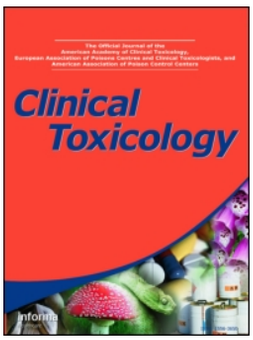

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Supraventricular tachycardia and acute confusion following ingestion of e-cigarette fluid containing AB-FUBINACA and ADB-FUBINACA: a case report with quantitative analysis of serum drug concentrations

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SHORT COMMUNICATION

Supraventricular tachycardia and acute confusion following ingestion of e-cigarette fluid containing AB-FUBINACA and ADB-FUBINACA: a case report with quantitative analysis of serum drug concentrations

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ABSTRACT

Background: AB-FUBINACA and ADB-FUBINACA are structurally similar synthetic cannabinoids with potent CB_1 receptor agonistic effects. Very little is known about their pharmacology and toxicology.

Objective: To report a case of supraventricular tachycardia and acute confusion after ingestion of e-cigarette fluid containing AB-FUBINACA and ADB-FUBINACA, with quantitative analysis of the serum drug concentrations.

Case report: A healthy 24-year-old man ingested two drops of e-cigarette fluid which were later found to contain AB-FUBINACA and ADB-FUBINACA. Within 30 min of ingestion, he became somnolent, confused, and agitated, with palpitation and vomiting. On arrival to the emergency department, a short run of supraventricular tachycardia was noted, which resolved spontaneously. Bedside urine immunoassay failed to detect recreational drugs. Laboratory blood tests showed mild hypokalemia. Exposure to AB-FUBINACA and ADB-FUBINACA was confirmed analytically, with serum concentrations of 5.6 ng/mL and 15.6 ng/mL, respectively, in the blood sample collected on presentation. The patient recovered uneventfully with supportive treatment and was discharged 22 h after admission.

Discussion: AB-FUBINACA and ADB-FUBINACA are orally bioavailable with rapid onset of toxicity after ingestion. In this case, supraventricular tachycardia was likely the result of exposure to AB-FUBINACA and ADB-FUBINACA. The serum concentrations of AB-FUBINACA and ADB-FUBINACA were higher than those previously reported in fatal cases.

Conclusion: In the context of acute poisoning, the presence of unexplained tachyarrhythmias, confusion, and a negative recreational drug screen should prompt clinicians to consider synthetic cannabinoid toxicity as a differential diagnosis.

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Introduction

AB-FUBINACA (N-[(2S)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide) and ADB-FUBINACA (N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide) are structurally similar synthetic cannabinoids with potent CB_1 receptor agonistic effects. Both have emerged as novel psychoactive substances "designed" as "legal" substitutes for marijuana. Owing to their novelty, very little is known about their pharmacology and toxicology. In particular, there is a paucity of human studies that correlate clinical toxicities with their serum drug concentrations [1]. In this article, we present a case of supraventricular tachycardia (SVT) and acute confusion following ingestion of e-cigarette fluid containing AB-FUBINACA and ADB-FUBINACA. The patient's serum drug concentrations on presentation were measured to complement our current understanding about the substances' acute toxicity profiles.

Case

A previously healthy 24-year-old man was brought to the emergency department (ED) for acute confusion, agitation, visual hallucinations, and palpitations. The patient told his twin brother that 30 min before presentation, he had ingested two drops of e-cigarette fluid from a bottle labeled "VaporFi", which was mixed with clear fluid from another unlabeled bottle believed to be "liquid cannabis" (Figure 1). The stated ingredients of "VaporFi" fluid include propylene glycol, glycerin, and natural and artificial flavorings, but the composition of the unlabeled clear fluid was unknown. Both bottles of fluid were purchased by the patient on the Internet and were intended for "vaping" with an electronic device that aerosolizes liquids without combustion (Figure 1).

On arrival, the patient was confused and had a Glasgow Coma Score (GCS) 14/15 (E4M6V4). His blood pressure was 163/93 mmHg, heart rate 169 bpm, respiratory rate 20 breaths per minute, temperature 36.3 °C, and oxygen

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Figure 1. (a) The e-cigarette fluid labeled "VaporFi" and the smoking device. (b) The unlabeled bottle of clear fluid.

saturation 98% on room air. Both his pupils were 5 mm in diameter and were reactive to light. Physical examination was notable for tachycardia, and the cardiac monitor showed SVT at a rate of 172 bpm. Examination of his cardiovascular, respiratory, and neurological systems was otherwise unremarkable. The patient was immediately sent to the resuscitation room. A 12-lead electrocardiogram (ECG) performed several minutes later showed sinus tachycardia (148 bpm) with multiple ventricular ectopic beats. Both a chest X-ray and spot glucometer test were unremarkable. Bedside urine toxicology immunoassay (ABON Biopharm, Hangzhou, China) was negative for amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), ketamine, and tetrahydrocannabinol (THC). The complete blood count was unremarkable. Biochemically, there were mild hypokalemia (3.2 mmol/L, reference interval (RI) 3.6–5.0 mmol/L), raised creatinine (119 μmol/L, RI 67–109 μmol/L), and mildly raised alkaline phosphatase (123 U/L; RI 42–110 U/L) and creatine kinase (519 U/L, RI 65–355 U/L). Paracetamol, salicylate, and ethanol were undetectable by quantitative analysis of patient's serum specimen.

The clinical impression was that of synthetic cannabinoid poisoning in view of the patient's history and negative bedside urine drug immunoassays. The patient was given intravenous fluid and potassium replacement therapy. He was placed on a cardiac monitor and admitted for close observation. The patient's GCS returned to 15/15 two hours after admission. Further history taking was attempted when the patient was fully awake. However, he could not recall further details of the incident and denied any suicidal thoughts. His heart rate and pupil size returned to normal eight hours after admission with no recurrence of dysrhythmia. An ECG repeated 19 h after admission showed normal sinus rhythm (82 bpm) with no ventricular ectopics or delta wave. No withdrawal symptoms were noted during observation, and the patient was discharged 22 h after admission. He defaulted subsequent follow-up appointments. The patient's blood and urine samples collected on presentation, together with the left-over fluids, were sent to the Hospital Authority Toxicology Reference Laboratory for further analysis.

Laboratory techniques and analysis

The two liquid products were subjected to systematic toxicology screening by high-performance liquid chromatography with photodiode array detection (HPLC-DAD) followed by confirmation using ion trap time-of-flight mass spectrometry (IT-TOF/MS). In brief, 0.5 mL of the sample was added to Toxi Tube-A extraction tube (Agilent Technologies Inc, Lake Forest, CA). The tube was shaken in an orbital shaker for 30 min and centrifuged at 2500 g for 5 min. The top phase (1.25 mL) was then dried under compressed air at room temperature and reconstituted in 0.8 mL of 30% acetonitrile (ACN). A 10 μL aliquot was injected into the HPLC system (Agilent HPLC-DAD 1260 Infinity, Germany) for analysis with detection at 210, 254, and 305 nm wavelengths. The retention time (RT) and UV spectrum (210 nm) were compared against those of the reference standard for compound identification. Another aliquot (5 μL) with 20-fold dilution was injected into the IT-TOF/MS analyzer (Shimadzu LCMS-IT-TOF, Kyoto, Japan). Q1 scanning (100–800 m/z) and product ion scanning (50–700 m/z) were performed at both positive and negative polarities. The internal standard (pinazepam) was

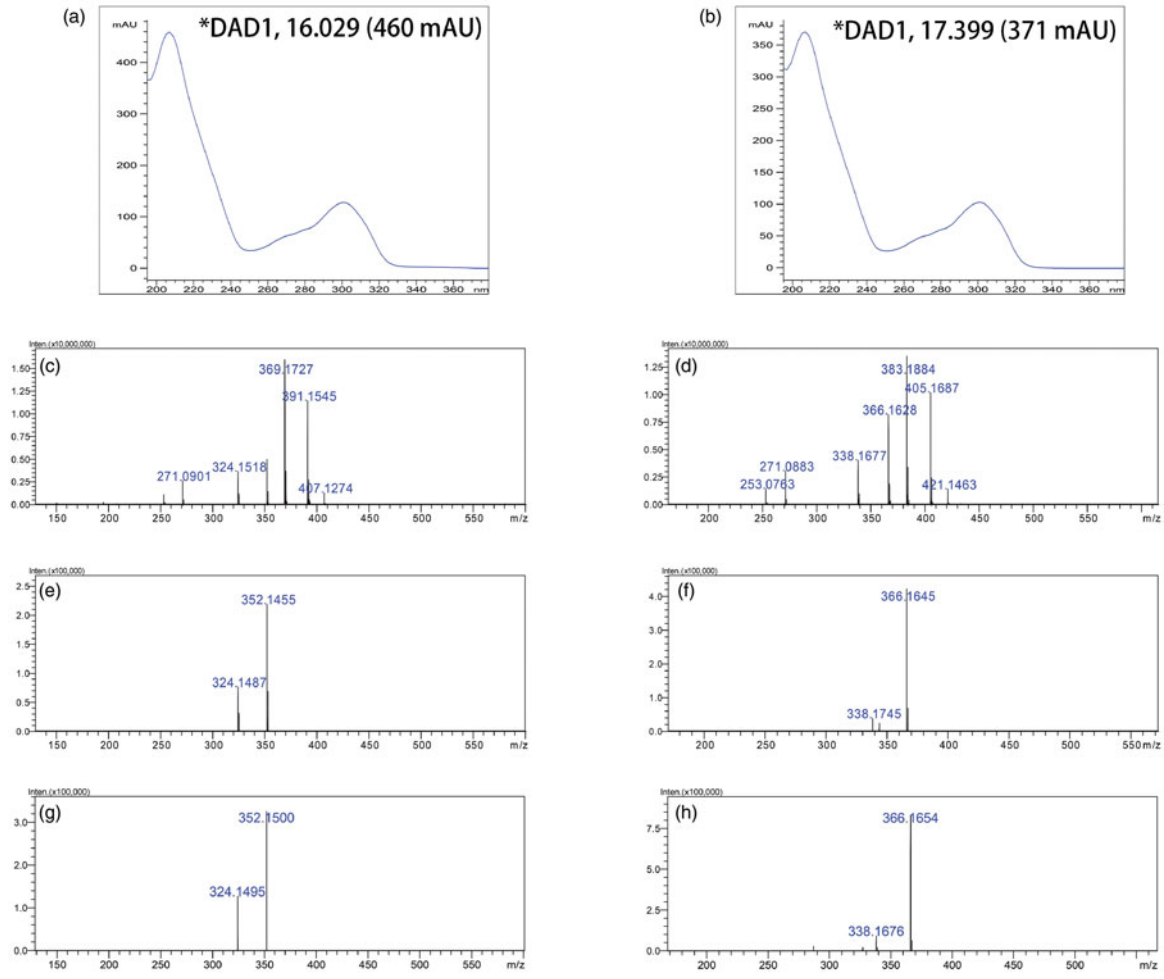

Figure 2. Analytical results of the e-cigarette fluid labeled "VaporFi". The UV spectra of the peak with RT (a) 15.954 min and (b) 17.299 min were found to match those of the reference standards of AB-FUBINACA and ADB-FUBINACA, respectively. In TOF/MS analysis, a Q1 scan revealed the parent m/z of (c) AB-FUBINACA (*m/z* 369.1727) and (d) ADB-FUBINACA (*m/z* 383.1884). The corresponding Na adduct (+22 amu) was also observed. Upon fragmentation, the product ion spectra of the two peaks (e) AB-FUBINACA and (f) ADB-FUBINACA were also found to match those of the respective reference standards (g) and (h).

used for mass calibration within each sample. The accurate mass and product ion spectrum were compared against those of the reference standards of AB-FUBINACA and ADB-FUBINACA (Cayman Chemical Company, Ann Arbor, MI).

For analysis of the two synthetic cannabinoids, the patient's urine sample (4 mL) was extracted with Toxi Tube-A. The top phase (1.25 mL) was dried under compressed air at room temperature and reconstituted in 0.2 mL of 50% v/v 1 mM ammonium formate, 0.1% formic acid in water and 1 mM ammonium formate, 0.1% formic acid in ACN. For liquid chromatography tandem-mass spectrometry (LC-MS/MS) analysis, 7.5 µL was injected into the column. In addition to specific analysis for the two compounds, the urine sample was also subjected to general toxicology screening covering common pharmaceuticals and drugs of abuse using LC-MS/MS and gas chromatography-mass spectrometry (GC-MS).

For quantitative analysis of the serum sample, calibrators (1–10 ng/mL for AB-FUBINACA; 0.1–10 for ADB-FUBINACA) were prepared in drug-free serum. 5F-AB-PINACA (Cayman Chemical Company) was used as the internal standard (I.S.). One part I.S. was pre-mixed with 10 parts sodium bicarbonate buffer (pH 10.2). Next, 250 µL of serum sample was added to 200 µL of this mixture. Then, 400 µL of this sample was loaded in the supported liquid extraction (SLE) column (ISOLUTE SLE+ 400 µL, Biotage, Sweden). The analytes were eluted by two sequential steps using 1 mL of hexane:ethyl acetate (98:2 v/v). The eluate was dried under nitrogen at 40 °C and then reconstituted in 100 µL of 50% ACN. A 7.5-µL aliquot was injected into the LC-MS/MS for analysis.

Urine and serum samples were analyzed on an AB Sciex 5500 QTrap triple-quadrupole linear ion trap mass spectrometer equipped with a turbo ion spray source (Framingham, MA) coupled with Waters ACQUITY ultra-performance liquid chromatograph (Waters Corporation, Milford, MA). Chromatographic separation was performed with a Waters ACQUITY UPLC BEH C8 column (1.7 µm, 2.1 × 100 mm) and gradient elution comprising 1 mM ammonium formate, 0.1% formic acid in water (mobile phase A, MPA) and 1 mM ammonium formate, 0.1% formic acid in ACN (mobile phase B, MPB). The gradient program began with 8% MPB, which was held until 0.5 min. The MPB content was increased stepwise as follows: 20% at 3.5 min, 30% at 4.5 min, 40% at 5.5 min,

and 80% at 7.5 min and then held until 8 min. At 8.5 min, MPB was returned to 8% and held until 10 min. The flow rate was 0.3 mL/min.

On the mass spectrometer, the following parameters were used: source temperature 600 °C, curtain gas flow rate 25 mL/min, ion spray voltage 5500 V, flow rates of ion source gas 1 and 2 50 mL/min. The identity of analytes was confirmed by an enhanced product ion (EPI) scan and comparison of the product ion spectrum with reference standards. For quantitation, analytes were detected by multiple reaction monitoring (MRM) in positive ionization mode. Two MRM transitions were monitored for each compound (collision energy in parentheses): AB-FUBINACA 369→324.1 (23), 253.1 (33); ADB-FUBINACA 383.2→253.2 (35), 109.1 (59); I.S. 349.4→304 (20), 213 (25). The declustering potential values were: 196 V (AB-FUBINACA), 126 V (ADB-FUBINACA), and 120 V (I.S.). Quantitation was performed by calculating the peak area/I.S. ratio.

Results

HPLC analysis of the e-cigarette fluid labeled "VaporFi" revealed two peaks at RT 15.954 min and 17.299 min, the UV spectra of which did not match any compound within the in-house library (Figure 2). The identity of the two unknown peaks was initially revealed by TOF/MS analysis, which showed that the earlier-eluting peak had a measured accurate mass of 369.1727. Literature review on synthetic cannabinoids revealed that this mass might correspond to AB-FUBINACA (theoretical mass 369.1721, mass error + 1.63 ppm). The accurate mass of the later-eluting peak measured 383.1884 and was suspected to be ADB-FUBINACA (theoretical mass 383.1878, mass error + 1.57 ppm). The Na adducts of both compounds were also observed (Figure 2). Reference standards of both compounds were available in the laboratory and were used to confirm the identity of AB-FUBINACA and ADB-FUBINACA in the sample by comparison of the RT, accurate mass and product ion spectra (Figure 2). With this piece of information, the reference standards were injected onto the HPLC, and the resulting RT and UV spectra confirmed the identities of the two initially unknown peaks at RT 15.954 min and 17.299 min to be AB-FUBINACA and ADB-FUBINACA respectively. Analysis of the other unlabeled liquid yielded results identical to those of the "VaporFi" fluid.

In the urine sample, specific analysis for AB-FUBINACA and ADB-FUBINACA revealed the presence of the latter drug, as confirmed by matching EPI spectra with the reference standard. The oxidation metabolite of ADB-FUBINACA was also tentatively identified by comparison of the MS product ion spectrum with reports published previously (data not shown) [2]. Neither parent drug nor metabolite was detected for AB-FUBINACA [3]. General urine toxicology screening showed the presence of lidocaine, clindamycin, and cetirizine. The serum drug concentrations of AB-FUBINACA and ADB-FUBINACA measured 5.6 ng/mL and 15.6 ng/mL, respectively. Patient's exposure to AB-FUBINACA and ADB-FUBINACA was thus confirmed analytically.

Discussion

AB-FUBINACA is a synthetic cannabinoid CB_1 receptor agonist first described in a patent by Pfizer in 2009 [4]. It was subsequently found in illegal products in Japan in 2012 [5]. ADB-FUBINACA, first identified in illegal herbal products in 2013, is structurally similar to AB-FUBINACA, with an additional methyl group at the 3′ position [6], and is 2.5-fold more potent than AB-FUBINACA [7]. Both cannabinoids are novel psychoactive drugs sold as "legal alternatives to marijuana" and are often mixed with plant materials, tobacco, e-cigarettes, and energy drinks [8]. Very little is known about their pharmacology and toxicology. Until now, only a few cases of human toxicity have been published, and misuse of the substances has been implicated in several cases of sudden death [8–10]. However, many of the reported cases were either not laboratory confirmed or confounded by co-consumption of other recreational drugs [8–10], weakening the association between the observed toxic effects and their exposure.

This case shows that both AB-FUBINACA and ADB-FUBINACA are orally bioavailable with rapid onset of cardiovascular and neurological toxicity after ingestion. The patient's presentation with somnolence, agitation, confusion, hallucination, dilated pupils, hypertension, sinus tachycardia, vomiting, and hypokalemia were compatible with clinical features previously reported after exposure to AB-FUBINACA, ADB-FUBINACA, or other synthetic cannabinoids [7,11,12]. In the ED, the patient's exposure to AB-FUBINACA and ADB-FUBINACA could not be detected using bedside urine immunoassay kits. Exposure was only confirmed retrospectively after analysis in a tertiary toxicology laboratory, which highlights the challenges clinicians face in managing synthetic cannabinoid poisoning and the need for maintaining a high index of suspicion for patients with similar presentations after recreational drug use. The laboratory in turn plays a pivotal role in the analytical confirmation of synthetic cannabinoid use. Urinary metabolites may be a suitable marker for detecting exposure. The oxidation metabolite of ADB-FUBINACA tentatively identified in the present study (authentic standard is not available for confirmation) correlates with previous reports on the metabolism of this group of drugs [2,3]. The metabolites of AB-FUBINACA were not observed; this correlates with the lower serum concentration observed for this drug in the patient.

In this case, the patient presented with a short run of SVT, although arguably sinus tachycardia at a rate of 172 bpm with indiscernible p wave could also lead to a similar cardiac tracing. It is noteworthy that SVT has also been associated with synthetic cannabinoid ingestion. Lapoint et al. reported a case of refractory SVT in a 48-year-old man after ingestion of JWH-018, which developed one day after hospital admission and required electrocardioversion [13]. Other tachyarrhythmias, such as atrial fibrillation and ventricular tachyarrhythmias, have also been linked to marijuana use, but the exact mechanism remains unknown. Several mechanisms, such as proarrhythmic effect mediated by catecholamines, cardiac ischemia, and oxidative stress from marijuana smoking, have been proposed [14]. Judging from the

temporal sequence of events, unremarkable findings during cardiovascular examination except SVT on presentation, the absence of analytical evidence of exposure to other recreational drugs, and a lack of recurrence of dysrhythmias and withdrawal symptoms in subsequent monitoring, the patient's SVT was mostly likely the result of acute intoxication following ingestion of AB-FUBINACA and ADB-FUBINACA.

Regarding the correlation between the observed toxic effects and serum drug concentrations in humans, current knowledge has largely been derived from a handful of case reports of fatalities associated with use of the substances. Fernandez et al. reported a case of death associated with AB-FUBINACA use in a 35-year-old man. The femoral blood level of AB-FUBINACA was >2.0 ng/mL [9]. Shanks et al reported a fatal case of coronary arterial thrombosis in a 41-year-old woman associated with ADB-FUBINACA use. Postmortem blood tests revealed the presence of ADB-FUBINACA (7.3 ng/mL), THC (1.1 ng/mL), and 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (4.7 ng/mL) [10]. In the present case, the serum drug concentrations of AB-FUBINACA and ADB-FUBINACA were apparently higher than those previously reported in these fatal cases. However, it is important to note that postmortem redistribution of drugs may have an effect on quantitative analysis results and the presence of other recreational drugs in both fatal cases may also be a contributory cause of death. The current case report provides additional human data that correlates the serum drug concentrations of AB-FUBINACA and ADB-FUBINACA with corresponding acute clinical toxicities without the confounding effects of other recreational drugs. Unfortunately, it was not feasible to determine the relative contribution of each in causing toxicity because the patient co-ingested AB-FUBINACA and ADB-FUBINACA.

The analysis of synthetic cannabinoids is a challenge partly due to the great diversity of structurally highly similar compounds. Authentic standards are useful in assisting identification by chromatography and mass spectrometry – in the present study, the retention times and MS2 product ion spectra helped confirm the identities of AB- and ADB-FUBINACA in the unknown liquid samples. It was noted that the MS2 product ion spectra observed deviated from those previously published [2,3,15] – namely the smaller fragments 253 and 109 were not presently observed, whilst only the larger fragments (352, 324 for AB-FUBINACA and 366, 338 for ADB-FUBINACA) resulting from the loss of NH_3 and $CONH_3$, respectively, could be detected (Figure 2).

The presence of positional isomers is another analytical challenge for synthetic cannabinoids. AB-FUBINACA (*para*) is known to have fluoro positional isomers at the *ortho*- and *meta* positions. It has recently been reported that the three isomers may be differentiated from one another by studying the abundance of product ions [15]. In the present study, it was not possible to confirm the isomer detected, although the retention time of the unknown sample matching with the authentic standard of AB-FUBINACA (*para*) may indicate the presence of the *para* isomer. Nevertheless, in the clinical management of patients the need to differentiate among isomers may not be as great as in the forensic setting.

In summary, we report a case of SVT associated with ingestion of e-cigarette fluid containing AB-FUBINACA and ADB-FUBINACA. Both drugs are orally bioavailable with rapid onset of clinical toxicity following ingestion. In the context of acute poisoning, the presence of unexplained tachyarrhythmias, confusion, and a negative recreational drug bedside immunoassay screening should prompt clinicians to consider synthetic cannabinoid toxicity as a differential diagnosis.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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