

Detoxification from methadone using low, repeated, and increasing doses of ibogaine: A case report

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Background and aims: Ibogaine is a natural alkaloid that has been used in the last decades as an adjuvant for the treatment of opiate withdrawal. Despite the beneficial results suggested by animal studies and case series, there is a lack of clinical trials to assess the safety and efficacy of ibogaine. Moreover, the majority of reports described cases of heroin-dependent individuals, with and without concomitant use of methadone, using high doses of ibogaine. Therefore, it is not clear if ibogaine at low doses could be used therapeutically in people on methadone maintenance treatments (MMT). *Methods:* Case report of a female on MMT for 17 years who performed a self-treatment with several low and cumulative doses of ibogaine over a 6-week period. *Results:* The patient successfully eliminated her withdrawals from methadone with ibogaine. Each administration of ibogaine attenuated the withdrawal symptoms for several hours, and reduced the tolerance to methadone until all signs of withdrawal symptoms disappeared at the end of the treatment. No serious adverse effects were observed, and at no point did the QTc measures reach clinically significant scores. Twelve months after the treatment, she was no longer on MMT. *Conclusions:* To our knowledge, this is the first case report describing an ibogaine treatment using low and cumulative doses in a person on MMT. Although preliminary, this case suggests that low and cumulative doses of ibogaine may reduce withdrawal symptoms in patients undergoing MMT.

Keywords: ibogaine, methadone, opioid substitution treatments (OST), methadone maintenance treatments (MMT), methadone detoxification, drug addiction

INTRODUCTION

Opioid misuse is increasing alarmingly in both the EU and North America. According to the US Centers for Disease Control and Prevention, “since 1999, the number of overdose deaths involving opioids (including prescription opioid pain relievers and heroin) nearly quadrupled. From 2000 to 2014 nearly half a million people died from drug overdoses. 78 Americans die every day from an opioid overdose” (Centers for Disease Control and Prevention, 2016). Since the problem has repeatedly been described as an “epidemic,” a drug abuse and treatment bill has recently been signed into US law after passing through the House and Senate (Spangler, 2016). Simultaneously, in the EU, and according to the 2016 European Drug Report, “Europe’s opioids problem remains a central issue in the 2016 analysis, reflecting the significant impact these drugs still have on mortality and morbidity. We see now an increasingly complex relationship between use of heroin and synthetic opioids, accompanied by a worrying increase in overall estimates of opioid-related deaths” (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2016).

The new epidemic of opioid overdoses is not only related to heroin misuse, as it has been in the past, but also to a high prevalence of the misuse of prescription opioids, including

methadone (Substance Abuse and Mental Health Services Administration [SAMHSA], 2016). The Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence of the World Health Organization (WHO) state that there are two strategies to treat opioid use disorders: (a) to progressively reduce the dose and (b) to begin an opioid substitution treatment (OST), generally using methadone or buprenorphine (WHO, 2009). According to those guidelines, opioid withdrawal (rather than maintenance treatment) results in poor outcomes over the long term (WHO, 2009). Although an OST is a successful approach to reduce opioid misuse and crime, it tends to become a perpetual treatment, and it has been shown that those stabilized on high doses in methadone maintenance treatments (MMT) have more medical, cognitive, and emotional problems and a decreased quality of life than people who terminated MMT (Pedrero-Pérez & MethaQoL, 2016). It is clear that novel pharmacological treatments that are effective in ceasing opioid misuse are necessary.

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Ibogaine is the principal alkaloid in *Tabernanthe iboga*, an African plant used in ethnomedicine in traditional communities (Alper, 2001). In 1956, a Ciba Pharmaceuticals patent was acquired for its properties to reduce tolerance to morphine (United States Patent Office, 1957). In the 1960s, Howard Lotsof serendipitously discovered the anti-withdrawal properties of ibogaine (Alper, 2001). Ibogaine has demonstrated efficacy in attenuating opioid withdrawal in animal models (Belgers et al., 2016), but the evidence in humans is scarce (Brown, 2013). Globally, approximately 70–100 private clinics and practitioners offer treatments with ibogaine, and in New Zealand and South Africa, ibogaine is listed as a prescription medication (Ibogaine Legal Status, 2016). The typical doses used for treating substance use disorders are between 15 and 20 mg/kg (Brown, 2013) in a single administration. High doses of ibogaine may induce bradycardia and prolong the QTc interval (Litjens & Brunt, 2016; Meisner, Wilcox, & Richards, 2016), which can be life-threatening. Indeed, ibogaine administration has been associated with several fatalities (>25 cases), which appear to involve increases in cardiac arrhythmias, previous cardiovascular diseases, and use of opiates/opioids or other drugs during the acute effects of ibogaine (Litjens & Brunt, 2016; Meisner et al., 2016).

In a recent clinical trial with noribogaine (Glue, Cape, Tunnicliff, Lockhart, Lam, Hung, et al., 2016), the main metabolite of ibogaine and a possible candidate for explaining its anti-addictive properties (Mash et al., 1998), this compound was administered to people on MMT who were switched to morphine. No significant reduction in withdrawal symptoms was observed after the administration of 60, 120, and 180 mg [the 180 mg dose of noribogaine is equivalent in noribogaine plasma concentration to a 286 mg dose of ibogaine (Glue, Cape, Tunnicliff, Lockhart, Lam, Gray, et al., 2016)] but was observed a concentration-dependent increase in QTc. The authors of that study speculated that the dose of noribogaine administered probably was too low, and repeated dosing would be necessary to achieve a reduction in withdrawal symptoms. A recent report establishes the safe dose to be administered in an ibogaine treatment in 0.87 mg/kg that is far from the 15–20 mg/kg doses (Schep, Slaughter, Galea, & Newcombe, 2016).

We present here the case of a successful detoxification from long-term methadone dependence using low, repeated, and increasing doses of ibogaine.

CASE PRESENTATION

The patient was a 47-year-old woman (58 kg), who was on MMT for 17 years to treat her previous heroin dependence. Three years before starting the ibogaine treatment, she tried to abruptly end her methadone intake with non-pharmacological support but was unsuccessful. After 3 months, she returned to the methadone program, as the abstinence syndrome (AS) was intolerable for her. She reinitiated the methadone treatment at a lower dose than before (from 70 to 37 mg). Upon initiating the ibogaine treatment, she was stabilized at 37 mg. Regarding her use of

other drugs, the patient occasionally used heroin (2–3 times per month, intranasally) and amphetamine (2–3 times per month, intranasally), and a limited use of ethanol (1/2 standard units per week). She was a daily cannabis user (1–2 joints per day).

During the ibogaine treatment, the patient had a stable work and partner, owned her own house, and was without socio-familiar and legal conflicts assessed by the ASI (McLellan et al., 1992).

As a consequence of her former intravenous use of heroin, the patient acquired the hepatitis C virus (HCV). Before initiating this treatment, the viral count for the HCV was 2,140,000 UI/ml (logarithm HCV = 6.33; interval of quantification = 15–69,000,000 UI/ml). An analytic exam was performed before the treatment, including complete blood count and biochemistry, hormones, urine biochemistry, coagulation, serology, and molecular biochemistry. From over 70 parameters measured in the analytical tests, only the following were out of the interval of reference (IR), but only slightly, and without clinical significance: leukocytes = $10.34 \times 10^9/L$ (IR = 4–10); LKS-basophils = 0.1% (IR = 0.2–2); lymphocytes = $3.09 \times 10^9/L$ (IR = 1–3); basophils = $0.01 \times 10^9/L$ (IR = 0.02–0.1); alanine aminotransferase; b = 0.72 $\mu\text{kat/L}$ (IR = 0.00–0.55); 43.20 U/L (IR = 0.0–33.0); and transferrin saturation = 46.18% (IR = 20–45). An electrocardiogram (EKG) was also performed before the treatment, and no abnormalities were found. Her QTc values were 425 ms, blood pressure (BP) = 120/70 mm Hg, and heart rate (HR) = 85 bpm.

The psychiatric examination performed using the M.I.N.I. (Mini-International Neuropsychiatric Interview, Version 5.0.0; Sheehan et al., 1998) did not result in any psychiatric diagnosis.

Objectives of the treatment, procedures, and assessment materials

The main objective of the treatment was to completely detoxify the patient safely and with as much comfort as possible from methadone. The Opiate Withdrawal Scale (OWS; Bradley, Gossop, Phillips, & Legarda, 1987) and the Short OWS (SOWS; Gossop, 1990) were used to assess withdrawal symptoms, the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) was used as a measure of psychiatric safety, and the Udvalg for Kliniske Undersøgelser Side Effects Rating Scale (UKU-SERS; Lingjaerde, Ahlfors, Bech, Denckes, & Elgen, 1987) was used to assess the side effects of ibogaine. The OWS was administered once a day throughout the treatment. The SOWS was administered before each ibogaine session and every hour for the first 6 hr, and at 8- and 12-hr post-ibogaine. The BPRS was administered before each ibogaine session and every hour for the first 6 hr, at 8- and 12-hr post-ibogaine, and also every morning during the treatment process. The UKU was administered for 24 hr after each ibogaine session. During each ibogaine administration, BP and HR were monitored every 30 min for the first 4 hr, then every hour for the next 12 hr, and at 18- and 24-hr post-ibogaine. EKG monitoring and measurement of the QTc were performed during each ibogaine session every 60 min for the first 8 hr and then at 10-, 12-, 16-, 20-, and 24-hr post-administration.

The patient had psychological support throughout the treatment. She continued with psychotherapy for 3-month post-treatment to reorient her life.

Treatment

The patient contacted the ICEERS Support Service (<http://iceers.org/support-service.php>) for advice, as she was planning to undergo a self-treatment with ibogaine. She felt that her methadone dependence was iatrogenic and wished to cease the treatment utilizing ibogaine, after considerable research. Since ICEERS is a non-profit research organization that does not provide ibogaine treatments but has contact with several treatment centers/providers, and after assessing that the patient had the irreversible plan of taking ibogaine for self-treating her methadone dependence, the Support Service put her in contact with Pangea Biomedics, a clinic in Mexico with 10 years of experience in treating substance dependencies, such as MMT with ibogaine (note: ibogaine is not scheduled in Mexico). Financial constraints denied her from traveling to Mexico, thus she and the clinicians at Pangea Biomedics decided to undergo the detoxification while she was being supervised live through Skype video in Spain, along with the ICEERS Support Service team who offered psychological support and collected the measures. The treatment consisted of low and increasing doses of ibogaine administered in between progressively decreasing methadone dosages. The dose and timing of dosing were chosen with the intention of finding a new and less risky ibogaine treatment, avoiding the higher doses. Ibogaine was donated to the patient by a private donor from South Africa (Anwar Jeeva) and by a laboratory based in Montreal, Canada (Phytostan Enterprises, Inc.) (note: ibogaine is not scheduled in Canada, South Africa, and Spain, and in South Africa, it is authorized to be used as medicine to treat drug dependence). However, the patient only needs to use the sample from South Africa one. The chemical analysis (using thin layer chromatography, high performance liquid chromatography, mass spectrometry, and nuclear magnetic resonance) showed that it contained 96.3% ibogaine hydrochloride.

An EKG machine with QTc lecture was used for cardiac monitoring. Ibogaine sessions were performed with medical supervision for the first four sessions.

The treatment consisted of alternating low but increasing oral doses ($n = 5$) of ibogaine with decreasing methadone doses. With this method, she stopped taking methadone and only when the withdrawal symptoms became physiologically evident (OWS = 23; SOWS = 9), she took 150 mg of ibogaine. One hour after ibogaine administration, all withdrawal symptoms disappeared (SOWS = 0), and reappeared 21 hr afterward (OWS = 24) (for a timeline of the SOWS scores for the first four doses of ibogaine, see Figure 1). Then the patient took half the basal dose of methadone (18 mg) and maintained that dose every morning for the following 3 days. She then ceased self-administering methadone, and when withdrawal symptoms became physiologically evident, she took 300 mg of ibogaine. This process was repeated three more times, alternating ibogaine doses (400, 500, and 600 mg) while reducing methadone doses in half. The time frame that the patient was administering

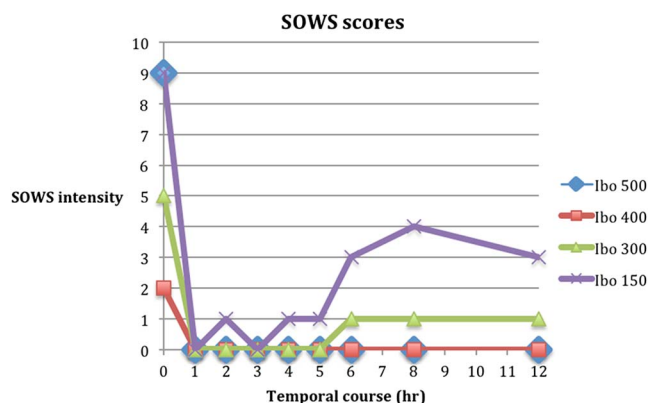


Figure 1. Short Opiate Withdrawal Scale (SOWS) scores for every ibogaine dose after its administration

methadone between ibogaine sessions varied between 3 and 7 days, depending on her work obligations. After the last dose of ibogaine (600 mg), the methadone AS ceased and never returned.

Outcome and follow-up

The patient successfully eliminated her withdrawals from methadone with ibogaine. Each administration of ibogaine attenuated or even eliminated the withdrawal symptoms for many hours (see Figure 1; there are no data for the 600 mg dose), and reduced the tolerance to methadone until all signs of withdrawal symptoms disappeared at the end of the treatment. The lower ibogaine doses taken by the patient were apparently devoid of visual effects, yet repressed memories and emotions did surface. There were no psychiatric effects according to the BPRS. There were few side effects according to the UKU. In a scale of gravity from 1 to 3, fatigability, memory impairment, akathisia, and orthostatic dizziness were rated as 1, constipation and tension headache were rated as 2, and reduction in the duration of sleep was rated as 3. The rest of the eventual side effects assessed by the UKU were rated as 0, and there was no dose effect. In fact, the most uncomfortable side effect reported by the patient was difficulty in sleeping after each ibogaine session, so the patient decided to use a benzodiazepine (diazepam 2 mg) after the first ibogaine session. After the other ibogaine sessions, she took cannabis oil orally acquired from her Cannabis Social Club in Barcelona, Spain (note: in Spain, the personal use and acquisition of cannabis in these clubs is not a criminal offense). After recovering from the last ibogaine session, she did not continue using methadone, benzodiazepines, nor cannabis oil.

Regarding QTc and BP, there were no clinically significant decrements. HR dropped with the 400 and 500 mg doses from 85 to 53 bpm between the first 2–3 hr. However, sitting or standing up effectively increased HR. At no point did the QTc measures reach clinically significant scores. The highest score (444 ms) was reached with the 500 mg dose at 3 hr.

The ibogaine sessions appeared to lack visionary content, although she had psychological insights regarding biographical events with emotional, non-distressing reactions. The patient reported feeling comfortable, relaxed, and

completely free of anxiety during the first 6–8 hr of the experience.

During this report, 12 months after the ibogaine treatment, she was no longer an MMT patient, and was without any symptoms of post-acute withdrawal syndrome (PAWS). Her life has improved in several ways (such as beginning to study, play music, and volunteer again), and her frequent use of drugs has been reduced. In an analytical test that the patient completed 7 months after the treatment, all the parameter values were within the IRs, including those that were not prior to the treatment. According to the patient, this analysis was the only one in the last 17 years where all the parameters were within the normal ranges, although the exact HCV viral load was not measured in the analysis.

DISCUSSION

To our knowledge, this is the first time that a protocol based on low and multiple doses of ibogaine administered intermittently between decreasing methadone doses has been performed to detoxify from methadone for the purposes of research and better outcomes. Standard treatments for detoxifying from methadone require many months to complete, and patients consider it significantly more difficult, with more protracted PAWS symptoms than that of heroin or other short-acting opioids (Gutwinski, Bald, Gallinat, Heinz, & Bempohl, 2014). The protocol based on low, multiple, ascending doses of ibogaine may provide a relatively brief but successful alternative to classical methods based on conventional detoxification. In addition, contrary to alpha2-adrenergic drugs that reduce abstinence symptoms but do not eliminate it, ibogaine seems to significantly reduce and even eliminate AS, returning the system to its normal physiological state. Because even very low doses of ibogaine may induce prolongations in the QTc interval and lower HR, which may be life-threatening (Litjens & Brunt, 2016; Meisner et al., 2016), it is critical and absolutely required that protocols based on low doses must be medically supervised.

The ibogaine literature is confusing regarding its efficacy with methadone-dependent patients because authors do not differentiate methadone-dependent from heroin-dependent patients, making it impossible to know precisely whether those for whom the treatment failed were dependent on methadone or not. According to the experience of the clinicians at Pangea Biomedics, a singular large dose of ibogaine, even with supplemental doses, over a short period of time, does not completely eliminate the withdrawal symptoms of methadone, especially PAWS that are so common to MMT detoxification (unpublished observations).

It is not well understood why ibogaine has withdrawal-mitigating properties. Ibogaine and noribogaine have a complex neuropharmacology, binding to multiple brain receptors, among them μ - and κ -opioid receptors, and increasing brain-derived neurotrophic factor (Maciulaitis, Kontrimaviciute, Bressolle, & Briedis, 2008). Noribogaine, the principal metabolite of ibogaine, has been proposed as the molecule responsible for its anti-withdrawal effects

(Mash et al., 1998). Earlier pharmacokinetics studies showed that the half-life of ibogaine was of 7.45 hr for extensive metabolizers, while noribogaine levels stayed in the 90% range of the C_{max} for 24 hr after an oral administration of 500 mg (female) and 800 mg (male) of ibogaine (Mash et al., 2000). A recent study has found a mean plasma elimination of 28–49 hr across dose groups after administration of doses of 3, 10, 30, and 60 mg (Glue, Cape, Tunnicliff, Lockhart, Lam, Hung, et al., 2016). This long action of ibogaine/noribogaine may explain the sustained anti-withdrawal effects of only one dose of ibogaine administered to heroin and/or other short-acting opiate users.

In this case report, the withdrawal symptoms appeared again after 6 hr with the initial lower dose, and after almost 24 hr following the incremental doses. There are several possible explanations for that. First, although it has generally been established that the half-life of methadone is 24 hr (Argoff & Silvershein, 2009), a recent pharmacokinetic study found a mean elimination half-life of 59 hr in methadone-dependent patients (Glue, Cape, Tunnicliff, Lockhart, Lam, Gray, et al., 2016), so it is possible that one administration of ibogaine could be insufficient, in pharmacokinetic terms, to completely counteract the effects of methadone withdrawal symptoms. Complementarily, the former studies of Ciba Pharmaceuticals showed that ibogaine reduced morphine tolerance (United States Patent Office, 1957), so it is possible that ibogaine could also reduce methadone tolerance. Therefore, in this case report, progressively increasing ibogaine doses could produce an accumulation of noribogaine in the organism, and thus the withdrawal symptoms would take longer to reappear until they completely disappeared after multiple increasing doses.

Finally, there is a discrepancy between this case and the lack of significant effects in the only clinical trial that assessed the anti-withdrawal properties of noribogaine (Glue, Cape, Tunnicliff, Lockhart, Lam, Hung, et al., 2016). Noribogaine and ibogaine have a different neuropharmacology. A recent study using oral doses of noribogaine in rodents found that it is necessary to administer high doses of noribogaine to reduce withdrawal symptoms (the half-efficacious dose was 13 mg/kg) (Mash, Ameer, Prou, Howes, & Maillet, 2016). It is possible that it may be necessary to combine both the effects of ibogaine and noribogaine to obtain a complete anti-withdrawal effect. A recent study showed that noribogaine, in contrast to ibogaine, is a weak μ -opioid receptor antagonist and an efficient κ -opioid receptor agonist (Maillet et al., 2015). Since ibogaine and noribogaine have different actions on the brain, it could be speculated that both of them “cooperate” to reach a final anti-withdrawal effect, at least in patients dependent on opioids with a long half-life. Thus, it is possible that because of the agonist action of ibogaine at μ -opioid receptor subjects may first experience a relief of withdrawal effects, and the action of noribogaine on κ -opioid receptors may be the responsible mechanism for reversing tolerance (Fujita-Hamabe et al., 2010). This suggests that it may not be necessary to use high doses of ibogaine to briefly reverse withdrawal, and that repeated doses of ibogaine would be necessary to reverse tolerance in methadone-dependent patients, so that noribogaine can

sufficiently accumulate in the brain until reaching the necessary levels to completely reverse/eliminate withdrawal symptoms. Because of the undesirable side effects of ibogaine, including emotional and memory processing, even at low doses, it is more tolerable for the patient to alternate the doses of ibogaine with periods of methadone, thereby progressively reducing the opioid dose until dependence has definitively been eliminated, and psychological integration is achieved. The use of benzodiazepines may be indicated to counteract insomnia and psychostimulant side effects. Our patient preferred to use legal cannabis, which may have anti-withdrawal properties as well (Scavone, Sterling, Weinstein, & Van Bockstaele, 2013). Clinical trials comparing single doses with multiple doses of ibogaine are necessary to establish which approach is the safest and most efficient in treating opioid withdrawal and dependence.

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Ethics: The patient signed a patient consent form giving her permit to publish this case report.

Conflict of interest: CW is the Director of Pangea Biomedics (Nayarit, Mexico), a clinic that runs legal ibogaine treatments in Mexico. RGdS is a Fellow of the Brazilian National Postdoctoral Program (PNPD/CAPES) and member of the ICEERS Advisory Board. JS, PC, EM, MAA-C, and JCB are ICEERS employees or collaborators. ICEERS is a non-profit organization that promotes the scientific research of ibogaine. JECH received a CNPq (Brazil) Productivity Fellowship Award. For the remaining authors, none were declared. None of the authors received any specific funding for participating in this investigation. All authors had full access to all the data in this study and had final responsibility for the decision to submit for publication.

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