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Selected Topics: Toxicology

IBOGAINE CONSUMPTION WITH SEIZURE-LIKE EPISODES, QTC-PROLONGATION, AND CAPTURED CARDIAC DYSRHYTHMIAS

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☐ **Abstract—Background: Ibogaine is a psychoactive indole alkaloid that has been investigated for use as a treatment for opioid addiction. While not commercially available in the United States, it is available via Internet suppliers. Ibogaine use has been associated with significant cardiac and neurologic effects, such as QT-segment prolongation, cardiac dysrhythmias, hallucinations, seizures, and central nervous system depression. We present a case of verified ibogaine exposure with associated QTc prolongation and torsade de pointes with qualitative analysis of the ingested substance, and examine the history, social context, availability, and perceptions of ibogaine's effects and safety. Case Report: A 34-year-old white woman with medical history significant for heroin and cocaine use disorder presented with reported seizures 1 day after ingestion of 2 g ibogaine powder purchased from an Internet supplier. Shortly after ingestion, she experienced hallucinations and was reported by family to have four to five seizure-like episodes, at one point becoming apneic. In the emergency department, she was noted to have QTc prolongation and several episodes of torsade de pointes. Qualitative analysis confirmed the presence of ibogaine in the empty foil packages containing the ingested substance. Why Should an Emergency Physician Be Aware of This?: As increasing numbers of opioid-dependent patients attempt to curtail their substance use disorders, we anticipate a rise in ibogaine exposures, necessitating awareness by front-line clinicians in recognizing and treating a drug exposure that can rapidly become life-threatening.**

☐ **Keywords—ibogaine; *Tabernanthe iboga*; indole alkaloid; addiction medicine; torsades de pointes; QTc; liquid chromatography-quadrupole time-of-flight mass spectrometry**

INTRODUCTION

Ibogaine is a psychoactive indole alkaloid found in numerous African plants, most commonly derived from bark and root of central African *Tabernanthe iboga*. It is the most abundant alkaloid of a dozen congeners found in *iboga*, representing approximately 80% of the active compound in *iboga* extracts, with 15% ibogaline, and 5% ibogamine (1). In rat models of morphine and cocaine addiction, one dose of ibogaine was found to decrease drug-seeking behavior in rats for several days up to 3 weeks (2). Similarly, after experiments in the 1960s, it has been a clinical target for humans facing substance abuse and addiction, purportedly expediting cessation and withdrawal from drug addiction, notably cocaine and opiates (3). However, large-scale studies and implementation into clinical practice have been stymied by well-reported cardiac and neurologic effects, specifically QT-segment prolongation, cardiac dysrhythmias, hallucinations, seizures, and central nervous system depression in humans and cerebellar neurotoxicity in rat models (4). Notably, ibogaine is illegal in the United States,

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recognized by the Drug Enforcement Administration as a Schedule I controlled substance without any recognized medical use and a high risk of abuse (5). Despite these barriers, research continues, with both academic studies and trials abroad and patients performing personal experimentation through Internet retailers and forums. Due to the varying legal status internationally, academic research on humans has continued, most recently with an observational study in New Zealand and an upcoming study on ibogaine and alcohol dependence in Brazil (6,7).

Mechanisms

Ibogaine and its principal metabolite, noribogaine, act on a variety of receptors, notably as an agonist of μ, 5HT2 and 5HT3, σ_2, and muscarinic acetylcholine receptors. It acts as a mixed agonist of κ_1 and κ_2 and is an antagonist of nicotinic and N-methyl-D-aspartate (NMDA) receptors. Ibogaine modulates serotonin activity, increasing its release and inhibiting its reuptake (8,9). Notably, the modulation of μ-opioid receptor activity is thought to suppress symptoms of withdrawal from opioids. Its antagonism of NMDA receptor and $\alpha 3\beta 4$ nicotinic receptors and increased levels of glial-derived neurotrophic factor in the ventral tegmental area can further contribute to reduce cravings (10,11). Moreover, there are reports of reduced efflux of dopamine from the nucleus accumbens, reducing the "rush" associated with opioid abuse (3). It is highly lipophilic, concentrating in fat and brain (1). Ibogaine's activity can be unpredictable, even in controlled settings, with interaction from concomitantly ingested drugs, preexisting liver or cardiac comorbidities, and the mixture of congeners in its raw form (9). It undergoes extensive first-pass metabolism by the liver and is processed by CYP450-2D6, which can further confound management due to unpredictable blood levels of ibogaine and noribogaine secondary to genetic differences between rapid and slow metabolizers and the effects of cytochrome inducers and inhibitors (12). Moreover, noribogaine may exhibit prolonged clearance and activity, despite more rapidly excreted ibogaine (13). It can be quantified with multiple laboratory modalities, including gas or liquid chromatography with mass spectrometry in its raw form, as well as in serum and urine samples (14,15).

Effects

Most reports describe use of purified ibogaine HCl, consumed in a dark, quiet environment (3,16). Patients report a phase of nausea, vomiting ("purging"), ataxia, and insomnia, followed by a dream-like trance of inward reflection (9). Many sources describe visions with their eyes closed, rather than the intrusive visual disturbances of other hallucinogic compounds, prompting some authors to label ibogaine as an "oneirophrenic" rather than a hallucinogen (9,16).

CASE REPORT

A 34-year old white woman with medical history significant for heroin use disorder presented to the emergency department (ED) with reported seizure activity. One day prior to presentation, the patient ingested 2 g ibogaine powder purchased from an Internet supplier, in an attempt to self-withdraw from opioids. She also admitted to cocaine and heroin abuse in the days before ibogaine ingestion. Shortly after ingestion of the ibogaine, family members reported that she experienced hallucinations and was noted by her daughter to have had four to five seizure-like episodes with altered mental status, clenching teeth, and extension of arms, each lasting 2–4 min, with no residual confusion afterward. During the worst spell, she became apneic, at which point Emergency Medical Services were contacted and she was transported to the ED.

On ED arrival, she was awake and alert. Her initial vital signs were: temperature 98.2°F, heart rate 76 beats/min, blood pressure 156/118 mm Hg, respiratory rate 14 breaths/min, and blood oxygen saturation 100% on room air. Her initial electrocardiogram (ECG) showed QTc prolongation at 788 ms (see Figure 1). While on cardiac monitoring, she was witnessed to have several episodes of torsades de pointes, accompanied by rigidity and clenching of teeth (see Figures 2 and 3). Due to altered mental status and persistent dysrhythmias, she was intubated for airway protection. She received 2 g i.v. magnesium sulfate, which terminated her dysrhythmias. One hour later, her QTc had decreased to 615 ms.

Pertinent laboratory results on presentation were: sodium 139 mmol/L (reference range 135–145 mmol/L), potassium 3.4 mmol/L (reference range 3.5–5.5 mmol/L), chloride 105 mmol/L (reference range 98–107 mmol/L), bicarbonate 25 mmol/L (reference range 21–32 mmol/L), blood urea nitrogen 20 mg/dL (reference range 7–18 mg/dL), creatinine 0.68 mg/dL (reference range 0.51–0.95 mg/dL), glucose 131 mg/dL (reference range 8.5–10.1 mg/dL), and magnesium 2.7 mg/dL (reference range 1.7–2.4 mg/dL). Urine drug screen detected cannabinoids, cocaine, and opiates.

The patient was admitted to the intensive care unit. She was extubated on her third day of admission, at which point her QTc had decreased to 464 ms, however, she was noted to have persistent confusion. On her fourth hospital day, she was transferred to an inpatient psychiatric unit for 5 days to monitor persistent confusion. Thereafter, she was cleared by Psychiatry for discharge home with outpatient treatment of her substance use disorder.

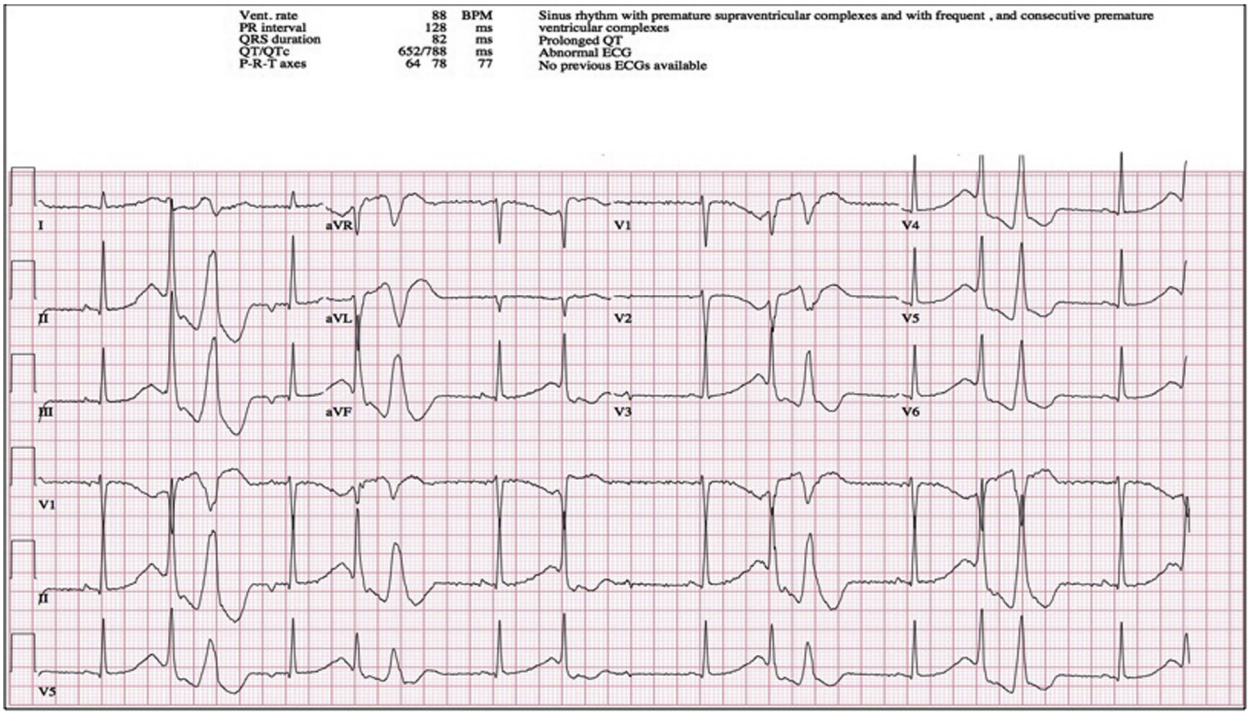

Figure 1. Electrocardiogram on presentation to the emergency department.

The patient's daughter surrendered two empty packages containing the purchased ibogaine, which were then submitted for laboratory analysis. The packages were labeled "Devil's Claw" and "Sutherlandia Frutescents" (see Figure 4).

Analysis of the residue from the packaging was performed using liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF/MS). Ibogaine was confirmed in both packages. However, because the trace amount of residue was too small to weigh in both samples, a quantitative analysis of ibogaine in the product could not be performed (see Figure 5). Likewise no biological samples were available for further laboratory testing using LC-QTOF/MS.

DISCUSSION

Ibogaine has significant implications in the realm of addiction management, though this is tempered by numerous case reports of dangers, both in the laboratory and clinical settings. The chief reported complaints include temporary nausea, vomiting, ataxia, and the

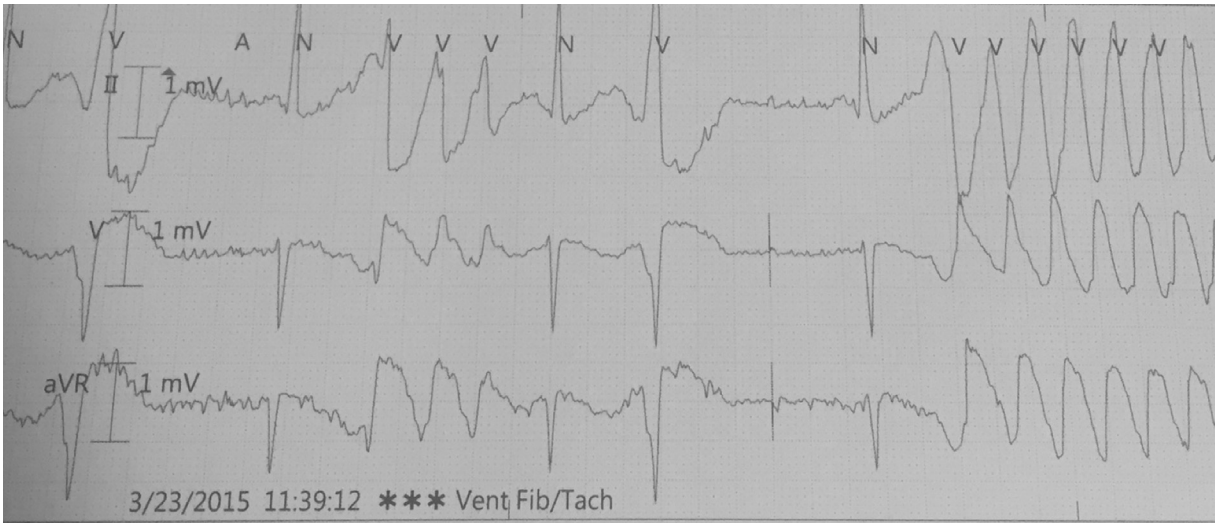

Figure 2. Electrocardiogram rhythm strip depicting entry into torsades de pointes, at time of patient's clenching spell.

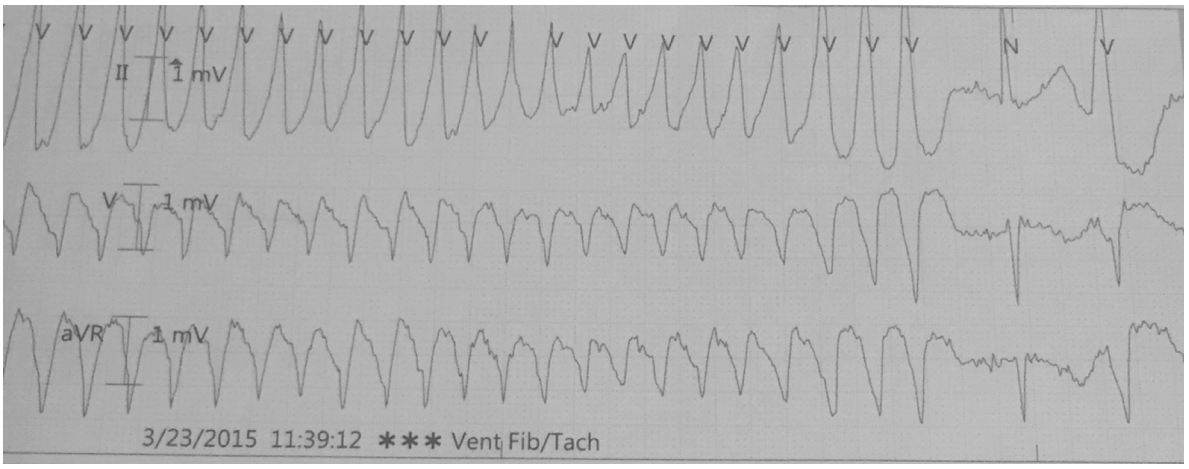

Figure 3. Electrocardiogram rhythm strip depicting exit out of torsades de pointes.

often-unpleasant perceptual disturbances in the dream-like state (16). More dangerous concerns have been the potential for neurotoxicity, either from high doses or persistent treatments, and the prodysrhythmic effects with potentially fatal QT interval prolongation and torsades de pointes. In a series of 19 deaths temporally associated with ibogaine consumption between 1990 and 2008, the majority involved a cardiovascular etiology, and most had some association with preexisting cardiac disease or co-ingestions with opioids or benzodiazepines (11).

Cerebellar toxicity has been reported in rat models, with a dose-related Purkinje layer atrophy in rats treated with ibogaine doses > 75 mg/kg, attributed to σ_2 activity (4). Similar studies note no histological changes to the cerebellums of model rats when exposed to frequent, low doses; one study administered 10 mg/kg every other day for 60 days (17).

In humans, the primary danger reported in the medical literature has been sudden death and cardiac effects, from either transient, self-limited bradycardia or a more dangerous prolonged QT interval with polymorphic ventricular tachycardia and cardiac arrest (14,18–22). Most of the reported patients with significant QT prolongation improved with supportive management, though there are reported cases of post-arrest neurologic deficits (18). This prodysrhythmic effect is thought to be from multiple actions, including direct cardiotoxicity and modulation of myocardial ion channels. In addition to its effects on neurotransmitters, ibogaine also inhibits cardiac hERG channels, with the effect of prolonging action potentials, complicated by blocking of voltage-gated cardiac $Na_v1.5$ sodium and $Ca_v1.2$ calcium channels. These changes, along with its muscarinic activity may account for its QTc prolongation (23–25).

Though considered for clinical trial funding in the 1990s by the Medication Development Division of the National Institute on Drug Abuse, all official U.S. testing was halted due to safety concerns after reports of patient deaths (22,26). Ibogaine's placement as a Schedule I controlled substance, which is banned in the United States and much of Europe, as well as lack of funding for clinical trials and societal aversions have limited formal clinical trials (9,10). This has not stopped a number of international treatment facilities from providing ibogaine therapy (22). Addiction clinics monitored by medical professionals have published some success regarding safety and efficacy, citing median abstinence of 5.5 months for a single dose and 8.4 months for patients treated multiple times and denying any cardiac events or fatalities in the reported case series of 75 patients. The reported treatment model included cardiac monitoring, adherence to an administration protocol, using a uniform ibogaine source, and employing multidisciplinary teams with physicians, psychologists, therapists, and nursing (3). However, in addition to ibogaine clinics

Figure 4. Foil packet containing the ingested substance.

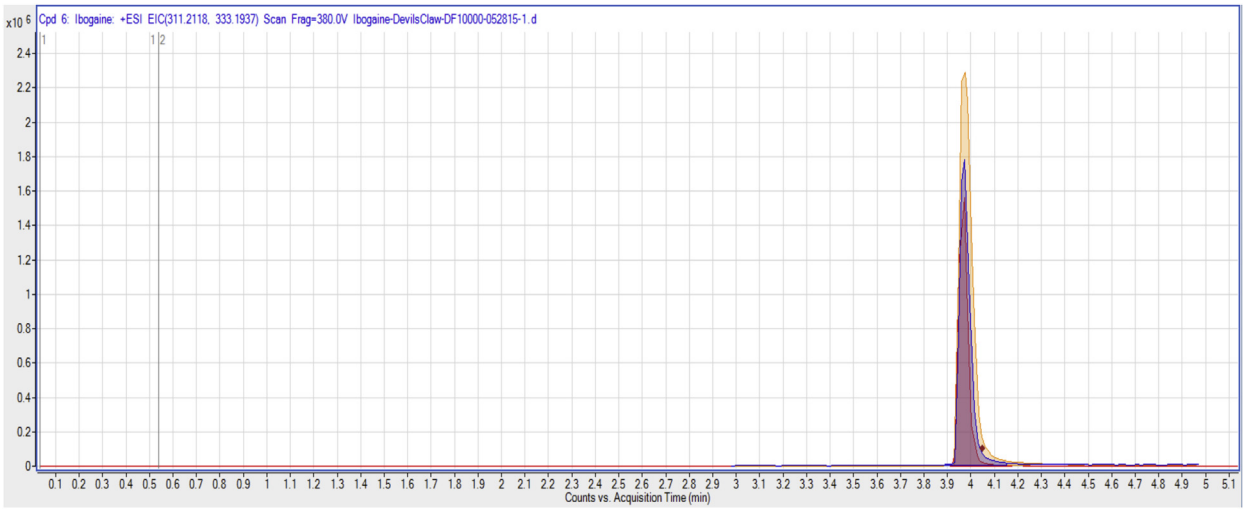

Figure 5. Extracted ion chromatogram of ibogaine detected in extracts from the product residues (red, blue traces) and 500 ng/mL reference standard for ibogaine in 10% acetonitrile (orange trace).

with established protocols and medical observation, the matter has been further muddied by unlicensed, unmonitored clinics and an online network of laypeople sharing advice and unregulated ibogaine (10,22,27). Depictions in popular television series of a cure for addiction have provided awareness for different treatment modalities, but they often overlook or downplay the potential adverse reactions. This has led to an increase in use by laypersons, endangered by a lack of clinical knowledge regarding the potential adverse outcomes of an unregulated substance (20,22).

Ibogaine's regulatory status in New Zealand allows for legal prescription, facilitating ongoing academic research. One study observed a cohort of patients seeking ibogaine for opioid addition. The authors report high rates of abstinence at 3-, 6-, and 12-month follow-ups (75–87.5%); however, the study was limited by a small cohort and a fatality attributed to ibogaine ingestion (6). In addition to opioid research, studies are underway for ibogaine as a treatment for alcohol use disorder, currently recruiting patients in São Paulo, Brazil (7). Outside of its applications in addiction medicine, the ibogaine congener 18-methoxycoronaridine is being studied in patients with cutaneous lesions of leishmaniasis (28).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

Ibogaine has proven itself repeatedly to be a complicated topic, with potential benefits for innumerable patients facing addiction. However, its well-documented dangers have limited its accessibility for rigorous, funded, legally sanctioned academic study. Ibogaine derivatives, such as its metabolite noribogaine and congener 18-methoxycoronaridine, offer future targets for study with reportedly similar anti-addictive properties, but fewer cardiotoxic and neurotoxic effects (1,9).

More readily available assays to identify ingested samples for contaminants and purity may guide treatment in the future, as ibogaine continues to become more prevalent, though treatment of patients with acute intoxication and cardiac effects is typically managed with conservative, supportive care.

As with our case, the high expectations of a miraculous cure with limited understanding of the potential risks, along with dubious suppliers with no clinical oversight or regulation, have led to scenarios in which patients endanger themselves in attempts to overcome their substance abuse. With the current barriers to studying *iboga*, awareness and education may offer the greatest benefit to patients who seek to use ibogaine to interrupt their addictive behaviors, and to the providers who care for patients suffering from dangerous sequelae.

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