Suicide by vaping the synthetic cannabinoid 4F-MDMB-BINACA : cannabinoid receptors and fluoride at the crossroads of toxicity?

Suicide by Vaping the Synthetic Cannabinoid 4F-MDMB-BINACA: Cannabinoid Receptors and Fluoride at the Crossroads of Toxicity?

Abstract

INTRODUCTION - We describe a lethal case of excessive 4F-MDMB-BINACA vaping and discuss possible pathways of toxicity.

CASE REPORT - A 22-year-old man was hospitalized after stating he would 'commit suicide in a non-detectable way'. He was admitted with a severe necrotizing pancreatitis and acute kidney injury, evolving to multiple organ failure. His condition rapidly deteriorated, and he died eleven days after hospital admission. Postmortem histopathology confirmed fulminant necrotizing pancreatitis, acute tubular necrosis, cerebral edema, pericentral/midzonal hepatocellular necrosis and acute respiratory distress syndrome. Metabolites of 4F-MDMB-BINACA, a synthetic cannabinoid, were detected in urine and serum collected at hospital admission. The same drug was found in a vapor fluid found in the man's apartment.

DISCUSSION – As cannabis use has been etiologically linked to acute pancreatitis, we hypothesize that the more afferent and potent 4F-MDMB-BINACA could induce pancreatitis via stimulation of cannabinoid (CB)1-receptors. Alternatively, terminal fluorination could have induced a dose-dependent toxic effect on a wide range of cellular processes, leading to cell dysfunction and death.

CONCLUSION – We report the first clinicopathological description of a lethal intoxication with 4F-MDMB-BINACA, following extensive vaping. Toxic effects could either relate to CB-receptor binding or to direct fluoride toxicity.

Keywords: 4F-MDMB-BINACA; vaping; acute pancreatitis; acute kidney injury; fluoride

Key Points

1. We report the first detailed clinicopathological description of a lethal intoxication with 4F-MDMB-BINACA following extensive vaping.
2. The pivotal clinical presentation was a necrotizing pancreatitis and acute kidney injury evolving into multiple organ failure.
3. Possible mechanisms of tissue toxicity, such as CB-receptor binding and terminal fluorination, are discussed.

4. Public awareness should be raised towards these emerging synthetic cannabinoid receptor agonists (SCRAs) and their toxicity.

Introduction

New psychoactive substances, a large portion of which are synthetic cannabinoid receptor agonists (SCRAs), are globally gaining popularity. Toxic effects of SCRAs vary widely, but neurological/neuropsychiatric, cardiovascular, and sympathomimetic symptoms are predominant [1]. Hospitalizations and deaths linked to SCRA-toxicity are increasing [2]. Terminal fluorination (5F-derivatives) of SCRAs has been observed, probably to improve affinity for and potency at CB1-receptors [3]. Concerns regarding the toxicity of fluorinated synthetic cannabinoids have risen, as biotransformation of such compounds can lead to the formation of toxic fluorinated metabolites [3].

4F-MDMB-BINACA ($C_{19}H_{26}FN_3O_3$) is a fluorinated synthetic cannabinoid, first detected in seized substances in 2018 [2]. It can be encountered as a powder, in liquids (vapor fluid) and in herbal plant mixtures [2]. Generally, it is a component added to a herbal mixture, rather than a pure substance [2]. Adverse effects of this substance are published in law enforcement encounters reports, but details are lacking [4]. In 2019, the World Health Organization announced a recommendation for listing this new drug into Schedule II of the Convention on Psychotropic Substances of 1971 [4].

We publish the first lethal case of an acute necrotizing pancreatitis and tubular necrosis, leading to multiple organ failure, after extensively vaping 4F-MDMB-BINACA.

Case Report

Clinical presentation

A 22-year-old man was admitted to the Emergency Department of a tertiary care hospital in a critical state, after stating he would 'commit suicide in a non-detectable way'. His medical background included attention deficit disorder, depression, alcohol addiction, and recreational (designer) drug use. He initially denied any drug and/or medication intake but later claimed to having vaped a lethal substance after extensive internet research.

The patient presented with an acute abdomen (as defined in the 27th Edition of Stedman's Medical Dictionary), hoarse voice (possibly linked to extensive vaping), tachycardia (144 beats per minute), and hypotension (107/74 mm Hg). Initial laboratory results were as follows: lactate 13.9 mmol/L, CRP 209 mg/L, lipase 2211 U/L, CK 1700 U/L, LDH 935 U/L, creatinine 3.30 mg/dL. Estimated glomerular filtration rate was 23.6 mL/min/1.73 m^2

(MDRD formula), indicating acute kidney injury (AKI). Beta-hydroxybutyric acid 5-oxoproline were elevated in blood serum (respectively 114 and 65.7 mg/L). Computed tomography revealed enlargement and steatosis of the liver and an acute pancreatitis, without gallstones.

During the first night of hospitalization, the patient developed cardiac arrest, with return of spontaneous circulation after 25 minutes of resuscitation. An urgent laparotomy was performed to treat abdominal compartment syndrome, impairing mechanical ventilation. Vacuum-assisted closure of the incision kept pressure low. Continuous renal replacement therapy was required. The patient subsequently developed multiple organ failure, including cerebral edema, and eventually died eleven days after hospital admission.

Postmortem evaluation

A forensic autopsy was performed with apparent generalized icterus on external examination. Fulminant acute necrotizing pancreatitis with peripancreatic bleeding was seen (Figure 1). Kidneys showed extensive acute tubular necrosis (Figure 2A). Acute respiratory distress syndrome was apparent in both lungs, as well as foci of organized bronchopneumonia. Apart from macrovesicular steatosis, the liver showed massive pericentral and midzonal necrosis (Figure 2B).

Toxicological analyses

4F-MDMB-BINACA was detected in vapor fluid found in the man's apartment and 4F-MDMB-BINACA metabolites (Figure 3) were detected in urine and serum samples (estimated LOQ as 1 ng/mL) collected at hospital admission. The qualitative analyses for 4F-MDMB-BINACA metabolites were performed by liquid chromatography coupled to mass spectrometry using a previously described protocol validated for human urine [5].

Tetrahydrocannabinol (THC) and its metabolites 11-OH-THC and THC-COOH were quantitatively measured in serum in the following concentrations: 1.4 ng/mL, 0.3 ng/mL, 2.8 ng/mL, respectively. The analysis was done by gas chromatography coupled to tandem mass spectrometry following liquid-liquid extraction and derivatization, in the frame of an in-house validated method under ISO17025 accreditation.

Discussion

This report is the first detailed clinicopathological description of a lethal intoxication with 4F-MDMB-BINACA following extensive vaping. The pivotal clinical presentation was a necrotizing pancreatitis and AKI evolving into

multiple organ failure (with cerebral, pulmonary, and hepatic shock-related lesions). The toxicological effects of this substance are largely unknown, but we suggest two potential pathophysiological pathways: cannabinoid (CB)-receptor binding and toxic effects of fluoride.

Since 2004, the use of cannabis has been suggested as a possible provoking factor for acute pancreatitis [6]. Pathophysiological mechanisms by which cannabis acts on the pancreas are still unclear, but some experimental data are available. Both known CB-receptors are present in endocrine and exocrine pancreatic tissue [6–8]. In a murine model with experimentally induced pancreatitis, the condition worsened, dose-dependently, after administration of an endogenous cannabinoid (anandamide). Moreover, when pre-treated with a CB1-receptor antagonist, the condition improved [9]. Whether or not the onset of pancreatitis can be induced by stimulation of CB1-receptors is actually unknown, the authors speculate this could be the case if the dose is high enough [9]. Several synthetic cannabinoids have proven to have more affinity for and to be more potent at CB1-receptors than THC [10]. Compared with THC, 4F-MDMB-BINACA functions as an agonist of CB-receptors with slightly higher potency (Ki of 14.3 nM as opposed to 22.5 nM), and higher affinity (EC_{50} 70 times lower) [4]. Hence, we suggest that the onset of pancreatitis can be induced by dose-dependent stimulation of CB-receptors.

Clusters of AKI following SCRAs use have been described, and a direct link between the fluorinated synthetic cannabinoid XLR-11 and AKI has been established [1, 11, 12]. Buser et al. [12] suggest that the cause of AKI could include direct toxicity from the SCRA, metabolic polymorphism, or nephrotoxic contaminants. These authors assume direct toxicity from XLR-11 by an endocannabinoid signaling system through CB-receptor activation [12]. Silva et al. [11] report that XLR-11 targets the mitochondrial function in the proximal tubule cells and triggers energy-dependent apoptotic pathways. Though this process appeared to be CB-receptor activation dependent, ATP-formation seemed to follow a CB-receptor independent pathway [11].

Terminal fluorination (5F-derivatives) of SCRAs has been described, and this could increase their toxicity [3]. Fluorination not only increases potency at CB1-receptors, excessive fluoride intake has also been linked with alterations in the energy metabolism and damage to soft tissues [13], including nephrotoxicity [14]. Fluoride has time-, concentration-, and cell-dependent toxic effects due to interactions with a wide range of cellular processes. Oxidative stress, leading to mitochondrial damage and apoptosis, seems to play a key role [13, 15]. The kidney is a primary target of fluoride toxicity, as it effectuates fluoride excretion [16]. Sodium fluoride exposure resulted in elevation of mitochondrial reactive oxygen species and downregulation of a mitochondrial antioxidant enzyme in a mouse kidney cell line [16]. This targeting of mitochondria is consistent with the thus far reported method of action of XLR-11 [11].

Araujo et al. [13] suggest that organisms can adapt to the toxic effect of fluoride over time by alterations in energy metabolism, leaving them vulnerable for acute and/or high dose toxicity. Song et al. [16] demonstrated fluoride-nephrotoxicity through an oxidative stress-regulated mitochondrial pathway, leading to mitochondrial damage and apoptosis. Where Silva et al. [11] could demonstrate an effect of XLR-11 on mitochondrial function, this process could be more dependent on fluoride toxicity than on CB-receptor activation [11]. This hypothesis seems be supported by findings by Buser et al. [12] suggesting a direct toxicity from fluorinated SCRAs.

Our patient had a highly elevated 5-oxoproline level, suggesting either interruption or upregulation of the γ-glutamyl cycle [17]. Elevated beta-hydroxybutyric acid and lactic acidosis levels suggest alternative energy pathways, due to impaired glycolysis and gluconeogenesis. Araujo et al. [13] demonstrated that fluoride both inhibits glycolysis, gluconeogenesis and antioxidant formation and enhances β-oxidation [13]. The presence of urinary oxalate crystals further supports an increased β-oxidation pathway [11, 12]. Fluoride mediates all the above-mentioned pathways and so affects all cells, resulting in extended and severe tissue damage.

Our patient vaped extensive amounts of 4F-MDMB-BINACA, strengthening the hypothesis of a dose-dependent involvement of fluoride. Our clinicopathological findings furthermore suggest toxic lesions in kidney, pancreas and liver but adverse effects on heart, lung, and brain tissue cannot be excluded. The biochemical findings related to impaired glycolysis and gluconeogenesis, combined with the elevated 5-oxoproline, further support this hypothesis. The THC concentration measured in serum (1.4 ng/mL) is slightly above the legal cut-off limit for THC in serum of drivers (1 ng/mL). This suggests a low/moderate use of THC, which would have at most impaired his judgement, but was probably insufficient to cause acute toxicity to kidney and pancreas. Nevertheless, synergistic actions with 4F-MDMB-BINACA cannot be ruled out.

Conclusion

We report the case of a man who developed acute necrotizing pancreatitis, acute kidney injury and multiple organ failure after the intentional, extensive vaping of the new synthetic cannabinoid, 4F-MDMB-BINACA. Possible mechanisms of tissue toxicity, such as CB-receptor binding and terminal fluorination, are discussed. Public awareness should be raised towards these emerging SCRAs and their toxicity.

Figure Captions

Fig. 1 A Macroscopic image of the acute necrotizing pancreatitis **B** Haematoxylin-eosin stain (scale bar 200 μm)

Fig. 2 A Microscopic image of the acute tubular necrosis, Haematoxylin-eosin stain (scale bar 50 µm)

B Microscopic image of pericentral / midzonal necrosis, Masson's trichrome stain (scale bar 500 µm).

Fig. 3 4F-MDMB-BINACA and most prominent metabolites

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