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Hallucinogens Causing Seizures? A Case Report of the Synthetic Amphetamine 2,5-Dimethoxy-4-Chloroamphetamine

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Abstract

Although traditional hallucinogenic drugs such as marijuana and lysergic acid diethylamide (LSD) are not typically associated with seizures, newer synthetic hallucinogenic drugs can provoke seizures. Here, we report the unexpected consequences of taking a street-bought hallucinogenic drug thought to be LSD. Our patient presented with hallucinations and agitation progressing to status epilepticus with a urine toxicology screen positive only for cannabinoids and opioids. Using liquid chromatography high-resolution mass spectrometry, an additional drug was found: an amphetamine-derived phenylethylamine called 2,5-dimethoxy-4-chloroamphetamine. We bring this to the attention of the neurologic community as there are a growing number of hallucinogenic street drugs that are negative on standard urine toxicology and cause effects that are unexpected for both the patient and the neurologist, including seizures.

Keywords

seizures, epilepsy, neurotoxicity syndromes, neurochemistry, techniques, neuropharmacology, techniques

Introduction

Traditional hallucinogens such as the cannabinoids in marijuana may actually be protective against seizures,[1,2] and lysergamide lysergic acid diethylamide (LSD) is not known to cause seizures. However, newer hallucinogens have been associated with seizures, including synthetic cannabinoids such as those in spice,[3] phenylethylamines such as ectasy,[1,4] and synthetic cathinones such as bath salts.[5] In the case of the designer amphetamines, many have little cross-reactivity with commercial urine toxicology screening immunoassays[6] and must be detected with other methods. We present a case of a patient who stated that he thought he took LSD and had a urine toxicology negative for amphetamines yet had seizures: additional testing was later positive for the phenylethylamine (2,5-dimethoxy-4-chloroamphetamine [DOC]). Limited clinical data are available for DOC, as there is only 1 previously reported case in the literature.[7]

Case Description

Our patient is an 18-year-old man with a history of migraines and a single febrile seizure at age 2 who presented to the emergency department in status epilepticus. His mother called emergency medical services (EMS) after the patient and his friend came home with agitation and hallucinations. The patient states that they had used what he thought was LSD as well as marijuana. While waiting for EMS, the mother noted the patient was unresponsive and shaking in all 4 extremities. Emergency Medical Services arrived and noted the patient to be seizing with left gaze deviation, dilated pupils, and abnormal movements of all extremities. He was given 2.5 mg of midazolam intranasally which stopped the seizures only briefly; a second dose of midazolam 2.5 mg had no effect. His triage vitals showed tachycardia and tachypnea (blood pressure 132/66, heart rate 125, Temp 37.3°C, respiratory rate 24, oxygen saturation 95%), and initial electrocardiogram showed sinus tachycardia with a prolonged QT interval (PR 176 milliseconds, QRS 94 milliseconds, QTc 492 milliseconds). On arrival to the emergency department,

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he was still having tonic head turning and gaze deviation, with improvement in the tonic head movement with 2 mg of intravenous (IV) lorazepam. He was then rapidly sedated and paralyzed with propofol and rocuronium for intubation, his given altered mental status and inadequate airway protection. Sedation was continued with a propofol drip started at 20 μg/min and increased over the course of the next hour to 100 μg/min. While waiting for electroencephalogram (EEG), the patient was noted to have rhythmic twitching movements of both toes as the paralytic wore off. He was given a total of an additional 9 mg of lorazepam IV, fosphenytoin 20 mg/kg IV, and the addition of a midazolam drip at 7 mg/h to his propofol drip. Continuous EEG then showed initial diffuse slowing with no seizure activity, thus the propofol drip was weaned off while the midazolam drip was continued.

Initial laboratory test results were notable for an anion gap metabolic lactic acidosis, profound leukocytosis, evidence of early rhabdomyolysis and hyperglycemia but otherwise normal electrolytes, and a negative troponin (see Table 1). Additional acute workup revealed toxicology testing which was negative for acetaminophen or salicylates, and a urine toxicology screen (UniCel DxC 800, Beckman Coulter, Brea, California) that was positive for benzodiazepines (given by EMS), opioids, and cannabinoids but negative for amphetamines and cocaine.

Once stabilized, additional workup was performed for causes of seizure. Laboratory testing was negative for provoked causes including a normal sodium, blood urea nitrogen, calcium, magnesium, and phosphorous and only mildly elevated calcium. He had a lumbar puncture at 12 hours of arrival that revealed only elevated glucose (see Table 1), likely a response to his recent serum hyperglycemia. Electroencephalogram showed no seizures or epileptiform activity over 32 hours of continuous recording. Cultures from cerebrospinal fluid (CSF) and blood were negative, CSF varicella-zoster virus and herpes simplex virus polymerase chain reactions were negative, and urine culture was not diagnostic of urinary tract infection (*Streptococcus viridans*, only 1000 colony-forming units). He was not given antibiotics at any time during his admission. Head computed tomography on arrival showed subtle hypodensities in the bilateral cerebellum and occipital lobes suggestive of posterior reversible encephalopathy syndrome versus toxic or ischemic etiology, but magnetic resonance imaging (MRI) of the brain the following day was unremarkable with no evidence of mesial temporal sclerosis and no areas of reduced diffusion or abnormal magnetic susceptibility.

Comprehensive toxicology screening of the serum and urine was analyzed by a liquid chromatography high-resolution mass spectrometry system (AB SCIEX TripleTOF 5600, AB SCIEX, Framingham, Massachusetts). It is particularly attractive in the clinical toxicology setting because knowledge of the drugs present in the sample is not required a priori; data can be collected in an untargeted manner and can be retrospectively analyzed. The samples were run in full-scan positive ion mode with information-dependent acquisition of product ion spectra. The data were searched against a library of approximately 200 compounds, which includes commonly abused prescription, illicit, and designer drugs. Compounds are identified based on their accurate mass, chromatographic retention time, isotope pattern, and product ion spectra match against the library. The patient's samples screened positive for DOC, which was confirmed by comparison to a reference standard. The serum concentration of DOC in the emergency department was measured to be 3 ng/mL approximately 5.5 hours after drug ingestion.

Table 1. Laboratory Findings in Acute 2,5-Dimethoxy-4-Chloroamphetamine Intoxication.[a]

Initial Results	
Arterial blood gas	
6.97/44/490	→ 7.43/30/81 (3.5 hours later)
Anion gap 30	→ 9 (3.5 hours later)
Lactate 21	→ 1.4 (3.5 hours later)
Metabolic panel	
Sodium	140
Potassium	3.7
Chloride	101
Bicarbonate	9
BUN	15
Creatinine	**1.4 → 2.50 (24 hours later, peak value)**
Glucose	**405** → 95 (24 hours later)
Calcium	**10.5**
Magnesium	2.4 (at 8 hours)
Phosphorous	3.9 (at 8 hours)
Total bilirubin	0.5
AST	41
ALT	25
Alkaline Phos	**135 → 97 (3.5 hours later)**
CK	182 → **3186 (24 hours later, peak value)**
Troponin	<0.02
CBC panel	
WBC	**36.1 → 15.3 (3.5 hours later)**
Hemoglobin	15.7
Hematocrit	47.6
Platelets	420
CSF analysis (at 12 hours)	
WBC	4
RBC	15
Protein	38
Glucose	**93**

Abbreviations: BUN, blood urea nitrogen; CSF, cerebrospinal fluid; CK, creatine kinase; AST, aspartate aminotransferases; ALT, alanine transaminase; WBC, white blood cell; RBC, red blood cell; Phos, phosphatase; CBC, complete blood count.

[a] Abnormal results highlighted in bold, relevant follow-up values noted after the arrows. Of note, this patient also tested positive for opioids and cannabinoids. Values reported in mmol/L (sodium, potassium, chloride, bicarbonate, and lactate), mg/dL (BUN, creatinine, glucose, calcium, magnesium, phosphorous, total bilirubin, CSF protein, and CSF glucose), μg/L (troponin), units/L (CK, AST, ALT, and alkaline phosphatase), 10^9 units/L (serum WBC and platelets), g/dL (hemoglobin), % (hematocrit), and 10^6 units/L (CSF WBC and CSF RBC).

It should be noted that other designer drugs that may produce DOC as a metabolite (ie, DOC-NBOMe, DOC-NBMD, DOC-NBF, and DOC-NBOH) but these compounds were not detected in either the serum or the urine.

The patient's laboratory abnormalities, including his leukocytosis and rhabdomyolysis, improved with supportive care, specifically anti-epileptic medications and liberal IV fluids. He was successfully extubated on hospital day 2 with amnesia for the event and mental status difficulties but an otherwise normal neurologic examination (perseverative with slow response times and 0/3 recall, with good repetition, naming, and ability to follow 3 step commands). His recall improved by hospital day 3 though he still had slowed response times.

Discussion

2,5-Dimethoxy-4-chloroamphetamine is an amphetamine that can be synthesized from 2,5-dimethoxyamphetamine hydrochloride and has a reported duration of 12 to 24 hours.[8] It is a 5-hydroxytryptamine (5-HT2) receptor agonist,[9] with hallucinogenic effects presumably mediated through the 5-hydroxytryptamine type 2A (5-HT2A) receptor as in other hallcinogens.[10] 2,5-Dimethoxy-4-chloroamphetamine appears to be metabolized by *O*-demethylation at positions 2 and 5 via CYP2D6.[9,11] Like many other synthetic amphetamines,[6] our patient's urine toxicology tested negative for amphetamines and was only detected with liquid chromatography high-resolution mass spectrometry.

As there is only 1 prior case report on DOC,[7] little is known about the exact effects of this particular synthesized amphetamine. Presumably DOC has similar effects to other amphetamines, including tachycardia, hypertension, anion gap acidosis, rhabdomyolysis, tremors, and seizures. Similar to the previously published case report, our patient ingested multiple recreational drugs and presented with rhabdomyolysis and seizure requiring emergent intubation. Unlike the previous report, our patient had a prolonged QTc, which may have been due to a different dose of DOC (no dose was reported in the prior report) and/or to his concurrent opioid use as seen on urine toxicology. In our patient, other causes of provoked seizures were negative, including CSF results, electrolyte results, infectious workup, and brain MRI. Although the patient did have a febrile seizure at 2 years of age, the rate of epilepsy in patients with febrile seizures before the age of 5 years is not significantly higher than those without febrile seizures.[12] Based on chemical similarity of DOC to other epileptogenic amphetamines and a negative workup for other causes of seizures, we propose that DOC was the cause of this patient's status epilepticus. When patients present with status epilepticus after using hallucinogens, several drugs not found on routine urine toxicology screening should be considered, including cannabinoid 1 receptor antagonists,[3] synthetic cathinones,[5] and phenylethylamines such as ectasy[4] and DOC.

Declaration of Conflicting Interests

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