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An outbreak of acute delirium from exposure to the synthetic cannabinoid AB-CHMINACA

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Abstract

Background: Synthetic cannabinoid containing products are a public health threat as reflected by a number of outbreaks of serious adverse health effects over the past 4 years. The designer drug epidemic is characterized by the rapid turnover of synthetic cannabinoid compounds on the

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Declaration of interest

Disclaimer for M.S.: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry. Disclaimer for J.T.: The views expressed herein are those of the authors and do not necessarily represent the views of the Drug Enforcement Administration, the United States Department of Justice, or any officer or entity of USA.

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market which creates a challenge in identifying the particular etiology of an outbreak, confirming exposure in cases, and providing current information to law enforcement.

Results: Between 28 May 2014 and 8 June 2014, 35 patients were evaluated and treated at the University of Florida Health Medical Center in Gainesville following reported exposure to a synthetic cannabinoid containing product obtained from a common source. Patients demonstrated acute delirium (24) and seizures (14), and five required ventilator support and ICU-level care; none died. The presence of N-[(lS)-l-(aminocarbonyl)-2-methylpropyl]-l-(cyclohexylmethyl)-lH-indazole-3-carboxamide (AB-CHMINACA), or one of its predicted metabolites was confirmed in 15 of 21 cases. A rapid public health response and aggressive public messaging prevented further morbidity, identified the source, and led to law enforcement seizure of the implicated product.

Discussion: The significance of this outbreak lies as much in the rapid occurrence of unpredictable, life- threatening adverse health effects from a newly identified synthetic cannabinoid compound as it does in the multidisciplinary investigation and novel partnership between local public health, the laboratory, and the chemical industry, resulting in termination of the outbreak.

Conclusion: A coordinated response and collaboration between law enforcement, the local public health, emergency medical services and Health Center staff, were all key interventions in preventing a more substantial public health outbreak resulting from use of a novel synthetic cannabinoid compound. Real time collaborations between toxicology laboratories, suppliers of analytical standards and the public health system may be useful in the face of future novel chemical exposures.

Keywords

CNS/psychological; Organ/tissue specific; Metabolic; Respiratory support; Synthetic cannabinoids

Introduction

Designer drugs present an ongoing challenge for clinicians, public health authorities, and law enforcement agencies. Products containing synthetic cannabinoids enter the market rapidly, leading to an increasing number of clusters of unusual and unpredictable illnesses associated with their use. There is a significant body of knowledge about the toxicology of the designer compounds that are used in the illicit manufacture of synthetic cannabinoids, however, the entry of new novel compounds and derivatives into the illicit drug market continues to present obstacles to public health investigations, epidemiological case finding, laboratory diagnosis, and the development of analytic methods.

Several states including Colorado, Texas, Georgia, New Hampshire and most recently New York, have reported large clusters of patients presenting to emergency departments (EDs) with a constellation of life-threatening symptoms following synthetic cannabinoid exposure.[1–4] Law enforcement agencies have responded to the public health threat of synthetic cannabinoids by attempting to curb their production and sale. Since 2011, the US Drug Enforcement Administration (DEA) has taken action to regulate synthetic cannabinoids on four occasions.[5–8] In 2012, the Synthetic Drug Abuse Prevention Act placed cannabimimetic agents and 26 specific synthetic compounds into Schedule I of the

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Controlled Substances Act.[9] Although 43 states have since taken similar actions to regulate synthetic cannabinoids, the creation of new compounds and derivatives that fall outside federal and state regulations until they can be further characterized and enforced under the DEA's emergency scheduling authority continues. Resulting outbreaks such as the one reported here continues to challenge clinicians and public health authorities. The objective of this article is to describe an outbreak of severe illness in USA that was associated with a novel synthetic cannabinoid molecule, highlighting the public health, law enforcement, and laboratory collaboration which, may have significant potential in combating future clusters of such epidemics.

Patients and methods

This is an observational case series with retrospectively performed laboratory analysis of patients presenting to the emergency department with a documented suspicion of use of synthetic cannabinoids. IRB approval from the University of Florida (UF) IRB-01 was obtained and approved with full waiver of informed consent and HIPAA waiver to disseminate the results being reported.

Patient data

Patients were identified by ED staff at the time of presentation and were also identified retrospectively by a search of the electronic health record of cases where there was a documented suspicion of ingestion of synthetic marijuana or a history of using a synthetic cannabinoid-containing product before the onset of illness. Between 1 June and 30 June 2014, clinical coordinators identified and obtained the medical records for all suspected cases of illness related to synthetic cannabinoid use. Medical records were reviewed and demographic and clinical data were manually abstracted, de-identified and entered into REDCap to be stored and later analyzed. SAS V9.4 (Cary, NC) was used to analyze and report the clinical data.

Clinical specimen collection and handling

Clinical samples of urine, plasma, and serum were collected as a part of routine clinical care and subsequently tested for the presence of synthetic cannabinoids to confirm patients' exposure. Routine clinical testing was performed using Siemens Advia 2120 (Malveme, PA) for hematological analysis and Roche Cobas 8000 (Indianapolis, IN) for blood chemistry analysis. Whole blood lactates were performed using a Radiometer ABL 800. After clinical testing, the samples were stored at UF Health Shands Hospital Core Laboratory and UF Health Pathology Laboratory facilities at 4 °C for a maximum of 2 weeks before being frozen at −20°C prior to shipping to the University of California, San Francisco, for testing. The majority of samples were collected during patients' initial presentations to the ED; lab receipt time and with sample collection time were recorded when available.

Laboratory techniques and analysis

The samples were analyzed by liquid chromatography/quadrupole time-of-flight mass spectrometry (LC/QTOF-MS). Plasma and serum samples (250 μl) were prepared for analysis by protein precipitation with 95:5 acetonitrile:methanol, and urine samples (500 μl)

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were analyzed by the “dilute and shoot” method. All urine samples are diluted with Burdick & Jackson liquid chromatography and mass spectroscopy grade water and acetonitrile to create a final urine solution with 10% acetonitrile similar in composition to initial mobile phase composition. Plasma/serum extracts and diluted urine samples (2.5 μl) were injected into an Agilent LC 1260 (Sta. Clara, CA) and separated by gradient elution.[10] Eluates obtained from the LC were ionized by an electron spray ionization (ESI) source in an Agilent QTOF/MS 6550 (Sta. Clara, CA).

In each sample run, a 2.5 μl diluted sample was injected in an Agilent Poroshell 120 (Sta. Clara, CA) C-18 column (2.1 mm × 100 mm, 2.7 μm) maintained at 55°C. Chromatographic separation was achieved by gradient elution using LC-MS grade water with 0.05% formic acid and 5 mM ammonium formate as mobile phase A and acetonitrile with 0.05% formic acid as mobile phase B. The elution gradient employed was 0−0.5 min = 5% B; 1.5 min = 30% B; 4.5 min = 70% B; 7.5 min =100% B; 7.5−10 min =100% B and 10.01–12 min = 5% B. In running the sample in negative mode, LC-MS grade water with 0.05% ammonium acetate and acetonitrile with 0.05% ammonium acetate were used as mobile phase A and B, respectively.

Ionization of chromatographic eluates was achieved in the QTOF/MS using an ESI source operated in the following conditions: gas temperature at 225 °C; sheath gas temperature at 350 °C; drying gas flow at 14 L/min; sheath gas flow at 11 L/min; nebulizer pressure at 14 psi; voltage cap at 3000 V and nozzle voltage at 500 V. Data acquisition was run at 2 GHz in extended dynamic range mode. Both TOF MS and MS/MS spectra were collected in automated MS/MS mode using 500 arbitrary units as threshold for inducing MS/MS data collection. Each sample was run in positive and negative polarity and injected twice in each polarity.

The total ion chromatogram obtained from each sample run was analyzed using the “Find by Formula” algorithm (MassHunter, Agilent Technologies, Santa Clara, CA) and various targeted designer drug panels consisting of: synthetic cannabinoids (50 parent compounds and metabolites); 84 amphetamines, cathinones, 2Cs (psychedelic phenethylamines), piperazines, indanes, and psychotropic alkaloids; and 214 other drugs of abuse. Formula matches were also sought for 157 other synthetic cannabinoid parent compounds and known metabolites and 13 predicted *N*-[(lS)-l-(aminocarbonyl)-2-methylpropyl]-l-(cyclohexyl-methyl)-lH-indazole-3-carboxamide (AB-CHMINACA) metabohtes since reference standards for these compounds were not available for the analysis. Metabohtes of AB-CHMINACA were predicted based on reported biological transformations observed in other synthetic cannabinoids which share structural similarity to AB-CHMINACA. A partnership with Cayman Chemical Company, an American biotechnology firm headquartered in Ann Arbor Michigan, allowed for the rapid synthesis of predicted metabohtes and the provision of these newly synthesized standards to the University of California San Francisco for confirmatory testing in outbreak clinical samples.

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Results

Patient clinical outcomes

Between May 28 and June 8, 2014, clinicians in the ED at the University of Florida in Gainesville treated 35 patients who presented after reported use of a product containing synthetic cannabinoids. An epidemic curve showing the progression of the outbreak over time is illustrated in Fig. 1. Thirty patients (85%) were transported via emergency medical services (EMS), 4 (11%) arrived via private vehicle, and one was transported by law enforcement. The patients' median age was 34.6 years (range, 14−58) and 31 were male and 4 female. Their symptoms included altered mental status (24 [61%]), hallucinations (2 [6%]), and seizures (14 [40%]). Five patients (14.3%) required ventilator support and were intubated. Significant clinical findings are listed in Table 1. Of note, none of the patients treated were hyperthermic on presentation.

All five patients requiring intubation had seizures and severe obtundation with bradypnea as well as concern for airway protection and were admitted to the medical intensive care unit (MICU) for further evaluation and monitoring. Two additional patients were admitted to the MICU for close monitoring and alteration of mental status. While in the MICU, three of the patients were evaluated for seizure activity with electroencephalograms. None revealed any form of ongoing seizure activity.

Twenty-five patients (71.4%) were managed and discharged from the ED, three of whom left against medical advice. The remaining 10 (28%) were admitted to the hospital, including 7 to the intensive care unit. All of the patients subsequently recovered. A review of standard laboratory measurements on all patients who presented for treatment revealed no significant changes in the white blood cell counts, hemoglobin, platelet counts, chemistries, glucose, lactate or creatinine. Seven patients had a positive alcohol level and six patients had a positive drug screen for cocaine.

Laboratory analysis results

In total, 53 biologic samples were submitted to the Clinical Toxicology and Environmental Biomonitoring Laboratory at the University of California, San Francisco. After accounting for samples of insufficient quantity for analysis ($n = 2$) and duplicate samples from the same patient and time point ($n = 6$), a total of 45 samples from 26 of the suspected 35 case patients were analyzed. About 19 of the 26 case patients had both a serum or plasma sample and urine available for analysis. Only a whole blood sample was available for two patients; and five patients had only a urine sample available for analysis. In one instance, source material (residue from a pipe) used by a patient as well as clinical samples from the same patient were sent for analysis to UCSF.

Serum or plasma samples from 13 patients contained quantifiable amounts of AB-CHMINACA with a median concentration of 8.3 ng/ml (Table 2). Two samples from two additional patients were confirmed to contain AB-CHMINACA but at levels below the lower limit of quantification (LLOQ, 0.3 ng/ml). All 15 of the samples that were positive for the presence of AB-CHMINACA (including the two with lower limit of quantification of parent compound) also contained quantifiable amounts of a predicted M2 metabolite of AB-

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CHMINACA (Table 2), the analytical standard for which was provided by a collaborating chemical synthesis company (Cayman Chemical, Ann Arbor, MI). Twenty of the patients' serum or plasma had other predicted metabolites of AB-CHMINACA (M6, M11) detected, but cannot be confirmed until these additional standards are synthesized (Table 2 and Fig. 2). Thus, among 26 suspected case patients with samples available for testing, 15 were confirmed AB-CHMINACA exposures and another 5 are suspected.

Not all patients had all three matrices (serum, plasma, and urine) available for analysis. Among 21 patients for whom a urine sample was available, 12 contained predicted metabolites, but none contained parent AB-CHMINACA compound.

The residue from the pipe submitted for analysis contained a combination of two synthetic cannabinoids: AB-CHMINACA and quinolin-8-yl-l-(4-fluorobenzyl)-lH-indole-3-carboxylate (FUB-PB-22). The concentration of FUB-PB-22 found in the pipe was trace and neither FUB-PB-22 nor its metabolites were detected in any of the clinical samples from the patient.

Discussion

This outbreak resulted in acute delirium and seizures and necessitated the hospitalization of 10 individuals as well as medical evaluation for another 25 individuals. The prompt and coordinated response by EMS, the local public health department, treating clinicians, and law enforcement agencies as well as the dissemination of public service announcements and control of the source of the implicated product substantially curtailed the availability of the illicit compound and promoted a rapid and substantial community awareness of the event. The multifaceted public service announcement (PSA) with the local County Office of Communications was coordinated resulting in the distribution to traditional print, television, and radio media outlets in addition to social media (Facebook and Twitter). The social media broadcast resulted in a record number of "hits" (>70 000) at the county's Facebook page within 24 h of the social media broadcast (the population of Alachua County numbers ~240 000). Additionally, FDOH-Alachua notified the Bureau of Environmental Health and Bureau of Epidemiology in the state's Department of Health. Eight days after the initial outbreak, the State Surgeon General and the secretary of the Florida Department of Health issued a statewide press release that warned against the dangers of designer drugs and cited the Alachua County cases. These actions may have been instrumental in abruptly ending the outbreak and perhaps preventing additional morbidity and possibly deaths. It should be noted that the identification of AB-CHMINACA as the specific putative agent was not in any way associated with the real time management of the outbreak, but the eventual identification of the agent resulted in the emergency scheduling action by the DEA.

AB-CHMINACA was not reported in the scientific literature prior to its appearance on the illicit drug market and was named based on nomenclature used before by Uchiyama and colleagues.[11] Its metabolites, optimal matrices for analysis, and routine toxicokinetics have been recently characterized by Erratico et al. in *in vitro* experiments conducted to predict *in vivo* metabolism with confirmation in urine samples of a AB-CHMINACA user.[12] In our collaboration, efforts between the Clinical Toxicology and Environmental

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Biomonitoring Laboratory at the University of California, San Francisco and a drug standard synthesis company (Cayman Chemical, Ann Arbor, MI) (G.E.) resulted in the rapid availability of predicted metabolite laboratory standards at the company's expense, which were subsequently used to identify additional people who had been exposed to the compound and whose biologic samples were initially negative for the parent compound, AB-CHMINACA. The response to this outbreak and the collaboration between the public health department, the analytic laboratory, and a commercial entity with the ability to rapidly provide putative metabolite standards could serve as a model for responding to future outbreaks involving unpredictable toxicity from the introduction of new designer drugs into the marketplace.

Synthetic cannabinoids, much like THC, bind to both cannabinoid receptors CB_1 and CB_2. CB_1 receptors are expressed throughout the central nervous system as well as the periphery, and activation of these receptors contributes to the typical psychotropic effects of cannabinoids.[14,15] The synthetic cannabinoid compounds that activate these receptors have receptor interactions ranging from partial to full agonist activity with varying degrees of binding affinity and selectivity for each receptor.[13,15] In addition, some synthetic cannabinoids have been found to interact with potassium, nicotinic, and serotonin receptors.[12] The significant variability in binding affinity and selectivity of synthetic cannabinoids to cannabinoid receptors as well as to potassium, nicotinic and serotonin receptors may account for the varying presentations, ranging from mild tachycardia to psychosis and death. The association of these agents with acute kidney injury has also been documented.[3,14]

The synthetic cannabinoid-containing product responsible for the outbreaks of acute delirium in 2013 in Colorado and Georgia (ADB-PINACA) is believed to have come from Asia. It was first sent to Florida and was then distributed to at least nine states.[1] The labeling of synthetic cannabinoid products as "not for human consumption" and marketing them as non-consumable products facilitates their promotion and sale on websites and in smoke shops to young people, who often mistakenly see synthetic cannabinoid s as a safe or legal alternative to marijuana.[16–18]

According to the National Forensic Laboratory Information System (NFLIS), 29 467 synthetic cannabinoid drug reports were issued in 2012, an increase of 1402% from 2009.[19] Although synthetic cannabinoid exposures reported to the American Association of Poison Control Centers (AAPCC) decreased since the first reports in 2011, exposure reports have surpassed the 5,230 cases reported in 2012, and in 2015, approaching the 2011 levels of 6968 calls (6310 - through September 2015). Exposures for April 2015 (1,506) were the highest ever received in a monthly period by the AAPCC.[20]

Since 2012, several large outbreaks of adverse health effects associated with synthetic cannabinoid use have occurred nationwide.[1–3,21]

One of the challenges faced by clinicians and public health officials is responding to clusters of unusual illness caused by exposure to previously unknown synthetic drugs of abuse. This challenge has necessitated new collaboration between public health, law enforcement,

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and laboratory experts to rapidly identify the causative agent, predict the metabolites and pathways of biotransformation, and develop analytic methods to identify the exposed in order to fully characterize the scope of the outbreak and ensure cessation of potential epidemics. Because of the novelty of AB-CHMINACA, no reference standards for its metabolites were available when the cases were initially analyzed. Through the collaboration with Cayman Chemical two of the standards (M2, M4) were made available during the initial investigation and analysis in this outbreak, collaboration between an academic laboratory and a chemical company for reference standards allowed rapid confirmation of synthetic cannabinoid metabolites in suspected exposures. In the outbreak a coordinated public health response, which was highlighted by the rapid synthesis and donation of 12 predicted synthetic cannabinoid metabolites by a laboratory standard manufacturer, allowed investigators to fully characterize the scope of the Gainesville outbreak. Previous outbreaks associated with products containing synthetic cannabinoids, a decrease in the interval between introductions of new synthetic cannabinoid compounds to the market, as well as new methods of synthetic cannabinoid consumption (e.g. the use of liquid preparations containing synthetic cannabinoid s as e-cigarette refills)[22] suggest that a significant public health risk remains from designer drugs of abuse. On 30 January 2015, the DEA placed AB-CHMINACA and two other synthetic cannabinoid s on Schedule I of the Controlled Substances Act.[23]

Conclusion

Synthetic cannabinoids along with other illicit substances have become a growing public health risk. The report of this outbreak, highlights the collaboration between the analytic lab and a provider of analytic standards, allowing for additional case finding and rapid development of laboratory methods in identifying the chemical exposure reported. Immediate notification and investigation by local public health authorities and health center staff and the issuance of public service announcements, led to control of the source, and termination of the outbreak. Real time collaborations between toxicology laboratories, suppliers of analytical standards and the public health system may be useful in the face of future novel chemical exposures.

Acknowledegments

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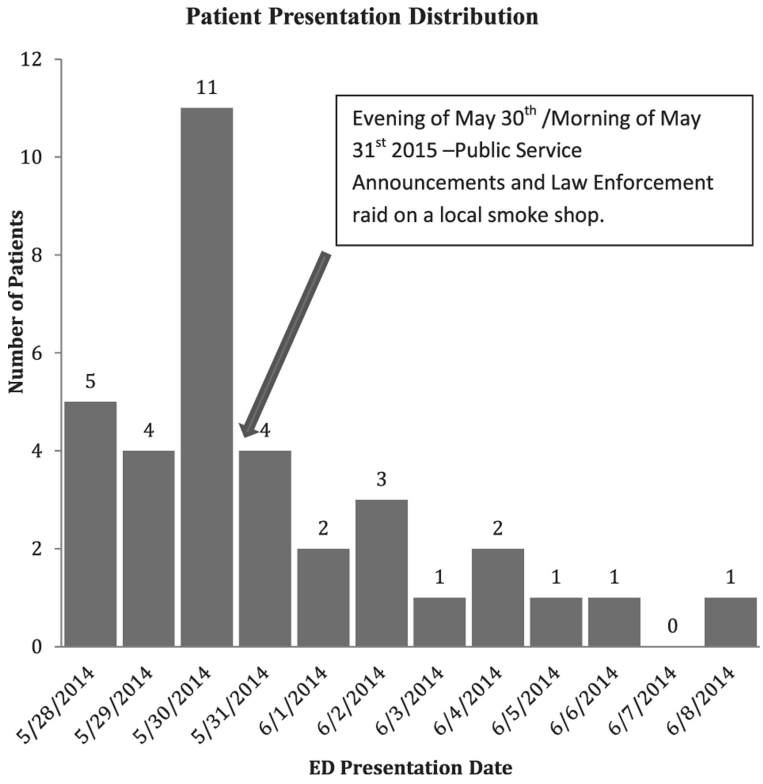

Fig. 1.
Epidemiologic curve for AB-CHMINACA outbreak.

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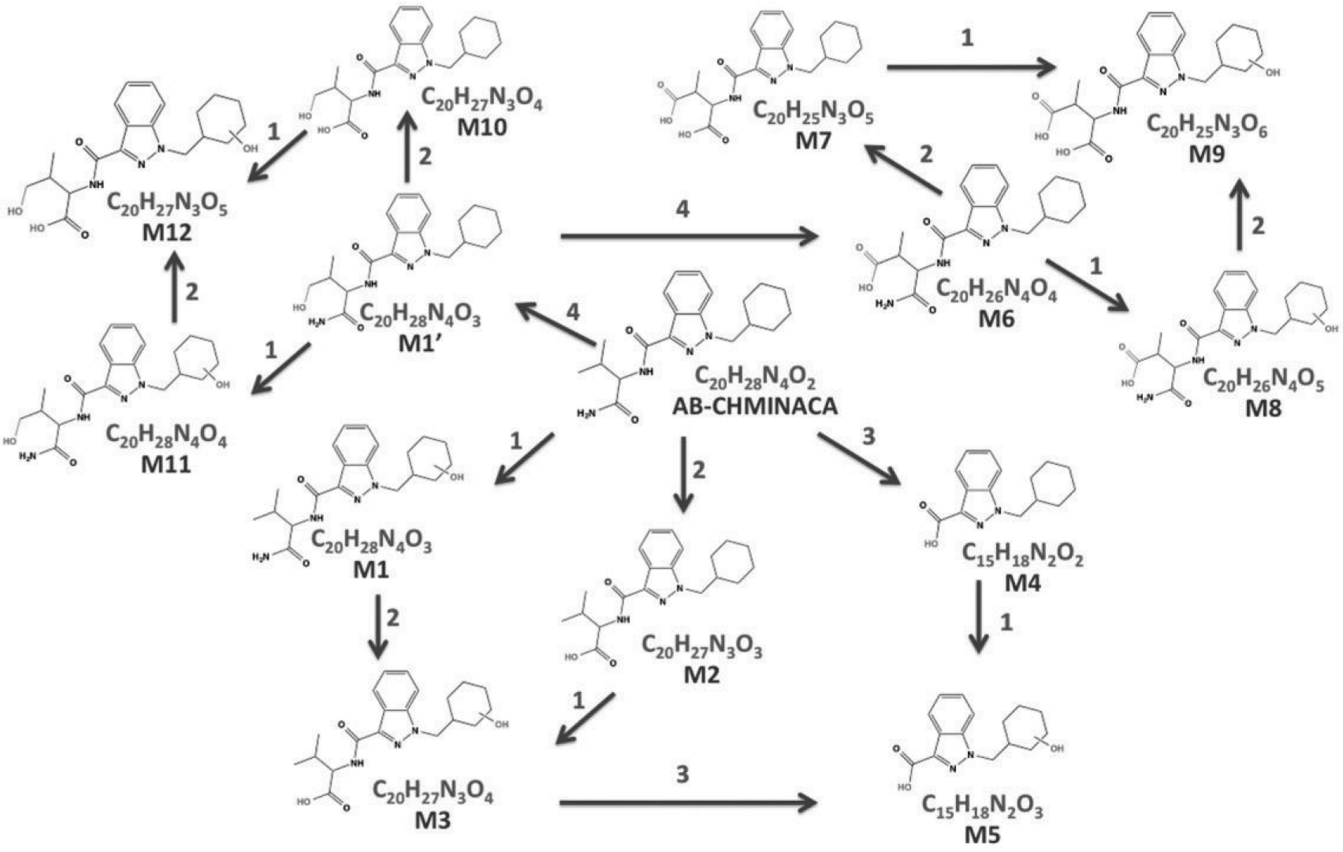

Fig. 2.

Predicted metabolites of AB-CHMINACA. Metabolites are generated from four predicted metabolic transformations - (1) hydroxylation of cyclohexyl ring, (2) hydrolysis of terminal amide, (3) hydrolysis of internal amide and (4) hydroxylation/oxidation of isopropyl group. The abbreviations refer to the numbering of the predicted metabolites (M) which was done in chronological order (Ml and M2).

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Table 1.

Patients' clinical presentation.

	Overall (*n* = 35)
Patients required intubation	14.3% (*n* = 5)
Patients with seizures	40.0% (*n* = 14)
Patients with ICU admissions	20.0% (*n* = 7)
Median hospital length of stay for admitted patients (days), median (IQR)	1 (0−1)
Patients with initial tachycardia (HR > 100)	45.7% (*n*= 16)
Patients with initial hypertension (systolic > 150 or diastolic >90)	17.1% (*n* = 6)
Patients with altered mental status (GCS ≤ 14)	54.3% (*n*= 19)
Median GCS among patients with altered mental status, median (IOR)	14 (12−15)

GCS, Glascow Coma Score; ICU intensive care unit; IQR, inter-quartile range

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Table 2.

Concentrations of AB-CHMINACA and metabolite M2 and presence of predicted metabolites.

Sample	[AB-CHMINACA] ng/ml	M1/M1'	[M2] ng/ml	M3	M6	M7	M11	Sample	M1/M1'	M2	M3	M10
UF-IP	8.3		216		+		+					
UF-2S					+	+	+	2U				
UF-3P					+		+					
UF-3S					+	+	+					
UF-4P	13.8	+	102		+		+	4U	+			
UF-5P	3.4	+	304	+	+	+	+	5U	+		+	
UF-6P					+		+	6U				
UF-8P					+	+	+	8U				
UF-9P					+	+	+	9U				
UF-10P	2.4		51		+	+	+	10U	+			
UF-11P	9.3	+	122		+		+	11U	+		+	+
UF-12P	5				+	+	+	12U				
UF-13P	<LLOQ		76				+	13U				
UF-14P	14.3	+	138		+	+	+	14U				+
UF-15P	11.9		37		+	+	+	15U	+		+	
UF-16P	13.1	+	136		+	+	+	16U	+			
UF-17P	10.7	+	117	+	+		+	17U	+		+	+
UF-18P	7.7	+	51		+	+	+	18U	+			+
UF-20P	5.6		303		+	+	+	20U	+	+		+
UF-21S			<LLOQ					21U				
UF-25P	0.4		39		+	+	+	25U	+		+	+
UF-26P	<LLOQ		66		+	+	+	26U 7U 19U	+			+

+Presence of pautative AB-CHMINACA metabolite identified without confirmation, pending analytical standard synthesis.

UF#, University of Florida case patient identifier; S, serum; P, plasma; U, urine.