Original Article

Clinical and toxicological findings of acute intoxication with synthetic cannabinoids and cathinones

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Aim: Reporting of the analytical and clinical findings of synthetic cannabinoids and cathinones is essential in carrying out a complete clinical assessment of new psychoactive substances.

Methods: From 2012 to 2014, we examined synthetic cathinone and cannabinoid poisoning in six patients aged 22–42 years old. Analyses of these compounds were carried out using liquid chromatography–tandem mass spectrometry.

Results: The observed clinical symptoms were similar to those reported for intoxication with synthetic cathinones and cannabinoids. In cases of intoxication with synthetic cathinones, the psychiatric and neurological symptoms were long-lasting, and these compounds were detected in serum for 15–48 h after use. Although the clinical symptoms induced by the synthetic cannabinoids disappeared within several hours after use, the range of serum concentrations of these compounds was ≤5 ng/mL for 1–3 h after use. In one fatal case, in which high serum concentrations of synthetic cathinones and cannabinoids were detected, the most plausible cause of death was heart failure due to overdose with these drugs. The long-lasting symptoms induced by synthetic cathinones correlated with the long detection window in serum, whereas the early disappearance of symptoms induced by synthetic cannabinoids corresponded to the short detection window in serum.

Conclusions: This study shows that the profiles of synthetic cathinones and cannabinoids in serum are closely related to the duration of the toxic symptoms and that concomitant use of two psychoactive drugs with different pharmacological actions may have the potential for fatal cardiotoxicity.

Key words: Designer drugs, drug abuse, psychoactive drugs, synthetic cannabinoids, synthetic cathinones

INTRODUCTION

SYNTHETIC CANNABINOIDS AND cathinones are new psychoactive substances that have emerged around the world over the past few years. A number of these compounds are highly addictive and have the potential to be poisonous, and abuse of these products could be very dangerous.[1–11] Herein, we present six cases of intoxication with synthetic cathinones and synthetic cannabinoids, along with the analytical and clinical documentation of these patients. Reporting of the analytical and clinical findings of these substances is essential in carrying out complete clinical assessments for new psychoactive substances.

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METHODS

FROM 2012 TO 2014, synthetic cathinone and cannabinoid poisoning was examined in six patients (five patients at Iwate Medical University Hospital [Morioka, Japan] and one patient at Hiroshima University Hospital [Hiroshima, Japan]). The patients were comprised of three men and three women, with ages ranging from 22 to 42 years and a mean age (± SD) of 30.5 ± 8.7 years (Table 1). The background data for these patients was obtained from their medical charts. The data for the patient at Hiroshima University Hospital was collected by mail. These data were

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Table 1. Profiles of patients with synthetic cathinone and cannabinoid poisoning

Case	Gender	Age, years	Clinical symptoms	Duration of psychiatric or neurological symptoms	Outcome	Detected compounds (serum concentration)	
1	M	22	Hyperthymia, agitation, excitement, hallucination, paranoia, consciousness disorder, tachycardia, ECG changes, elevated CK	24 h	Survival	α-PVP† (43 ng/mL) Me-PHP† (0.55 ng/mL)	15 h after use
2	F	42	Nausea, anorexia, ataxia, neck pain	2 days	Survival	α-PVP† (1.3 ng/mL)	2 days after use
3	F	39	Vomiting, convulsion, loss of conscious, hypotension	3 h	Survival	MAM-2201‡ (5.3 ng/mL) XLR-11‡ (1.3 ng/mL)	1 h after use
4	F	33	Nausea, vomiting, hyperthymia, confusion, tachycardia	5 h	Survival	PB-22‡ (trace) 5F-PB-22‡ (trace)	1.5 h after use
5	M	24	Consciousness disorder, hypertension, tachycardia, elevated CK	10 h	Survival	AB-PINACA‡ (4.3 ng/mL)	3 h after use
6	M	23	Acute circulatory failure, congestion of organs, gastrointestinal bleeding	–	Death	Mepirapim‡ (0.95 μg/mL) α-EAPP† (3.1 μg/mL)	3.5 h after use

†Synthetic cathinones. ‡Synthetic cannabinoids. AB-PINACA, N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide; CK, creatine kinase; α-EAPP, α-ethylaminopentiophenone; ECG, electrocardiogram; 5F-PB-22, 1-(5-fluoropentyl)-8-quinolinyl ester-1H-indole-3-carboxylic acid; MAM-2201, [1-(5-fluoropentyl)-1H-indol-3-yl](4-methyl-1-naphthyl)methanone; MePHP, 4′-Methyl-α-pyrrolidinohexiophenone; mepirapim, (4-methylpiperazin-1-yl)(1-pentyl-1H-indol-3-yl)methanone; PB-22, 1-pentyl-8-quinolinyl ester-1H-indole-3-carboxylic acid; α-PVP, α-pyrrolidinovalerophenone; XLR-11, (1-(5-fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone.

collected and analyzed at the Department of Emergency Medicine, Iwate Medical University School of Medicine.

Standards for the synthetic cannabinoids and cathinones were purchased from Cayman Chemical (Ann Arbor, MI, USA) and D_5-diazepam (internal standard; IS) was purchased from Hayashi Pure Chemical Industries (Osaka, Japan). Methanol and acetonitrile (both high-performance liquid chromatography grade) and ammonium formate were purchased from Kanto Chemical Company (Tokyo, Japan). A QuEChERS prepacked extraction pack containing 6 g magnesium sulfate and 1.5 g sodium acetate and a dispersive solid-phase extraction kit containing 25 mg primary secondary amine, 25 mg end-capped octadecylsilane, and 150 mg magnesium sulfate were purchased from Agilent Technologies (Santa Clara, CA, USA).

Analyses of these compounds were carried out using liquid chromatography (LC)–tandem mass spectrometry (MS/MS) at the Poisoning and Drug Laboratory Division, Iwate Medical University. Liquid chromatography was carried out on a UFLC instrument (Shimadzu, Kyoto, Japan); MS/MS was carried out on a 3200 QTRAP instrument (AB SCIEX, Framingham, MA, USA).

Synthetic cathinones and cannabinoids in serum were extracted according to the QuEChERS method described by Usui *et al*. with minor modifications.[12] Briefly, a 0.5-mL serum aliquot was diluted with 1.0 mL deionized water in a glass tube. The diluted sample was transferred to a plastic tube with 0.5 g pre-packed extraction salt, one stainless steel bead, and 1.0 mL acetonitrile containing 20 ng IS. The mixture was shaken vigorously for 30 s by hand and centrifuged at 2,300 g/ for 5 min. The supernatant (600 μL) was transferred to a 2-mL centrifuge tube containing the dispersive solid-phase extraction kit. The tube was mixed by vortexing for 10 s and then centrifuged at 17,000 g/ for 5 min. The upper layer (200 μL) was transferred to a glass tube to which 20 μL of 0.1% trifluoroacetic acid in acetonitrile was added. The solution was evaporated to dryness under a nitrogen stream at room temperature, and the residue was reconstituted in 200 μL methanol.

RESULTS

Clinical symptoms

A SUMMARY OF THE background data for the six patients with synthetic cathinone and cannabinoid poisoning is presented in Table 1. In cases of intoxication with the synthetic cathinones (cases 1 and 2), psychomotor excitement persisted for approximately 24 h after use in case 1, and nausea, anorexia, ataxia, and neck pain persisted for approximately 2 days after use in case 2. Case 1 had repeatedly taken designer drugs that had been purchased on the

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Internet over the course of approximately 1 month, and case 2 had ingested a liquid aphrodisiac during every episode of sexual intercourse with her partner over the course of 2 months. In cases of intoxication with the synthetic cannabinoids (cases 3, 4, and 5), the psychiatric symptoms improved at an average of 6 h (range, 3–10 h) after use. For the fatal case (case 6) in which synthetic cathinones and cannabinoids were detected, the patient fell into bed and fell asleep after ingestion of the drugs in the restroom. After 2 h, he was found without respiratory signs and was transferred to a hospital. On arrival at the hospital, he experienced cardiopulmonary arrest and was confirmed dead approximately 3.5 h after drug use. Congestion of the organs (particularly the lungs) and gastrointestinal bleeding from the stomach into the duodenum were revealed by autopsy. It was concluded that acute circulatory failure due to drug action was the cause of the death.

Toxicological analysis

Figure 1 shows selected reaction monitoring chromatograms of human serum spiked with reference standards obtained using LC-MS/MS. Table 1 and Figure 2 show the serum concentrations and the selected reaction monitoring chromatograms of the detected compounds in the intoxication cases, respectively. In case 1, α-pyrrolidinovalerophenone (α-PVP, 43 ng/mL) and 4'-Methyl-α-pyrrolidinohexiophenone (MePHP, 0.55 ng/mL) were detected in serum for 15 h after use. In case 2,

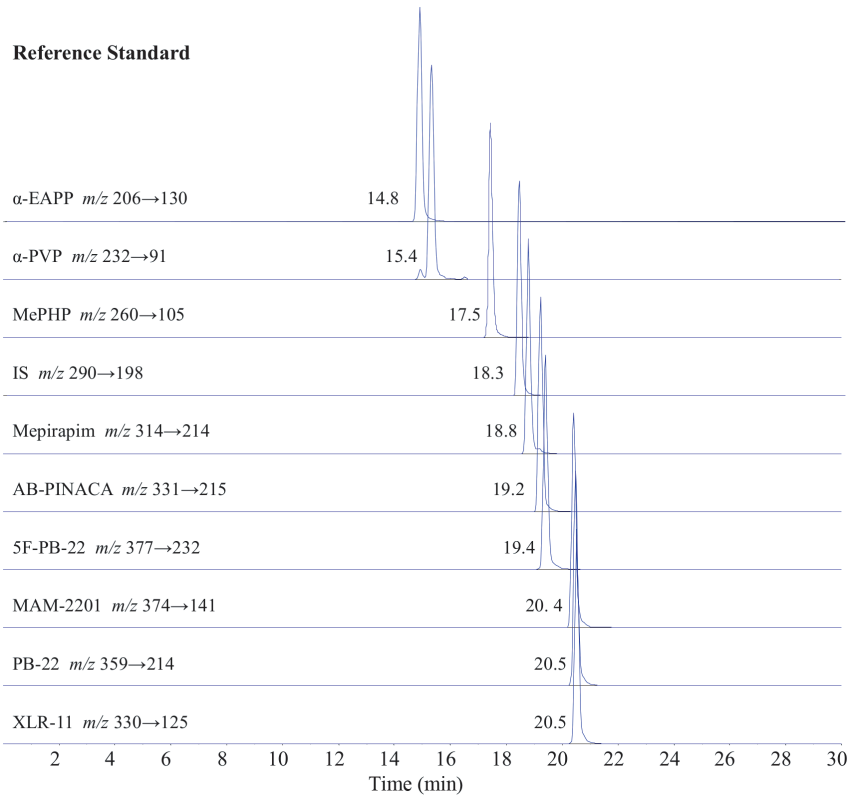

Fig. 1. Selected reaction monitoring chromatograms obtained after extraction of human serum spiked with α-ethylaminopentiophenone (α-EAPP), α-pyrrolidinovalerophenone (α-PVP), 4'-Methyl-α-pyrrolidinohexiophenone (MePHP), (4-methylpiperazin-1-yl)(1-pentyl-1H-indol-3-yl)methanone (mepirapim), N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (AB-PINACA), 1-(5-fluoropentyl)-8-quinolinyl ester-1H-indole-3-carboxylic acid (5F-PB-22), [1-(5-fluoropentyl)-1H-indol-3-yl](4-methyl-1-naphthyl)methanone (MAM-2201), 1-pentyl-8-quinolinyl ester-1H-indole-3-carboxylic acid (PB-22), (1-(5-fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethylcyclopropyl)methanone (XLR-11), and internal standard (IS) using liquid chromatography–tandem mass spectrometry. Column: L-column (150 mm × 1.5 mm i.d., 5 μm particle size; CERI, Tokyo, Japan). Mobile phase: solvent A, 95% 10 mmol/L ammonium formate–5% methanol; solvent B, 5% 10 mmol/L ammonium formate–95% methanol. Gradient: solvent B 0% to 100% in 15 min (hold 10 min). Flow rate: 0.1 mL/min. Column oven: 40°C, Injection volume: 5 μL. Polarity: positive.

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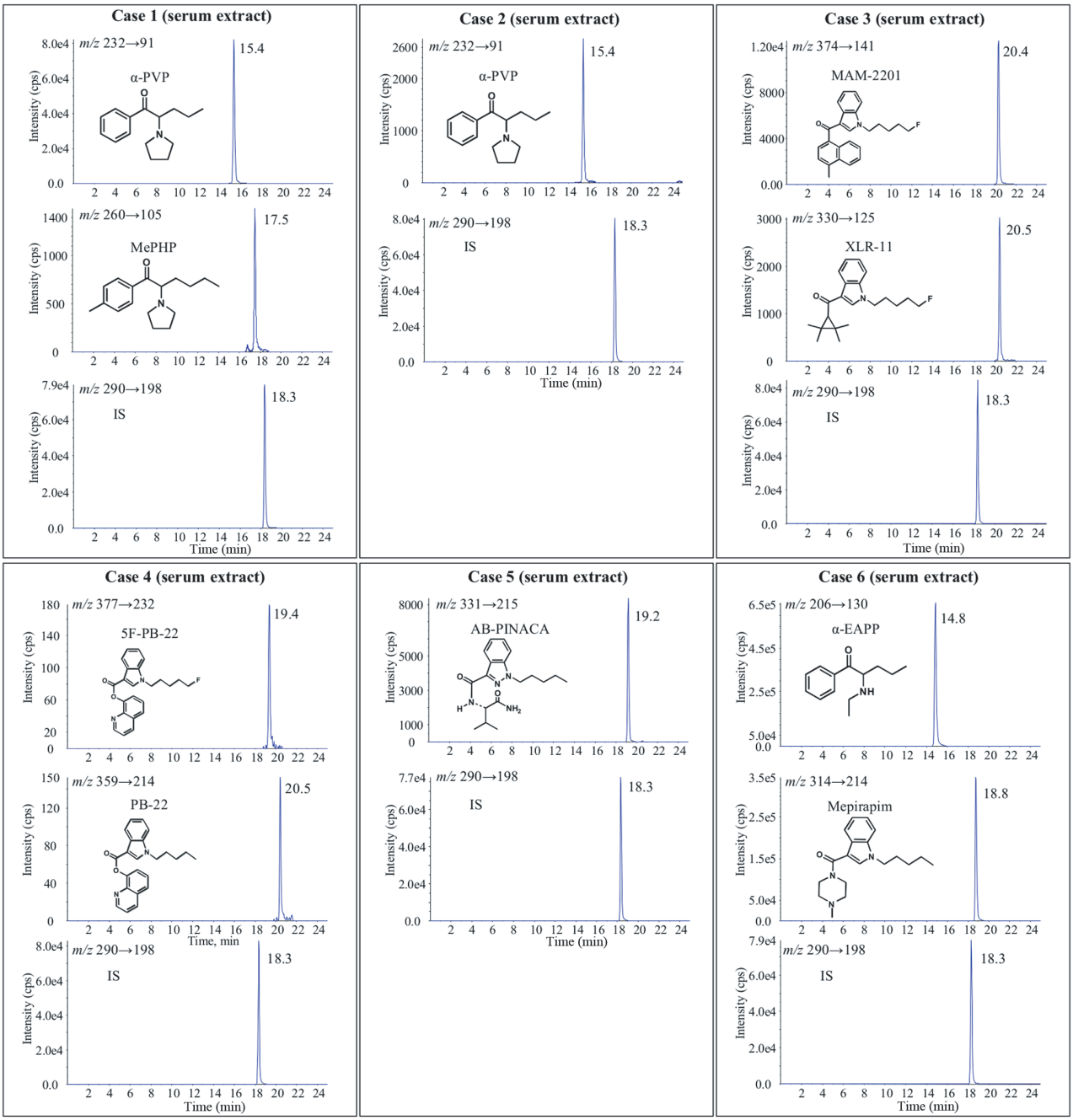

Fig. 2. Selected reaction monitoring chromatograms obtained after extraction of the serum from cases of acute intoxication with synthetic cannabinoids and cathinones using liquid chromatography–tandem mass spectrometry. Column: L-column (150 mm × 1.5 mm i.d., 5 μm particle size; CERI, Tokyo, Japan). Mobile phase: solvent A, 95% 10 mmol/L ammonium formate–5% methanol; solvent B, 5% 10 mmol/L ammonium formate–95% methanol. Gradient: solvent B 0% to 100% in 15 min (hold 10 min). Flow rate: 0.1 mL/min. Column oven: 40 °C. Injection volume: 5 μL. Polarity: positive.

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α-PVP was detected in serum (1.3 ng/mL) for 2 days after use. In case 3, [1-(5-fluoropentyl)-1H-indol-3-yl](4-methyl-1-naphthyl)methanone (MAM-2201, 5.3 ng/mL) and (1-(5-fluoropentyl)-1H-indol-3-yl)(2,2,3,3-tetramethyl-cyclopropyl)methanone (XLR-11, 1.3 ng/mL) were detected in serum for 1 h after use. In case 4, 1-pentyl-8-quinolinyl ester-1H-indole-3-carboxylic acid (PB-22, trace) and 1-(5-fluoropentyl)-8-quinolinyl ester-1H-indole-3-carboxylic acid (5F-PB-22, trace) were detected in serum for 1.5 h after use. In case 5, N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (AB-PINACA, 4.3 ng/mL) was detected in serum for 3 h after use. In case 6, (4-methylpiperazin-1-yl)(1-pentyl-1H-indol-3-yl)methanone (mepirapim, 0.95 μg/mL) and α-ethylaminopentiophenone (α-EAPP, 3.1 μg/mL) were detected in serum for 3.5 h after use. The quantitative analyses for mepirapim and α-EAPP were determined in 10- and 50-fold-diluted serum samples, respectively.

DISCUSSION

IN THIS REPORT, cases of intoxication with synthetic cathinones and cannabinoids presented with psychiatric, neurological, gastrointestinal, cardiovascular, and muscular manifestations. These observed clinical symptoms are similar to the reported symptoms of synthetic cathinone and cannabinoid intoxication.[10] In the cases in which synthetic cathinones were detected, that is, cases 1 and 2, the psychiatric and neurological clinical symptoms were long-lasting. The effect of the synthetic cathinone naphyrone, which has a structure similar to those of α-PVP and MePHP, lasts for 2 days and the half-life has been calculated to be 34 h.[4] In addition, pyrovalerone derivatives, such as naphyrone, α-PVP, and MePHP, easily cross the blood–brain barrier due to their high lipophilicity.[8,13,14] Thus, the long-lasting effects of the pyrovalerone-type cathinones appear to be associated with their long half-life and blood–brain barrier transit. In contrast, in the cases of synthetic cannabinoids intoxication, the clinical symptoms disappeared within an average of 6 h after use. This tendency is consistent with other reports of intoxication with synthetic cannabinoids.[6]

In the fatal case 6, higher concentrations of synthetic cannabinoids and cathinones were detected in serum compared with the other surviving cases, and the pulmonary congestion was more severe than that of other organs. We could not find any other cause of death except for heart failure in the fatal case. We therefore reason that the heart failure due to overdose with these drugs is the most plausible cause of death. Deaths have also been reported to be associated with cardiotoxicity to the synthetic cathinones and cannabinoids.[5,7,9,11] Synthetic cathinones inhibit monoamine transport, similar to methamphetamine and cocaine. The cardiovascular effects of methamphetamine and cocaine have been well documented.[15–17] Alpha-EAPP, which exhibits similar pharmacological actions, appears to show the same cardiotoxicity as methamphetamine and cocaine. Synthetic cannabinoids are cannabinoid receptor agonists and most have affinity not only for cannabinoid receptor 1 but also for cannabinoid receptor 2.[18] Cannabinoid receptor 1 is distributed throughout the central nervous system and is responsible for the psychotropic effects. Meanwhile, cannabinoid receptor 2 is mainly expressed in immune and hematopoietic cells. Recent studies have reported expression of cannabinoid receptors 1 and 2 in the myocardium and cannabinoid receptors are involved in a variety of cardiovascular effects.[19] The cardiovascular symptoms that are induced by synthetic cannabinoids appear to occur through cannabinoid receptors. Concomitant use of synthetic cathinones and cannabinoids, which show different pharmacological mechanisms of action, may have the potential to induce severe or fatal cardiotoxicity. It is therefore conceivable that acute circulatory failure may lead to synergistic fatal cardiovascular effects following concomitant use of the synthetic cathinone α-EAPP and the synthetic cannabinoid mepirapim.

Our analytical method was able to successfully detect synthetic cathinones and cannabinoids in cases of intoxication. Although the method did not use deuterium-labeled analogs for internal standards, the overall precision and accuracy of the method were acceptable (data not shown). Pyrovalerone-type cathinones were detected in serum from case 1 (α-PVP and MePHP) and case 2 (α-PVP) up to 15 h and 2 days after use, respectively. Cases 1 and 2 had ingested the drug for 1 month and 2 months, respectively. The extended window of detection in serum may be attributed to redistribution of these compounds into the bloodstream from tissues that have accumulated these compounds, especially after continuous ingestion, in addition to the long half-lives of pyrovalerone-type cathinones.[4]

Synthetic cannabinoids were detected in serum samples from cases 3, 4, and 5. Both MAM-2201 and XLR-11 were detected in serum from case 3, with AB-PINACA in serum from case 5, and PB-22 and 5F-PB-22 in serum from case 4. The serum concentrations of the detected synthetic cannabinoids were ≤5 ng/mL for 1–3 h after use. Kacinko *et al.*[20] reported that the peak whole blood concentrations of JWH-018 and JWH-073 in one human subject were 4.8 and 4.2 ng/mL, respectively, 19 min after smoking and the blood concentrations were <1 ng/mL within 2 h after smoking. Teske *et al.*[21] reported the serum concentrations of JWH-018 in two humans that peaked (8.1 and 10.2 ng/mL) within 5 min after smoking and were reduced to <0.5 ng/mL within 3 h after smoking. It has been reported that the majority of

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the clinical effects in cases of synthetic cannabinoid intoxication last for less than 8 h.[6] A similar trend was seen in the symptoms of our cases of synthetic cannabinoid intoxication. It is therefore considered that synthetic cannabinoids are rapidly metabolized or eliminated from the body.

The synthetic cannabinoids, PB-22 and 5F-PB-22, are the first marketed synthetic cannabinoids with an ester group. It has been reported that PB-22 and 5F-PB-22 degrade significantly over 1 h and are not detectable after 3 h in human hepatocytes, and it is assumed that these compounds would undergo extensive ester hydrolysis *in vivo* due to the widespread distribution of esterases.[22] In case 4, PB-22 and 5F-PB-22 were present in serum at trace levels 1.5 h after use. However, detection of PB-22 has been reported in serum following long-term use (i.e., daily for several weeks) in one case; the concentrations at the time of hospital arrival and 12 h later were 50 ng/mL and 28 ng/mL, respectively.[23] Detection of ester-bond compounds that can undergo extensive ester hydrolysis in serum may indicate long-term exposure.

In the fatal case (case 6), the serum concentrations of the synthetic cannabinoid mepirapim and the synthetic cathinone α-EAPP were 0.95 and 3.1 μg/mL, respectively. These serum concentrations were much higher than those of the surviving cases. Mepirapim is a JWH-018 analog with a 4-methylpiperazine group inserted in place of the naphthyl group in JWH-018. Concentrations of JWH-018 in postmortem whole blood range from 0.1 to 199 ng/mL.[24] It has been reported that the blood concentrations of several fatal cases in which death was attributed to mephedrone, which has a structure similar to α-EAPP, ranged from 0.98 to 22 μg/mL.[1–3] Although there are some differences in the pharmacological effects and pharmacokinetics, these serum concentrations of α-EAPP and mepirapim appear to lead to fatality.

Although there have been reports of serum concentrations of a number of synthetic cathinones and cannabinoids as well as the symptoms induced by these compounds, there is very little information regarding the relations between the serum concentrations and the symptoms. In this study, the long-lasting symptoms induced by synthetic cathinones correlated with the long detection window in serum, whereas the early disappearance of symptoms induced by synthetic cannabinoids correlated with the short detection window in serum.

CONCLUSIONS

THIS STUDY SHOWS that the serum profiles of synthetic cathinones and cannabinoids are closely related to the duration of the toxic symptoms and that concomitant use of the two psychoactive drugs, with different pharmacological mechanisms of action, may have the potential to induce fatal cardiotoxicity. We consider that our findings will contribute to the development of clinical investigations into new psychoactive drug poisonings.

CONFLICT OF INTEREST

NONE.

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