Treatment of Acute Opioid Withdrawal with Ibogaine

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Ibogaine is an alkaloid with putative effect in acute opioid withdrawal. Thirty-three cases of treatments for the indication of opioid detoxification performed in non-medical settings under open label conditions are summarized involving an average daily use of heroin of .64 ± .50 grams, primarily by the intravenous route. Resolution of the signs of opioid withdrawal without further drug seeking behavior was observed within 24 hours in 25 patients and was sustained throughout the 72-hour period of posttreatment observation. Other outcomes included drug seeking behavior without withdrawal signs (4 patients), drug abstinence with attenuated withdrawal signs (2 patients), drug seeking behavior with continued withdrawal signs (1 patient), and one fatality possibly involving surreptitious heroin use. The reported effectiveness of ibogaine in this series suggests the need for systematic investigation in a conventional clinical research setting. (Am J Addict 1999;8:234–242)

Detoxification is a necessary step in the treatment of opioid dependence. Ibogaine, an indole alkaloid found in the bark of the root of the African shrub *Tabernanthe iboga,* is alleged to have anti-addictive qualities, including efficacy in acute opioid withdrawal.[1] The Medications Development Division of the National Institute on Drug Abuse (MDD-NIDA) has given serious consideration to a clinical trial of ibogaine.[2] Currently, research on humans receiving ibogaine conducted in a conventional U.S. research setting has been limited to the administration of low subtherapeutic dosages in initial phase I dose escalation studies under the US Food and Drug Administration (FDA).[3] In contrast to the limited clinical experience with ibogaine in conventional U.S. research settings, an unofficial network has been providing treatment with ibogaine for over 30 years. Most of the clinical observations on ibogaine treatment of

drug dependence in humans have been provided by this treatment network, which exists as a consequence of demand by addicts regardless of ibogaine's legal status in the U.S. While the existing informal treatment context is not optimally suited to conventionally rigorous clinical research, it appears warranted to direct some attention toward reports of efficacy of ibogaine for opioid withdrawal.

Evidence for ibogaine's effectiveness includes observations of reductions in morphine and cocaine self administration in animals and anecdotal reports in humans.[1] The reported efficacy of ibogaine in multiple substance dependence syndromes raises the possibility of implementing a pharmacologic strategy suggested by Leshner[4] of targeting "common effects that may underlie some common properties of all addictions."[4] If ibogaine is indeed effective, it is of great potential interest as representing a novel pharmacologic approach to treating addiction. Ibogaine does not appear to be a conventional dopamine or opioid agonist or antagonist or an amine re-uptake inhibitor.[1,5,6] Ibogaine has significant affinities for multiple binding sites within the central nervous system, including N-methyl-D-aspartate (NMDA), kappa opioid, and sigma and nicotinic receptors.[6] Ibogaine's mechanism of action is not known; however, interest has been focussed on NMDA antagonism as one possible mechanism of particular relevance to its putative effect on opioid withdrawal.[5–10] Because ibogaine apparently does not exert its effects by mechanisms of drugs currently in use for the treatment of drug dependence syndromes, it represents a potentially new strategic approach to understanding the neurobiology of addiction and the development of new treatments.

In this report, we present observations on patients treated with ibogaine for opioid detoxification over the time interval of 3 days after their last use of opiates. A specific focus on opioid withdrawal, in evaluating clinical reports from the existing informal ibogaine treatment network, is suggested for several reasons. One reason is that opioid dependence is the major reported indication for which addicts have sought out ibogaine treatment. Another reason to specifically focus on acute opioid withdrawal is to minimize the methodologic limitations of the informal treatment context by choosing to study a clinically robust phenomenon occurring within a relatively limited time frame. With respect to data that is currently available, the basic question of efficacy of ibogaine can possibly be most effectively addressed by studying opioid withdrawal due to the clinically obvious and unambiguous nature of the acute withdrawal syndrome. The distinctive, well recognized syndrome of opioid withdrawal contrasts, for example, with the lesser consensus regarding the clinical syndrome of cocaine withdrawal.[11,12] The current state of ibogaine research is such that the basic question of any human efficacy must be addressed, and opioid withdrawal provides a clearer and more readily available set of outcome measures than other drug withdrawal syndromes, such as cocaine or nicotine.

The support for efficacy of ibogaine in opioid withdrawal consists of animal studies and anecdotal reports in humans. In rats, ibogaine has been observed to attenuate the signs of morphine withdrawal[13–15] and to reduce heroin or morphine self administration.[16–18] Similar effects on morphine withdrawal have been reported in monkeys[19] and mice.[5] There are some case studies in humans in the literature[20–23] that describe ibogaine treatment in an aggregate total of 13 patients, as well as recent preliminary reports from a private clinic in the Caribbean.[3,24] Common features of these reports are reductions in drug craving and opiate withdrawal signs and symptoms within 1 to 2 hours and relatively complete resolution of the opioid withdrawal syndrome within 24 to 48 hours af-

ter the ingestion of ibogaine. These case studies appear consistent with general descriptions of ibogaine treatment.[25–27]

Patients treated with ibogaine describe the persistent elimination of withdrawal symptoms and craving beginning within hours of initiating treatment. Within 1 to 3 hours of ingestion, ibogaine produces its most intense subjective effects during a state lasting approximately 4 to 8 hours. The acute phase is characterized by the panoramic recall of a large amount of material relating to prior life events from long-term memory, primarily in the visual modality. Hallucinations have also been described but do not appear to be as prominent an aspect of the experience as the volume of images recalled from visual long-term memory. Following the acute phase is a state lasting approximately 8 to 20 hours in which the density of recall of visual images is greatly reduced and attention is directed toward evaluating the material recalled in the acute phase. The emotional tone of this second state appears to be generally characterized as neutral and reflective. Insomnia is often evident for 72 hours following administration of ibogaine to both opioid and non-opioid dependent patients, and it is responsive to sleep medication.[26] Patients have reported significant reductions or total cessation of substance use and craving for weeks to months or longer following treatment, although methodologically adequate follow-up observations are lacking. The purpose of this work is to systematically present a series of case reports of the possible efficacy of ibogaine in acute opioid withdrawal.

METHODS

The cases presented in this paper are a subset of 41 cases of patients treated with ibogaine between 1962 and 1993 that were presented at the Ibogaine Review Meeting held by MDD-NIDA in Rockville, MD, on March 8, 1995. Thirty-three of these cases were selected according to the following criteria:

(1) Heroin dependence, with or without other comorbid substance use disorders, as an indication for treatment with ibogaine (all 8 of the subjects who were receiving methadone at the time of their treatment also reported concurrent use of heroin). All patients in this study retrospectively met the DSM IV criteria[28] for Opioid Dependence with Physiological Dependence at the time of their treatment.

(2) Having been directly observed by either or both co-authors H.S.L. and/or G.M.N.F., continuously at the scene for at least 48 hours following treatment with ibogaine.

Eight of all 41 cases presented at the NIDA Ibogaine Review Meeting were excluded from this series. Five of those patients were not opioid dependent, and post treatment observation was lacking on 3 patients.

The demographic and drug use characteristics of the patients are summarized in Table 1. Treatments were provided in the setting of a hotel room or apartment under an open label condition with H.S.L. and/or G.M.N.F. continuously present on site to observe the patients for at least the first 48 hours following ibogaine administration. Observers well known to the above co-authors were additionally present when the co-authors slept and immediately notified the co-authors of withdrawal signs or symptoms or drug seeking behavior.

Patient behaviors between 48 and 72 hours were monitored by H.S.L., G.M.N.F., and/or their observers. In 1962 and 1963, a total of 7 treatments were carried out in the U.S., with the remaining 26 treatments taking place in the Netherlands between 1989 and 1993. Twenty-three of these treatments were observed by H.S.L., 9 by G.M.N.F., and 1 by both. Eighteen of the 33 patients in this study were under the care of Jan Bastiaans, M.D., Professor

TABLE 1. **Demographic and drug use characteristics of study sample**

Gender	22 (67%) male, 11 (33%) female
Mean Age	27.3 ± 4.7 years
Ethnicity	32 Caucasian, 1 Surinamese
Mean daily heroin use	.64 ± .50 grams/day
Predominant route of heroin self administration	26 intravenous, 4 intranasal, 3 smoking
Mean duration of heroin use	6.2 ± 5.8 years
Number of subjects with concurrent methadone maintenance	8 (24%)
Mean methadone dose (N = 8)	48 ± 30 milligrams
Number of subjects additional seeking treatment for concurrent cocaine use	8 (24%)
Mean daily cocaine use (N = 8)	1.4 ± 2.3 grams

Emeritus and former Chairman of the Department of Psychiatry at the State University of Leiden, whose areas of research emphasis within psychiatry included psychosomatic medicine and the medical uses of hallucinogens.[29,30] Dr. Bastiaans saw the patients before and after their treatments and was typically present for the first 4 to 8 hours, returning 24 hours post ibogaine administration. When present, Dr. Bastiaans provided corroboration regarding the observations made by H.S.L. and G.M.N.F. on the presence or absence of the clinical features of acute opioid withdrawal.

The subjects in this series of cases received an average dose of ibogaine of 19.3 ± 6.9 mg/kg (range of 6 to 29 mg/kg). Patients were instructed to ingest their last food, liquids, heroin, or other substances the night before treatment and received the ibogaine approximately 8 to 10 hours later the following morning. Patients on methadone took their last methadone dosage the morning before the next day's ibogaine treatment, approximately 24 hours prior to receiving ibogaine. During treatments, subjects were instructed to lie down in a dimly lit room whose location and ambient activity were made to be as quiet as possible. Both H.S.L. and G.M.N.F. kept journals and recorded their observations of patient behaviors during treatment, which included assessment of signs of opioid withdrawal such as midriasis, sweating, elevated pulse rate, shivering, piloerection, or diarrhea. Vomiting is common during ibogaine treatment, but it typically occurs relatively suddenly as a single episode and is usually related to motion. Therefore, a single episode of vomiting was not regarded as an opioid withdrawal sign, although sustained vomiting and nausea persisting more than 2 hours was regarded as a sign of opioid withdrawal. Subjective symptomatic complaints such as chills, muscle pain, abdominal pain and nausea were also noted.

Both co-authors who assessed and recorded the presence or absence of withdrawal signs and symptoms were very experienced and familiar with the clinical syndrome of opioid withdrawal. H.S.L. has had clinical experience with withdrawing and detoxifying addicts over a 30 year period in the context of his involvement with the development of ibogaine as a treatment for acute opioid withdrawal.[31] G.M.N.F. has been involved with the Dutch and US addict self help and harm reduction movements since 1985, and is experienced in ethnographic field work with injection drug users.[32]

RESULTS

The outcomes with respect to opioid withdrawal signs and drug seeking behavior following ibogaine treatment are summarized in Table 2. Twenty-five (76%) of the patients had no signs or subjective complaints at 24 and 48 hours and did not seek to obtain or attempt to use opioids for at least 72 hours after the initial dose of ibogaine. The reported onset of relief of symptoms was rapid—within 1 to 3 hours for these patients, many of whom were already at least mildly symptomatic from having abstained from opioid use overnight prior to the morning of the ibogaine treatment.

An additional patient was noted to have sweating at 24 hours but not at 48 hours post treatment and did not seek, obtain, or attempt to use opioids within 72 hours post treatment. Another patient had chills that were present at 24 hours and 48 hours but nonetheless did not seek to obtain or use opioids for at least 72 hours post treatment. This particular patient was using 1 gram of heroin intravenously daily and received an ibogaine dose of 25 mg/kg. Four patients appeared to achieve resolution of opioid withdrawal, as judged by an absence of signs and subjective symptoms at 24 and 48 hours, but nonetheless returned immediately to opioid use within 72 hours. Two of these subjects, males aged 26 and 20, explicitly acknowledged a continued interest in pursuing a heroin-centered lifestyle despite the apparent elimination of the signs and symptoms of their opioid withdrawal. These two individuals received doses of only 8 mg/kg, and they were each using approximately only 0.1 grams per day of heroin. The two other individuals who relapsed immediately to continued heroin use, despite the apparent resolution of the opioid withdrawal syndrome, were both 27 year old males who were using approximately 0.4 grams and 0.75 grams of heroin a day, and received 23 and 25 mg/kg of ibogaine, respectively.

The only patient with clear objective signs and subjective complaints of opioid withdrawal following ibogaine treatment was a 27 year old female who used an average of 0.4 grams of heroin a day intravenously and received 10 mg/kg of ibogaine. This case is the only one in which ibogaine did not appear to provide significant relief from the opioid withdrawal syndrome, as this patient complained of nausea, chills, muscle aches, and was observed to be sweating with dilated pupils. This patient left the treatment environment and used heroin approximately 8 hours after the administration of ibogaine. The failure of ibogaine in this particular case was felt to be due to a dosage that was inadequate to the patient's level of opioid dependence.

Lastly (and importantly) is the case involving a fatal outcome in a 24-year-old female treated in the Netherlands in 1993.

TABLE 2.   **Opioid detoxification with ibogaine: outcomes (N = 33)**

N	Signs of Opioid Withdrawal Post-Treatment	Drug Seeking During the 72 Hour Post-Treatment Interval
25	Fully resolved at 24 hours	−
4	Fully resolved at 24 hours	+
1	Partial resolution at 24 hours (sweating) fully resolved at 48 hours	−
1	Partial resolution at 24 and 48 hours (chills)	−
1	Multiple opioid abstinence signs	+
1	Fatality at 19 hours	?

This patient had a history of intravenous and smoking use of approximately 0.6 grams of heroin per day, and received an ibogaine dose of 29 mg/kg. The patient complained of muscle aches and nausea at 17 hours following the administration of ibogaine, without other evidence of signs of withdrawal. About an hour later, she suffered a respiratory arrest, possibly involving aspiration, and was pronounced dead at about 19 hours post treatment. Forensic pathological examination revealed no definitive conclusion regarding the probable cause of death[33] and cited the lack of information correlating ibogaine concentrations with possible toxic effects in humans. Another problem regarding the interpretability of postmortem levels of ibogaine, or its principal metabolite noribogaine, relates to potential for artifactual elevations of serum levels of drug or metabolites with a large volume of distribution due to postmortem release from tissue.[34–36] An additional source of uncertainty was the possibility of surreptitious opioid use, which was suggested by the finding of charred tin foil among the patient's effects, which is used to smoke heroin by the method of "chasing the dragon" (which is popular in the Dutch heroin scene).[37] There is evidence that suggests that the toxicity of opioids may be relatively greater following treatment with ibogaine.[5,38] Analysis of gastric contents for heroin or morphine, which might have confirmed recent heroin smoking, and analysis of blood for 6-monoacetyl morphine, a heroin metabolite whose presence indicates recent use,[39] were not performed.

DISCUSSION

Within the context of the methodological limitations imposed by the informal treatment setting, this series of open label case studies appears to provide some evidence for the efficacy of ibogaine in acute opioid withdrawal. Seventy-six percent of the patients in this series were reportedly free of opioid withdrawal signs and symptoms at 24 hours and did not seek drugs over the period of observation of 72 hours. Another 12 percent were without evidence of withdrawal but nonetheless chose to resume opioid use. While the lack of formal clinical research methodology such as a structured instrument rating withdrawal is unfortunate, the apparent validity of the findings rests largely on the ability of the two co-authors H.S.L. and G.M.N.F. to reliably recognize the features of the acute opiate withdrawal syndrome. Both of the above co-authors had extensive experience in observing the clinical features of opioid dependence including the acute withdrawal syndrome. The corroboration of Dr. Bastiaans on over half the cases provides some additional support for the accuracy of the above co-author's assessment regarding the presence or absence of acute opioid withdrawal.

The safety concern that has currently been most problematic for the development of ibogaine has been the one fatality in this series, following the administration of ibogaine in a female patient in the Netherlands in 1993. This incident was a significant factor in the decision not to pursue a clinical trial of ibogaine following the NIDA Review Meeting held in March of 1995 {F. Vocci, director, MDD-NIDA, personal communication, 1998}. This incident also underscores the need for the security procedures and medical supervision available in a conventional medical setting and for completion of the FDA dose escalation studies[3] to allow systematic collection of pharmacokinetic and safety data.

Another safety concern regarding potential neurotoxicity was raised by the observation of cerebellar damage in rats treated with ibogaine at a high dose of 100 mg/kg.[40] However, no evidence of toxicity was seen at the dose of 40 mg/kg demonstrated to reduce morphine or cocaine self-

administration in rats.[16,18,41,42] Helsley et al[43] treated rats with 10 mg/kg ibogaine every other day for 60 days and observed no evidence of neurotoxicity. Likewise, Mash et al[3] observed no evidence of neurotoxicity in monkeys treated for 5 days with repeated oral doses of ibogaine of 5 to 25 mg/kg or subcutaneously administered doses of 100 mg/kg. J. W. Olney has described the rationale for the use of ibogaine as an actual neuroprotective agent to minimize excitotoxic damage in stroke and anoxic brain injury.[44] The available evidence appears to suggest that the neurotoxic effects of ibogaine occur at levels higher than those observed to have effects on opioid withdrawal and self administration. In addition, the neurotoxic effects of ibogaine appear to be specifically mediated by activity at the sigma type 2 receptor and to be potentially dissociable from ibogaine's putative antiaddictive effect.[6] An ibogaine congener with relatively less sigma 2 activity, 18-methoxycoronaridine, reportedly produces effects similar to ibogaine on morphine and cocaine administration in rats, but has shown no evidence of neurotoxicity even at high dosages.[6]

The cases and literature reviewed here indicate significant clinical issues that will need to be addressed if ibogaine is to be considered as a clinical option for opioid detoxification. There are safety concerns (as discussed above) that must be addressed by careful investigation in clinical research settings. Ibogaine can presently be purchased at a wholesale price of approximately 200 US dollars per treatment, and that price could drop considerably if significant demand were to stimulate increased production. The time frame of treatment with ibogaine places it competitively within the time frame of rapid detoxification.[45] However, despite ibogaine treatments having taken place under conditions of relatively "low tech" improvisation, there is a question of whether ibogaine in a conventional medical setting,

with its attendant evaluation and supervision, would still be economically competitive with other existing approaches to opioid detoxification. The need for supervisory personnel to serve the functions presently served by volunteer participants in the existing informal treatment network must be included in the overall cost of ibogaine treatment in a conventional medical setting. The significant subjective psychoactive state produced by ibogaine might not be widely desired or tolerated. Although anecdotal evidence suggests that ibogaine is well tolerated and that the material recalled in the psychoactive state might have potential psychotherapeutic significance,[21,25,27,46,47] a follow-up study of individuals treated with ibogaine assessing the tolerability of treatment would be useful. One limitation of such a study, however, would be the possible bias of self selection on a sample that has been sufficiently motivated to seek out ibogaine treatment in the existing unconventional network. It also remains to be seen whether a pharmacologic intervention or molecular modification of ibogaine can provide the option of resolving the psychoactive effects of the drug from its putative anti-addictive qualities.

The results reported here originate from an informal treatment context that presents methodologic disadvantages compared to a conventional clinical research setting. Nonetheless, the observations made in this setting do appear to provide some support for the efficacy of ibogaine in the treatment of acute opioid withdrawal. Whether or not ibogaine emerges as a viable conventional treatment option, the question of its pharmacologic effectiveness is interesting. If the results obtained under open label conditions summarized here are confirmed in controlled clinical studies, it would appear that ibogaine represents a novel pharmacologic mechanism that is not currently being utilized in the treatment of drug dependence. If it is in-

deed effective, ibogaine could eventually prove to be a productive paradigm for the study of the neurobiology and development of new approaches to addiction.

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