2, DS10[®] was negative, but THC-COOH was identified in a serum sample. Therefore, it is possible that the DS10[®] was conducted too early in that case and that a slightly later collection would have resulted in a positive result. This suggests that, even if an initial urine drug test is negative, it may be necessary to retest following a delay.

THC-COOH test results may vary, owing to the nature of THC and individual differences in THC metabolism. THC is highly fat-soluble and is distributed and stored in adipocytes. A study that administered synthetic cannabinoids to rats found that the drug was still present in adipose tissues 1 month after its apparent effects had subsided. Therefore, THC continues to accumulate in the body for an extended period.⁹ The difference in the test results between Cases 4 and 5 may have been due to variations in fat tissue content between the individuals. For Case 5, this was not the first time the drug had been consumed, suggesting the possibility of accumulation from previous uses as well.

Physicians in some countries use CBD as a medicinal treatment, and there has been a recent movement to allow its use in Japan. This movement proposes to legalize the use and cultivation of medicines made from cannabis plants. To prevent the abuse of cannabis, a new crime of “use” will be established in addition to the already banned crime of “possession.” Beginning in December 2023, THC analogs such as HHC will also be treated as illegal drugs. It is well known that the use of cannabis is prohibited in Japan; however, few emergency physicians are familiar with its actual symptoms and ingredients. Therefore, deepening physicians' levels of understanding regarding CBD and THC through such case reports is important to the future of medicine in Japan. There is a significant possibility that new products will be introduced in the future, and it is important to note that qualitative tests may not always be positive. This experience will be useful in the treatment of such cases.

CONCLUSION

Patients who consume CBD products and exhibit the symptoms described herein are likely to have also been affected by THC. Therefore, THC-focused treatments may be required. A final diagnosis requires a thorough analysis of blood and urine samples, which can be done with simple kits such as DS10[®]. Currently, CBD products for sale in Japan may not be safe. The current situation needs to be understood, and legislation should be adjusted accordingly, alongside careful medical treatment.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Approval of the research protocol: N/A.

Informed consent: Informed consent was obtained from the patients or their families.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

ORCID

Yukari Maki  <https://orcid.org/0000-0002-6739-592X>

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