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Synthetic cannabinoid "Black Mamba" infidelity in patients presenting for emergency stabilization in Colorado: a P SCAN Cohort

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Abstract

Background—Use of new psychoactive substances (NPS) has increased over the last decade. During this period, variability of both clinical presentations and chemical compositions of these compounds has increased. Synthetic cannabinoids (SCs) are the most commonly used NPS and there are more than 100 documented unique molecules in this class. "Black Mamba", often associated to ADB-FUBINACA, is the most commonly used SC in Colorado. It has been linked to kidney injury, myocardial toxicity, seizures, and death.

Objectives—We aim to identify the chemical constituents and quantification of eight cases of reported "Black Mamba" use in order to further understand the clinical variability in patients presenting for emergency stabilization.

Methods—We report data from eight cases of reported "Black Mamba" use prospectively captured through the Colorado site of the Psychoactive Surveilance Consortium and Analysis Network (P SCAN). P SCAN is a geographically representative group of academic hospitals that capture clinical presentation, outcome, and biologic samples from patients that present for emergency stabilization following NPS use. Serum and urine samples were analyzed and quantified by liquid chromatography-quadrupole time-of-flight mass spectrometry after a qualitative screen for over 600 unique NPS compounds.

Results—In the reported eight cases, the median age was 28 years old. There were four male and four females. Four patients had agitation/delirium and four patients had chest pain. Normal saline, benzodiazepines and ondansetron were the common treatment provided in the emergency department (ED). Two patients were discharged from the ED and six patients being admitted for

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Supplemental data for this article can be accessed here.

emergency observation with a median length of stay (LOS) of six hours. No deaths were reported. Confirmatory testing revealed that only five patients (62.5%) had SCs found in blood or urine samples. Cocaine, NRG-3, 3-methoxyphencyclidine hydrochloride (MeO-PCP), and methamfetamine were identified in other presentations.

Conclusions—The wide range of clinical presentations from "Black Mamba" use may be explained by the wide variability of chemical constituents found by laboratory analysis.

Keywords

Black Mamba; synthetic cannabinoid; novel psychoactive substances; public health

Introduction

New psychoactive substances (NPS) are the fastest growing class of illicit drugs in the United States [1]. Their potency and molecular variability have contributed to numerous outbreaks of severe clinical illness [1,2]. Synthetic cannabinoid (SC) use, a subclass of NPS, has increased dramatically over the last decade [1,3–5]. In the early 2000s, SCs became available on internet marketplaces and were sold as "natural herbs." These products are typically labeled as "not for human consumption" though their use became widespread in the United States and Europe. Buyers quickly found an intoxicating substance they could purchase legally. Creative names for these products include "Spice", "K2", "Bubblegum Kush", "AK-47", and "Scooby Snak" among others. Illness associated with SCs ranges from mild nausea [6], kidney failure [7], cerebrovascular accidents, seizures [8], myocardial toxicity [9] and death [7]. There is a lack of quality control in the manufacturing of these products and subsequently, buyers may not receive the drug they intended to buy.

"Black Mamba" is the colloquial name of a commonly used SC in Colorado. During a major outbreak of severe clinical illness in 2013, the novel SC ADB-FUBINACA was identified as the etiologic compound causing over 70 emergent presentations at two local emergency departments (EDs) over less than a two-week period [1,8]. Patients continue to present for emergency stabilization following reported use of Black Mamba though clinical presentations and response to treatment vary widely.

There are multiple possible explanations for this wide range of clinical illness. Variability in dose, adulteration with other illicit drugs, or substitution with other more dangerous drugs all may contribute. Therefore, in this study, we aim to identify the chemical constituents and quantification of eight cases of reported "Black Mamba" use in order to further understand the clinical variability in patients presenting for emergency stabilization.

Methods

Study design

We describe a cohort of patients presenting for emergency stabilization after reported Black Mamba use from the Psychoactives Surveillance Consortium and Analysis Network (P SCAN) Colorado site. These cases were collected between August and November, 2016. Briefly, this consortium prospectively collects de-identified clinical data and biologic

samples from patients that present for emergency stabilization after NPS use. P SCAN is a geographically representative group of academic emergency departments with medical toxicology co-investigators. Data are captured in a Health Insurance Portability and Accountability Act (HIPPA) compliant database for future analysis.

Study setting and patient enrollment

The University of Colorado Department of Emergency Medicine is an urban academic ED that has approximately 100,000 visits per year. Patients are eligible for the study if they endorse NPS use, or if the ED provider determines NPS use is the most likely etiology of the patients symptoms. A medical toxicologist records the clinical data obtained during the index visit and de-identified biologic samples are collected for analysis. Patients verbally consent for the study. This study was approved by the local institutional review board and the P SCAN protocol is approved at each individual consortium site.

Sample preparation

Leftover blood and/or urine samples were collected at the time of presentation. Blood was obtained on arrival when an intravenous catheter was placed. Urine was obtained at the time patient went to use the restroom or a Foley catheter was placed. Any drug or paraphilia found with the patient was confiscated and tested if possible. Samples were stored on ice for less than 12 hours. Urine was then frozen at −80 °C. Whole blood was separated into plasma and red blood cell fractions, and then frozen at −80 °C. Samples were then shipped on dry ice to the reference laboratory at the University of California-San Francisco for drug identification.

Drug testing/bioanalytical investigation

Serum and urine samples were analyzed using liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF/MS). For qualitative screening, non-targeted data acquisition was performed during the sample run followed by targeted data analysis using a reference database of 615 compounds with known retention times. Suspect screening of parent drug or metabolites including novel SCs (498), stimulants (400 cathinones and phenethylamines), hallucinogens (158 arycyclohexylamines and tryptamines) and depressants (120 opioid analogs, barbiturates and benzodiazepines) was also performed (see online appendix A for the full list of drugs and metabolites detected by this assay). Quantification of each confirmed drug was done using 10-point calibration curve by isotope dilution using deuterated internal standards. The details of LC-QTOF/MS method used were published previously [5].

Statistical analysis

We utilized descriptive statistics to describe demographic data, clinical presentation variables, treatments, and drug identification.

Results

Patient presentation

Between August 1 and November 30, 2016, eight patients presented to our emergency department with reported smoking of Black Mamba and all presented with acute intoxication; there were four males and four females with a median age of 28 (range: 16–43) (Table 1). Agitation and/or delirium was reported in four presentations. Chest pain was present in four presentations and one had T-wave inversions on electrocardiogram. One patient, with a previous seizure history, had a generalized tonic–clonic seizure. All but one case had elevated blood pressures with a median blood pressure of 143 mmHg systolic and 87 mmHg diastolic. Only two cases presented with a heart rate greater than 100 beats per minute (bpm). Two patients were hypokalemic (2.6 and 2.7 mmol/L) and one case had a bicarbonate of 17 mEq/L. The remainder of the laboratory testing was within normal limits. The urine immunoassay screens were positive for cocaine, benzodiazepine, and marijuana in Case 1, amfetamine/methamfetamine in Case 2, ethanol in Case 6, and marijuana and cocaine in Case 8. The urine immunoassay screen for Case 5 was negative and three cases did not have the urine screen performed.

Treatments

Four patients received either diazepam or lorazepam for agitation. One of these patients also received haloperidol and diphenhydramine in addition to the lorazepam for agitation. Three patients had full resolution of agitation and one patient had partial resolution of symptoms after receiving sedatives. Four patients received ondansetron for nausea. Three patients received at least 1 l of normal saline. Other treatments received were directed towards the clinical presentations of seizure and chest pain (Table 1).

Clinical outcomes

Six patients were admitted to an emergency observation unit until their symptoms resolved. Two were discharged directly from the ED after resolution of symptoms. The median length of stay (LOS) for seven patients was six hours (range: 2–10 hours). One patient had a LOS of 26 hours due to social complications around housing with resolution of symptoms within the first few hours. All patients had normal vitals at discharge. No deaths were reported.

Drug confirmation

A wide variety of xenobiotics were confirmed in blood and urine samples (Table 2). Only 62.5% of these cases were confirmed to have SCs in their biologic sample. Of the confirmed cases, a variety of SCs were detected. There was no correlation between confirmed drug and clinical symptoms (i.e., agitation, chest pain, etc.).

For the ester indole carboxamides, AMB-FUBINACA and MDMB-FUBINACA, the acid metabolites instead of the parent compounds were detected in both serum and urine. The concentration ranges observed for the metabolites are 45.3–115.9 ng/mL and < Lower Limit of Quantification (LLOQ) – 1599 ng/mL in serum and urine, respectively (see Table 2 for LLOQ limits for respective metabolites). The three cases of ADB-FUBINACA had serum concentrations <31.25 ng/mL (LLOQ). The three cases of AMB-FUBINACA had detectable

serum concentrations ranging 58.7–115.9 ng/mL. The NRG-3 detected in one case has a concentration <15.6 ng/mL (LLOQ) in serum and 11.2 ng/mL in urine. 3-MeO-PCP was found in three urine samples at a concentration range of 60.3–114.1 ng/mL.

Discussion

This study demonstrates profound molecular variability and a wide range of NPS drugs sold as “Black Mamba” in Colorado. The SCs AMB-FUBINACA, MDMB-FUBINACA and ADB-FUBINACA are chemically similar to AB-FUBINACA, a well-described SC [10]. All three have high affinities for the CB1 receptor, which causes their clinical effects. AMB-FUBINACA is an ester analogue of AB-FUBINACA. ADB-FUBINACA structurally varies from AB-FUBINACA by replacement of an isopropyl moiety with a tert-butyl moiety [11]. MDMB-FUBINACA is an ester analogue of ADB-FUBINACA. ADB-FUBINACA’s clinical effects are not well understood though it is hypothesized the clinical effects are similar to that of AB-FUBINACA [12]. 3-MeO-PCP, along with 4-MeO-PCP, are designer dissociatives structurally and pharmacologically similar to PCP [13]. NRG-3 is naphyrone, a cathinone structurally similar to mephedrone and MDPV [14]. It is a “triple reuptake inhibitor” causing decreased reuptake of dopamine, serotonin and norepinephrine.

All of the NPS and most of the psychoactive xenobiotics identified are known to cause agitation, delirium, tachycardia, hypertension, hyperthermia, seizures, multi-system organ failure and potentially death. However, the pathophysiology of the elicited clinical effects varies considerably between the agents. Most users likely prefer a known drug in a known dose for predictable clinical effects and ease of titration. Variability in drug and dose complicates the ideal emergency treatment strategy given that anti-dopamine, serotonin antagonists, or GABA antagonism may be preferred, depending upon the agent ingested.

It is impossible for clinicians and public health officials to have a uniform approach that keeps SC users safe. Increasing chemical variability, rising potency, clandestine methods of production and sale leads to reactive rather than proactive identification of potentially harmful NPS drugs. The Analog Act of 1986 aimed to schedule synthetic analogs of drugs such as methamfetamine and meperidine as Schedule I illicit substances. This law only applied to drugs developed for “human consumption”. In order to circumvent this law, sellers of NPS labeled their product as “plant food” or “incense” with packaging labeled as “not for human consumption”. In response, the Synthetic Drug Abuse Prevention Act of 2012 was passed to extend Drug Enforcement Agency (DEA) temporary scheduling authority of synthetic analogs, specifically in response to SCs analog manufacturing. We further demonstrate that NPS can contain a variety of xenobiotics, many with new variations of chemical structures. This highlights the need for a more proactive surveillance and drug enforcement strategy.

Despite the efforts of congress and medical researchers, the continuing rapid evolution of NPS continues to have serious implications for both healthcare providers and law enforcement. Users are prone to severe clinical illness due to variability in the products they consume. Our data demonstrate a wide range of drugs sold under the Black Mamba product name (Table 2). While some argue that patients are disingenuous about their drug ingestion

history in the ED, this cohort is unique in that all patients freely admitted to use illegal substances. However, the drug they ingested was not what they believed they ingested 37.5% of the time when confirmed in biologic samples. The variability in half-lives of different SCs can further complicate laboratory confirmation. SCs that are quickly metabolized may not be detected without proper testing methods. We believe clinical history and confirmatory drug testing discordance is more likely due to product variability than misleading patient histories given their admission of use and confirmation with an extremely sensitive testing methodology.

These findings present a plausible explanation for the variability of clinical symptoms of Black Mamba in Colorado and this problem is likely pervasive with other NPS drugs sold with brand name recognition. This molecular infidelity should be used in public health messaging to educate prospective users about the inherent risks of product discordance. P SCAN provides a unique method of surveillance that can proactively identify emerging trends in NPS use. This consortium provides the framework for rapid molecular identification, which may limit progression of future outbreaks due to emerging NPS-induced clinical illness.

Conclusions

Black Mamba is one of many SCs sold using brand name recognition. Consumers believe they are receiving a specific product with anticipated effects though they actually receive a wide range of illicit drugs. These findings should prompt public health substance abuse education targeted at prospective SC users.

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Disclosure statement

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Table 1

Patient demographics, clinical presentation variables, treatments, and disposition.

Case	Age	Sex	Reported NPS	Reported co-ingested drugs	LOS	Clinical course	Treatments	Maximum BP (systolic/diastolic) observed (mmHg)	Heart rate maximum (per min)	Notable labs	Disposition
1	42	Female	Black Mamba	Cocaine	26 hours	Depressed mental status with combative behavior, seizure	Diazepam 5 mg, Potassium, Levetirecetam	139/80	92	K+: 2.7 mmol/L	Discharged after ED observation
2	36	Female	Black Mamba	Methamfetamine	8 hours	Agitated, chest pain	Normal saline 2 l, Diazepam 25 mg, Ketorolac 15 mg, Lisinopril 20 mg, Hydrocodone 5/325 mg	199/118	147	HCO_3: 17 mEq/L	Discharged after ED observation
3	25	Female	Black Mamba	Not applicable	10 hours	Agitated and combative behavior	Lorazepam 2 mg, Haloperidol 5 mg, Diphenhydramine 50 mg	143/106	155	Not applicable	Discharged after ED observation
4	27	Male	Black Mamba	Marijuana	3 hours	Palpitations, bilateral hand numbness, and nausea/vomiting	Lorazepam 1 mg × 2, Normal saline 1 l	155/85	94	Not applicable	Discharged
5	23	Female	Black Mamba	Not applicable	9 hours	Chest pain, T-wave inversions on EKG, diarrhea, nausea, resolved, Mamba 2 days prior	Ketorolac 15 mg, Ondansetron 4 mg, Acetaminophen 1 g, Aluminum/ magnesium/ simethicone 30 mL, Viscous lidocaine 2% 15 mL	148/100	67	K: 2.6 mmol/L +	Discharged after ED observation
6	29	Male	Mamba	Ethanol	5 hours	Agitation/CNS depression	None	120/70	93	Not applicable	Discharged after ED observation
7	16	Male	Mamba	Not applicable	2 hours	Nausea/vomiting, chest pain, body aches	Normal saline 1 l, Ondansetron 4 mg	131/86	74	Not applicable	Discharged
8	43	Male	Mamba	Cocaine	6 hours	Chest pain, confused	Ceftriaxone 1 g, Azithromycin 500 mg	143/88	79	Creatinine: 1.1 mg/dL	Discharge

Table 2

Identification and quantification of serum and urine drugs.

Case	Age	Sex	Serum concentration (ng/mL)	Urine concentration (ng/mL)	Confirmatory drug testing concordant with patient history?
1	42	Female	Benzoylecgonine (3078) Cocaine (<LLOQ) * Cocaethylene (<LLOQ) * Methamfetamine (59.5)	Benzoylecgonine (29,368) Cocaine (2362) Cocaethylene (103.6) Ecgonine methyl ester Methamfetamine (177.0) **3-MeO-PCP (114.1)**	No
2	36	Female	Methamfetamine (349.1) Caffeine Cimetidine	**Methamfetamine (765.2)** **3-MeO-PCP (60.3)** Fluoxetine	No
3	25	Female	**AMB-FUBINACA acid met (58.7)** **ADB-FUBINACA (<LLOQ) *** Methamfetamine (1461) Diphenhydramine (270.6) Lorazepam Haloperidol	Not reported	Yes
4	27	Male	**MDMB-FUBINACA acid metabolite (45.3)**	**MDMB-FUBINACA acid met (<LLOQ)**	Yes
5	23	Female	**AMB-FUBINACA acid met (115.9)** **NRG-3 (<LLOQ) *** Diphenhydramine (239.1) Trazodone Acetaminophen Theobromine Theophylline Cotinine	**AMB-FUBINACA acid met (817.8)** **NRG-3 (11.2)** Cocaine (59.5) Diphenhydramine (2567) Risperidone Acetaminophen Theophylline Cotinine	Yes
6	29	Male	**AMB-FUBINACA acid met (99.0)** **ADB-FUBINACA (<LLOQ) *** Theobromine Cotinine	**AMB-FUBINACA acid met (1599)** **3-Meo-PCP (103.2)** Methamfetamine Nicotine Cotinine	Yes
7	16	Male	Prednisolone Theobromine Cotinine	11-nor-9-carboxy THC Ibuprofen Prednisolone Theobromine Cotinine	No
8	43	Male	**ADB-FUBINACA (<LLOQ) *** Cocaine Theobromine Cotinine	Cocaine (2203) Benzoylecgonine (25,710) Ecgonine methyl ester Theobromine Cotinine	Yes

ADB-FUBINACA = N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide.

AMB-FUBINACA = 2-(1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamido)-3-methylbutanoate.

MDMB-FUBINACA = methyl (S)-2-(1-(4-fluorobenzyl)-1H-indazole-3-carboxamido)-3,3-dimethylbutanoate.

NRG-3 = 2-(methylamino)-1-(naphthalen-2-yl)pentan-1-one, monohydrochloride.

3-MeO-PCP=3-methoxyphencyclidine hydrochloride.

* For analytes with reported values < LLOQ, the established LLOQs are – ADB-FUBINACA = 31.25 ng/mL, cocaine = 7.8 ng/mL, cocaethylene = 15.6 ng/mL, NRG-3 = 15.6 ng/mL, and MDMB-FUBINACA acid metabolite = 31.25 ng/mL. Items in bold denote a NPS.