Toxicology Reports 14 (2025) 101930

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Involuntary intoxication caused by vaping the synthetic cannabinoid ADB-BUTINACA: A case report

Elise M.A. Slob [a,b,1], Maryam Lyousoufi [a,c,*,1], Sharif Pasha [d], Erik B. Wilms [c]

[a] Department of Clinical Pharmacy, Haaglanden Medical Center, The Hague, the Netherlands
[b] Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, the Netherlands
[c] Apotheek Haagse Ziekenhuizen (AHZ), Laboratory of TDM and Toxicology, The Hague, the Netherlands
[d] Department of Internal Medicine, Haaglanden Medical Center, The Hague, the Netherlands

ARTICLE INFO

Keywords:
ADB-BUTINACA
Vaping
Synthetic cannabinoid
E-cigarette

ABSTRACT

Synthetic cannabinoids are gaining popularity globally and detection is not commonly available. We report a 27-year-old man who was admitted to the emergency room because of sudden headache, nausea, vertigo, red eyes and palpitations. He confirmed that he had been vaping an electronic cigarette (e-cigarette) earlier that day just before the onset of his symptoms. Despite all negative results in the point-of-care test for recreational drugs, the liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) analysis showed that the liquid of the e-cigarette contained ADB-BUTINACA, a synthetic cannabinoid. LC-QTOF-MS represents a significant advancement in the field of drug detection, offering higher sensitivity, specificity, and a broader spectrum of detectable substances. Clinicians should be aware that besides the harmful effects of nicotine and toxic metals in e-cigarettes, e-cigarettes may also contain synthetic cannabinoids or other recreational drugs including new psychoactive substances (NPS), which can cause involuntary intoxication with potentially severe adverse effects. When clinical presentation and/or initial recreational drugs testing results are inconclusive, additional testing with LC-QTOF-MS can be valuable.

1. Introduction

Electronic cigarettes (e-cigarettes) were introduced as a gentle path to cessate smoking. The false advertisement and misinformation about e-cigarette vaping may not show the harmful sights of e-cigarette use. Smoke of e-cigarettes contains toxic metals and nicotine, and due to the added flavours it has even become more easy to become addicted to vaping. Moreover, associations between vaping and pulmonary diseases have been shown and addition of vitamin E to the liquid of e-cigarettes (e-liquid) can lead to severe lung tissue damage when vaped.

What is also not known to the general public, is that besides nicotine recreational drugs e.g. cannabis/cannabinoids, cocaine and other psychostimulants, hallucinogens, opioids, methadone, or fentanyl can be added to the liquid of e-cigarettes [1] and this may not be described in the claims on labels or the described concentrations are inaccurate. Furthermore, users of these vapes and alerting authorities may not notice the addition of recreational drugs to the e-liquid as the smell of recreational drugs is lost during vaping due to the specific smell of added flavours [2]. Vaporisation of recreational drugs results in high bioavailability and fast onset of drug effects due to rapid absorption of the drug and avoidance of the first pass effect [1]. The vaping community has also confirmed that dosing can be increased by turning up the wattage/voltage of the device [3]. These characteristics can increase the risk of an overdose. Therefore, clinicians should be aware that the toxicological presentation of the patient at the emergency room (ER) may be caused by (involuntary) vaping of recreational drugs.

As synthetic cannabinoid receptor agonists (SCRA) are gaining popularity globally, clinicians have to understand that intoxication caused by vaping SCRA is not detected by commonly available tests. There are several pitfalls in the detection of SCRA in samples taken from the patient. Low concentrations in blood and/or urine, extensive metabolism, and lack of efficient immunochemical urinary detection tests complicate analytical detection. Combined with non-specific, transient symptoms, clinical recognition of SCRA intoxication is challenging [4]. We report a case of an involuntary intoxication of the SCRA ADB-BUTINACA after vaping.

* Correspondence to: Apotheek Haagse Ziekenhuizen, Laboratory of TDM and Toxicology, Charlotte Jacobslaan 70, 2545 AB The Hague, the Netherlands.
E-mail address: m.lyousoufi@ahz.nl (M. Lyousoufi).
[1] Contributed equally to this work.

https://doi.org/10.1016/j.toxrep.2025.101930
Received 22 July 2024; Received in revised form 15 November 2024; Accepted 24 January 2025
Available online 26 January 2025

2. Case

A 27-year-old man with no relevant medical history was admitted to the ER because of a sudden headache, nausea, vertigo, red eyes and palpitations. He usually smokes a pack of cigarettes a day and sometimes smokes e-cigarettes. No previous use of recreational drugs was reported. On primary survey at the ER, he was responsive to questions and had a blood glucose level of 5.8 mmol/l. During palpation of the abdomen, the patient experienced epigastric abdominal pain. He confirmed drinking 750 ml energy drink without any further consumption of food and using an e-cigarette from Gaziantep, Turkey 10 seconds before the onset of his first symptoms. After 30 minutes, his palpitations disappeared. His vertigo continued for 90 minutes. He reported that his headache and nausea remained at the ER.

A point-of-care drugs of abuse (DOA) test was initially performed on the urine of the patient. Results of the DOA test (including testing for amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opioids, cannabis, tricyclic antidepressants) were available within 30 minutes and were all negative. After eating a light meal and drinking caffeinated sports drinks at the ER, the nausea complaints of the patient were reduced and the patient was discharged home. Because the point-of-care DOA test is generally not able to detect synthetic recreational drug substances, the liquid of the e-cigarette was thereafter screened using liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF-MS) on the Waters™ Xevo G3 QTOF MS system. High resolution mass spectrometry such as LC-QTOF-MS allows the detection and identification of a broad spectrum of recreational drugs, including new psychoactive substances. The LC-QTOF-MS analysis showed that the e-liquid contained nicotine and ADB-BUTINACA (Fig. 1). Informed consent for this report was obtained from the patient.

3. Discussion

This is the first case report that describes the toxicological symptoms of vaping ADB-BUTINACA. ADB-BUTINACA is a SRCA also referred to as ADB-BINACA (*N*-[(2S)-1-amino-3,3-dimethyl-1oxobutan-2-yl]-1-benzyl-1H-indazole-3-carboxamide). It is a full agonist of the cannabinoid receptor 1 (CB_1) with high potency (half maximal effective concentration (EC_{50}) 6.4 nM) [5] compared to tetrahydrocannabinol (THC, EC_{50} 14.2 nM), the partial agonist being responsible for the psychoactive effects of cannabis, indicating that toxic effects of SRCAs occur at lower doses compared to THC [6]. SCRAs can easily be mixed into e-liquids. SCRAs belong, together with synthetic opioids, cathinones, amphetamines and hallucinogens to the new psychoactive substances (NPS) that are currently developed at high speed. As they are designed to

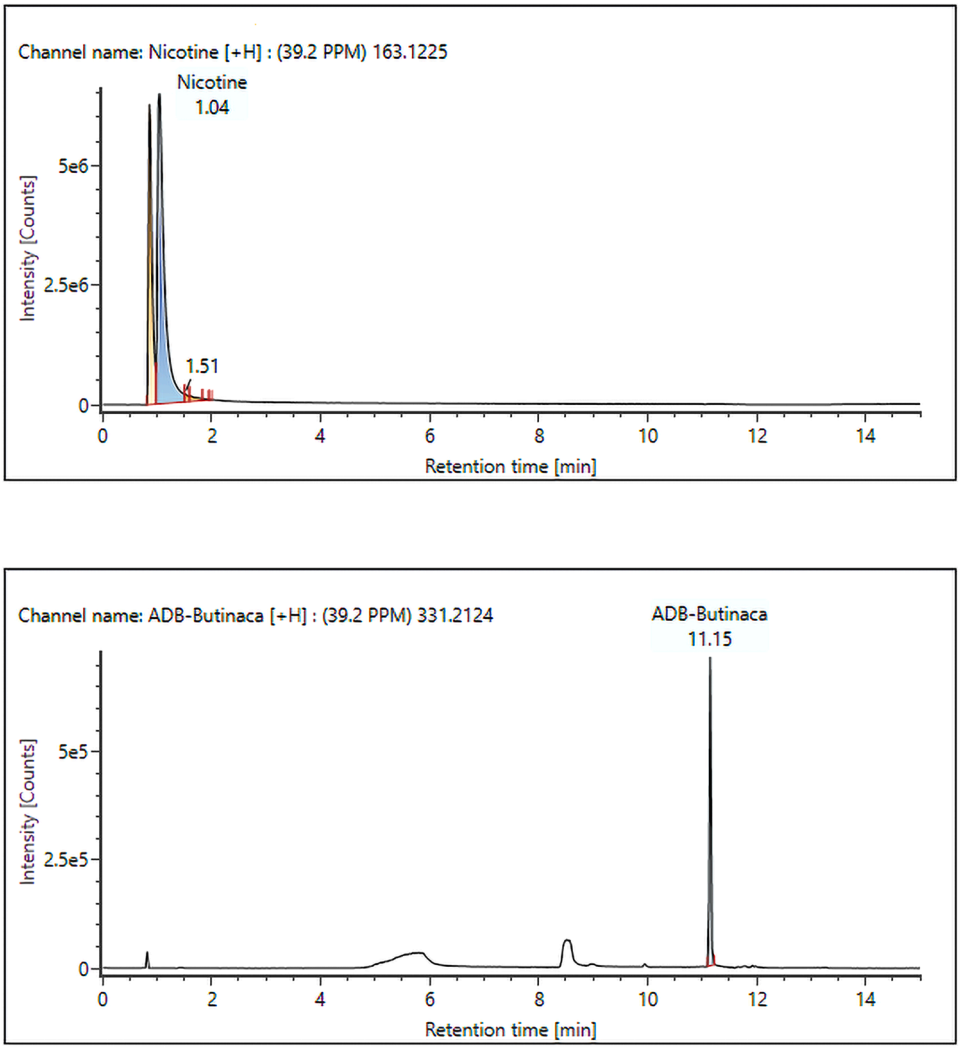

Fig. 1. LC-QTOF-MS Chromatograms of Nicotine (Top) and ADB-BUTINACA (Bottom) in the Vape Liquid used by the patient. The smaller peaks may represent other compounds or impurities in the sample. The intensity is plotted against the retention time for both chromatograms, demonstrating the presence and elution profiles of nicotine and ADB-BUTINACA in the analysed vape liquid sample.

evade the current generic definitions and legislations, they enter the illegal drug market in large numbers challenging international drug policies and health care providers [7]. There is difficulty in finding the right information about the NPS, defining their potency and confirmation of their existence in e-liquids or urine samples.

There are two case-reports published describing severe toxicological effects of vaping SCRA in humans, indicating that the EC_{50} of the SCRA may provide an estimate of the severity of intoxication. The first is a lethal intoxication with 4F-MDMB-BINACA (EC_{50} 0.20 nM) in a 22-year-old man with suicidal thoughts following extensive vaping resulting in a severe necrotising pancreatitis and acute kidney injury, evolving to multiple organ failure [8]. The second was an involuntary 5F-ADB-related intoxication (EC_{50} 0.59 nM) in a 16-year-old man who presented symptoms evocating of a seizure disorder in the minutes following e-cigarette use [9,10].

About 15 % of individuals registered at forums for drug users such as erowid.org who vaped cannabis have also vaped SRCAs. Of all e-cigarette users registered at this forum, 7.8 % vaped SCRAs [11]. Moreover, a study conducted in the United Kingdom investigated components of e-liquids in 112 samples originating from prisoners, teenagers and test purchases of commercially available e-cigarettes taken between 2014 and 2021 [12]. Of these samples, 22 contained one or more SCRAs, THC was only detected in 11 samples, only one contained cannabidiol and 6 contained a mixture of THC and cannabidiol.

A systematic review including data of 114 patients of which the majority was intoxicated due to SCRA smoking revealed that 45 % of the patients who present at the ER after an intoxication due to SCRA smoking recovered within 24 hours [12]. 55 % of the patients required a longer admission due to symptoms such as severe tachycardia, hypertensive crise, convulsions, acute kidney insufficiency but also long-lasting, severe psychological problems [12]. There are fatal cases described due to cardiac arrest, asphyxia and multi organ failure [13].

When patients are admitted to the hospital due to severe symptoms, we recommend intensive monitoring and supportive care depending on the symptoms that the patient is showing. In the case of insults, panic attacks, hallucinations or psychosis a benzodiazepine agonist is indicated [14]. Long lasting acute psychotic or paranoid reactions can be treated with haloperidol 5 mg (maximum of 10 mg per 24 hours) and promethazine 50 mg. Hypotension or renal failure should be treated with fluids or electrolytes [15].

Whether a recreational drug can be administered via vaping, depends on whether the drug becomes volatile under the evaporation temperature of the e-cigarette. THC, methamphetamine, SRCA, lysergic acid diethylamide (LSD), gamma-hydroxybutyrate (GHB) and ketamine are likely to become volatile under the temperature of current e-cigarettes, while crack cocaine is hard to vaporise. Besides increasing the temperature to enlarge the drug aerolisation and bioavailability, one can elevate the flow rate of air through the e-cigarette and/or add a diluent [1]. Addition of the diluent can lead to an eutectic mixture, where the diluent interacts with the recreational drug at a specific ratio and thereby reduces the melting point to a temperature lower than the melting temperature of the recreational drug. In this way, the aerolisation will become more efficient.

Point-of-care DOA tests using urine to screen for misuse of multiple substances, regularly include cannabis, amphetamines, cocaine, opioids, benzodiazepines and methadone. These traditional point-of-care DOA tests often rely on immunoassay techniques, which have limitations in terms of sensitivity and specificity, particularly for detecting low concentrations or chemically modified substances like NPS. Immunoassay results in a higher number of false negatives and false positives due to higher cut-off concentrations and interfering matrix, respectively, requiring careful clinical interpretation. The LC-QTOF-MS method offers a more comprehensive and sensitive approach for drug detection, covering hundreds of recreational drugs, including NPS. It can detect drugs and metabolites at much lower concentrations and the library can be rapidly updated with novel substances, meeting the challenges of a fast-changing drug landscape. LC-QTOF-MS combines liquid chromatography (LC) and quadrupole time-of-flight mass spectrometry (QTOF-MS). LC separates the urine or blood sample and QTOF-MS provides high-resolution and accurate mass measurements for precise identification and structural elucidation of compounds. There are limited laboratories that have this technique available and skilled and experienced operators are required [16].

Immunoassay screening techniques are limited to detecting a predefined set of substances and have limited diagnostic efficiency for detecting NPS such as synthetic cannabinoids, as demonstrated by studies showing that many synthetic cannabinoids are not detected due to low or absent cross-reactivity with assay antibodies [16]. In this case, the point-of-care DOA urine screening was not able to detect the synthetic cannabinoid ADB-BUTINACA.

A limitation of this case report is that we did not have a urine sample available for additional NPS testing. While the patient's symptoms strongly suggest the inhalation of ADB-BUTINACA, it is worth considering that these symptoms could also be attributed to nicotine exposure, as the symptoms partially overlap with known nicotine effects. However, given that the patient is a frequent smoker who has not previously experienced such symptoms, we can conclude that the adverse effects were caused due to vaping ADB-BUTINACA. Second, we could not retrieve further detailed information about the e-cigarette that was used by the patient such as the label or the region of origin. This limits further research.

To conclude, as vaping recreational drugs, especially NPS, gains popularity and enter the illicit drug market rapidly due to challenges in legislation [7], it is important to raise awareness of the possibility that e-cigarettes may contain recreational drugs such as SCRAs and that fast absorption may lead to specific toxicity. SCRAs and other NPS may not be detected by point-of-care DOA tests. When clinical presentation and/or initial DOA testing results are inconclusive, additional testing with LC-QTOF-MS can be valuable and is recommended. Future research should provide information to define which cases are at risk of hospital admission to help decision making at the ER. It should also invest in designing point-of-care tests for early NPS detection. Ultimately, new legislation making it more difficult for NPS to enter the market without any legal consequences is needed.

CRediT authorship contribution statement

Slob Elise M.A.: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Lyousoufi Maryam:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Pasha Sharif:** Writing – review & editing, Conceptualization. **Wilms Erik B.:** Writing – review & editing, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

References

[1] L. Reveil, A.C. Pearcy, J. Povlick, J.L. Poklis, M.S. Halquist, M.R. Peace, A determination of the aerosolization efficiency of drugs of abuse in a eutectic mixture with nicotine in electronic cigarettes, Drug Test. Anal. 15 (10) (2023) 1091–1098, https://doi.org/10.1002/dta.3343.

[2] A.K. Breitbarth, J. Morgan, A.L. Jones, E-cigarettes-An unintended recreational drug delivery system, Drug Alcohol Depend. 192 (2018) 98–111, https://doi.org/10.1016/j.drugalcdep.2018.07.031.

[3] M. Peace, J. Turner, Characterization and Abuse of Electronic Cigarettes: The Efficacy of "Personal Vaporizers: As an Recreational Drug Delivery System, National Institute of Justice, 2018.
[4] S. Salle, C. Sevestre, C. Richeval, F. Hakim, D. Allorge, J. Gaulier, Involuntary 5F-ADB-related intoxication following e-cigarette use, Int J. Leg. Med 135 (2021) 1467–1470, https://doi.org/10.1007/s00414-021-02561-8.
[5] A. Cannaert, E. Sparkes, E. Pike, J.L. Luo, A. Fang, R.C. Kevin, R. Ellison, R. Gerona, S.D. Banister, C.P. Stove, Synthesis and in Vitro Cannabinoid Receptor 1 Activity of Recently Detected Synthetic Cannabinoids 4F-MDMB-BICA, 5F-MPP-PICA, MMB-4en-PICA, CUMYL-CBMICA, ADB-BINACA, APP-BINACA, 4F-MDMB-BINACA, MDMB-4en-PINACA, A-CHMINACA, 5F-AB-P7AICA, 5F-MDMB-P7AICA, and 5F-AP7AICA, ACS Chem. Neurosci. 11 (24) (2020) 4434–4446, https://doi.org/10.1021/acschemneuro.0c00644.
[6] B. Tokarczyk, M. Suchan, P. Adamowicz, New synthetic cannabinoid ADB-BUTINACA-related death of a police dog, J. Anal. Toxicol. 47 (2) (2023) e23–e28, https://doi.org/10.1093/jat/bkac097.
[7] EMCDDA, European Drug Report 2023: Trends and Developments, Publications Office of the European Union, Luxembourg, 2023.
[8] B. Van Rafelghem, A. Covaci, K. Anseeuw, A.L.N. van Nuijs, H. Neels, B. Mahieu, W. Jacobs, Suicide by vaping the synthetic cannabinoid 4F-MDMB-BINACA: cannabinoid receptors and fluoride at the crossroads of toxicity? Forensic Sci. Med Pathol. 17 (4) (2021) 684–688, https://doi.org/10.1007/s12024-021-00424-7.
[9] S. Salle, C. Sevestre, C. Richeval, F. Hakim, D. Allorge, J.M. Gaulier, Involuntary 5F-ADB-related intoxication following e-cigarette use, Int J. Leg. Med 135 (4) (2021) 1467–1470, https://doi.org/10.1007/s00414-021-02561-8.
[10] S.D. Banister, M. Longworth, R. Kevin, S. Sachdev, M. Santiago, J. Stuart, J. B. Mack, M. Glass, I.S. McGregor, M. Connor, M. Kassiou, Pharmacology of Valinate and tert-Leucinate Synthetic Cannabinoids 5F-AMBICA, 5F-AMB, 5F-ADB, AMB-FUBINACA, MDMB-FUBINACA, MDMB-CHMICA, and Their Analogues, ACS Chem. Neurosci. 7 (9) (2016) 1241–1254, https://doi.org/10.1021/acschemneuro.6b00137.
[11] Blundell M.S., Dargan P.I., Wood D.M. The dark cloud of recreational drugs and vaping. QJM 111, 145-148.
[12] A. Frinculescu, G. Coombes, T. Shine, J. Ramsey, A. Johnston, L. Couchman, Analysis of recreational drugs in purchased and seized electronic cigarette liquids from the United Kingdom 2014-2021, Drug Test. Anal. 15 (2023) 1058–1066.
[13] J. Tournebize, V. Gibaja, J.-P. Kahn, Acute effects of synthetic cannabinoids: update 2015, Subst. Abus. 38 (3) (2017) 344–366, https://doi.org/10.1080/08897077.2016.1219438.
[14] G.L. Buser, R.R. Gerona, B.Z. Horowitz, K.P. Vian, M.L. Troxell, R.G. Hendrickson, D.C. Houghton, D. Rozansky, S.W. Su, R.F. Leman, Acute kidney injury associated with smoking synthetic cannabinoid, Clin. Toxicol. (Philos.) 52 (7) (2014) 664–673.
[15] V.L. Alves, J.L. Gonçalves, J. Aguiar, H.M. Teixeira, J.S. Câmara, The synthetic cannabinoids phenomenon: from structure to toxicological properties. A review, Crit. Rev. Toxicol. 50 (2020) 359–382.
[16] D.R. Allen, B.C. McWhinney, Quadrupole time-of-flight mass spectrometry: a paradigm shift in toxicology screening applications, Clin. Biochem Rev. 40 (3) (2019) 135–146, https://doi.org/10.33176/AACB-19-00023.