——Chapter 8——

IBOGAINE IN THE TREATMENT OF HEROIN WITHDRAWAL

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I. Introduction

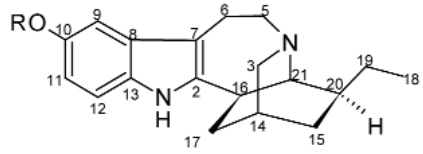
Ibogaine, is a naturally occurring, psychoactive indole alkaloid derived from the roots of the rain forest shrub *Tabernanthe iboga*. Indigenous peoples of Western Africa use ibogaine in low doses to combat fatigue, hunger, and thirst, and in higher doses as a sacrament in religious rituals (*1*). The use of ibogaine for the treatment of drug dependence has been based on anecdotal reports from groups of self-treating addicts that the drug blocked opiate withdrawal and reduced craving for opiates and other illicit drugs for extended time periods (*2-4*). Preclinical studies have supported these claims and provided proof-of-concept in morphine-dependent rats (*5,6*). While ibogaine has diverse CNS effects, the pharmacological targets underlying the physiological and psychological actions of ibogaine in general, or its effects on opiate withdrawal in particular, are not fully understood. Pharmacological treatments for heroin addiction currently employ two treatment strategies: detoxification followed by drug-free abstinence or maintenance treatment with an opioid agonist. Because agonist maintenance with methadone usually has the goal of eventual detoxification to a drug-free state, the use of medications to facilitate this transition is a clinically important treatment strategy. Anecdotal reports suggest that ibogaine has promise as an alternative medication approach for making this transition (*4*). Ibogaine has an added benefit to other detoxification strategies in that the treatment experience seems to bolster the patient's own motivational resources for change.

There have been few reports of the effects of ibogaine in humans. Anecdotal accounts of the acute and long-term effects of ibogaine have included only a small series of case reports from opiate and cocaine addicts with observations provided for only seven and four subjects, respectively (*2,3*). A retrospective case review of 33 ibogaine treatments for opioid detoxification in nonmedical settings under open label conditions has suggested further that the alkaloid has ameliorative effects in acute opioid withdrawal (*4*). However, objective investigations of ibogaine's effects on drug craving, and the signs and symptoms of opiate withdrawal, have not been done in either research or conventional treatment settings. Ibogaine is a drug with complex pharmacokinetics and an uncertain mechanism of action with regards to its alleged efficacy for the treatment of opiate dependence. Ibogaine is metabolized to noribogaine, which has a pharma-

cological profile that is different from that of the parent drug. We report here that ibogaine is effective in blocking opiate withdrawal, providing an alternative approach for opiate-dependent patients who have failed other conventional treatments. Identifying noribogaine's mechanism of action may explain how ibogaine promotes rapid detoxification from opiates after only a single dose.

II. Identification of a Primary Metabolite of Ibogaine

Our group developed an analytical method for quantifying ibogaine in blood samples from rats, primates, and humans (*7*,*8*). Using fullscan electron impact gas chromatography/mass spectrometry (GC/MS), a primary metabolite, 12-hydroxyibogamine (noribogaine) was detected for the first time in blood and urine samples. The analytical procedure involved a solvent extraction under basic conditions with D_3-ibogaine as an internal standard. Urines taken from dosed monkeys and humans were extracted under strongly basic conditions, extracts were evaporated, reconstituted, and analyzed by GC/MS in full scan electron impact ionization mode. Analysis of the resulting total ion chromatograms revealed a peak identified as ibogaine by comparison with an authentic standard. All samples were found to contain a second major component eluting after ibogaine. Similar spectral characteristics of this peak to ibogaine's spectrum defined it as an ibogaine metabolite, which is formed by the loss of a methyl group (Figure 1). The site for metabolic demethylation of ibogaine was the



Ibogaine, R = CH_3 (Le Men-Taylor numbering)
Noribogaine (10-Hydroxyibogamine)*, R = H

*Noribogaine has frequently been referred to as 12-hydroxyibogamine in the biological and medical literature, based on the Chemical Abstracts numbering system for this alkaloid skeleton.

FIGURE 1. Molecular structures of ibogaine and noribogaine. Ibogaine undergoes *O*-demethylation to form 12-hydroxyibogamine (noribogaine).

methoxy group, resulting in the compound 12-hydroxyibogamine (noribogaine). The identity of the desmethyl metabolite was confirmed using an authentic standard of noribogaine (Omnichem S.A., Belgium) and gave a single peak at the same retention time and with the same electron impact fragmentation pattern as the endogenous compound isolated from monkey and human urine (*7*).

III. Cytochrome P450 Metabolism and Genetic Polymorphisms

Ibogaine, like most CNS drugs, is highly lipophilic and is subject to extensive biotransformation. Ibogaine is metabolized to noribogaine in the gut wall and liver (Figure 2, schematic). Ibogaine is *O*-demethylated to noribogaine primarily by cytochrome P4502D6 (CYP2D6). An enzyme kinetic examination of ibogaine *O*-demethylase activity in pooled human liver microsomes suggested that two (or more) enzymes are involved in this reaction (*8*). In this study, ibogaine was incubated with a set of microsomes derived from cell lines selectively expressing only one human cytochrome P450 enzyme and with a series of human liver microsome preparations, characterized with respect to their activities toward cytochrome P450 enzyme selective substrates to estimate the relative contributions of the various P450 enzymes to the metabolism of ibogaine *in vitro*. The enzyme CYP2D6 showed the highest activity toward the formation of noribogaine, followed by CYP2C9 and CYP3A4 (*9*).

Depending on whether a particular isoenzyme is present or absent, individuals are classified as extensive or poor metabolizers. The influence of genetic polymorphisms on the biotransformation of ibogaine under *in vivo* clinical conditions has been examined in recent studies (*9*). The results demonstrate that there are statistically significant differences in the two populations with regard to Cmax and $t_{1/2}$ (elim) and area under the curve (AUC) of the parent drug and metabolite, indicating that the disposition of ibogaine is dependent on polymorphic CYP2D6 distribution (Table 1). Since some of the CNS activity may be the result of noribogaine, the CYP2D6 phenotype may prove to be an important determinant in the clinical pharmacology of ibogaine. Many CYP2D6 substrates are subject to drug interactions. In considering the potential patient population who might benefit from ibogaine, many of these patients may have taken other medications (prescription and/or illicit), increasing the potential for serious adverse drug interactions.

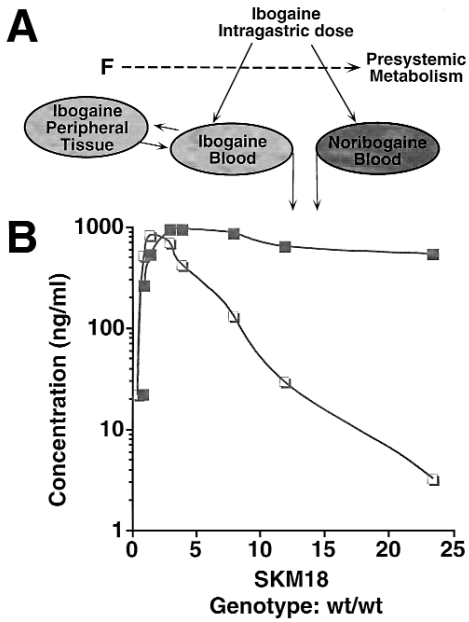


FIGURE 2. Time course of whole blood concentrations of ibogaine and noribogaine after oral administration to drug-dependent volunteer. Pharmacokinetics of ibogaine and noribogaine over the first 24 hours after oral dose in a human subject. Data shown are from a representative male subject (wt/wt, extensive metabolizer). Values for parent drug and desmethyl metabolite were measured in whole blood samples at the times indicated. Open squares indicate ibogaine concentrations and shaded squares indicate noribogaine concentrations. SK, St. Kitts, W.I., Subject Code.

TABLE 1.
PHARMACOKINETIC PARAMETERS OF IBOGAINE AND NORIBOGAINE IN HUMAN EXTENSIVE AND POOR METABOLIZERS (CYP2D6)

	*Extensive Metabolizers	**Poor Metabolizers
Ibogaine		
t_{max},hr	1.70 ± 0.15	2.50 ± 1.04
C_{max},ng/ml	737 ± 76	896 ± 166
$AUC_{0\text{-}24}$hr,ng • hr/ml	3936 ± 556	11471 ± 414
$t_{1/2}$,hr	7.45 ± 0.81	NQ
Noribogaine		
t_{max},hr	6.17 ± 0.85	3.17 ± 1.36
C_{max},ng/ml	949 ± 67	105 ± 30
$AUC_{0\text{-}24}$hr,ng • hr/ml	14705 ± 1024	3648 ± 435
$t_{1/2}$,hr	NQ	NQ

* N = 24 (10.0 mg/kg), 16 males and 8 females

** N = 3, 3 males (10.0 mg/kg)

IV. Ibogaine Pharmacokinetics

Pharmacokinetic measurements have been obtained from human drug-dependent patient volunteers who had received single oral doses of ibogaine (Table 1; Figure 2). Figure 2 illustrates the pharmacokinetic profile of ibogaine and the metabolite following oral doses of the drug in a representative male subject. Table 1 shows that CYP2D6 mediated metabolism of ibogaine resulted in high levels of noribogaine in blood, with Cmax values in the same range as the parent drug. The time required to eliminate the majority of absorbed ibogaine (>90%) was 24 hours post-dose (Figure 2). The pharmacokinetic profiles measured in whole blood demonstrate that the concentrations of noribogaine measured at 24 hours remained elevated, in agreement with previous findings (*10*). The still elevated concentrations of noribogaine in blood at 24 hours after drug administration limited the quantitation of the terminal half-life of the metabolite. Noribogaine was measured in CYP2D6 deficient subjects, but at concentrations that were markedly lower than for the extensive metabolizers. Conversion of the parent to noribogaine in CYP2D6 deficient subjects may reflect the metabolic contribution of other cytochromes (CYP2C9, CYP3A4). The concentration of noribogaine measured at 24 hours post-dose in the subject in Figure 2 was in the range of 800 ng/ml, similar to the peak concentration of ibogaine that was measured in this representative subject. Pharmacokinetic measurements in human volunteers administered oral doses of ibogaine showed that the area under the curve (AUC) for the parent compound was approximately three-fold less than for the active metabolite (Table 1). Thus, noribogaine reaches sustained high levels in blood after a single administration of the parent drug.

Since the metabolite has been shown in radioligand binding assays to have higher affinities for certain CNS targets, it can be estimated that the contribution of the metabolite to the total pharmacodynamic profile of ibogaine is significant. To display *in vivo* activity, it is necessary for CNS drugs to reach the brain. Since it is difficult to study these processes in humans, it is common to study the penetration of a CNS active drug into the brains of laboratory animals. The concentrations of ibogaine and noribogaine have been measured in rat brain following both oral and intraperitoneal (i.p.) administrations (*11,12*). The significance of micromolar interactions of ibogaine and noribogaine with various radioligand binding sites was related to the concentration of parent drug and metabolite in brain (Table 2). Regional brain levels of ibogaine and noribogaine were measured in rat cerebral cortex, striatum, brainstem, and cerebellum at 15 minutes, 1 and 2 hours postdrug administration. We have shown that ibogaine is rapidly detected in brain following oral administration. The metabolite was detected at the earliest time point (15 minutes), consistent with first pass metabolism of the parent drug (*11*). Administration of ibogaine (40 mg/kg i.p., 50

TABLE 2.
PHARMACOKINETIC PARAMETERS OF IBOGAINE AND NORIBOGAINE IN MALE RAT (SPRAGUE-DAWLEY)

	*Whole Blood 40 mg/kg i.p.	*Brain 40 mg/kg i.p.	**Brain 50 mg/kg p.o.
Ibogaine			
t_{max},hr	0.10 ± 0.03	1.00 ± 0.14	1.00 ± 0.21
C_{max},ng/ml or	3859 ± 789	3782 ± 418	5210 ± 480
ng/g [μM]	[11.2 ± 2.3]	[11.0 ± 1.2]	[15.1 ± 1.4]
AUC, ng • hr/ml or	10636 ± 341	22098 ± 922	NQ
ng/g [μM • hr]	[30.7 ± 1.0]	[63.9 ± 2.7]	
$t_{1/2}$,hr	2.38 ± 0.50	11.05 ± 1.15	NQ
Noribogaine			
t_{max},hr	2.40 ± 0.04	2.00 ± 0.16	2.00 ± 0.28
C_{max},ng/ml or	7265 ± 953	3236 ± 514	3741 ± 423
ng/g [μM]	[21.9 ± 2.9]	[9.8 ± 1.6]	[11.3 ± 1.3]
AUC, ng • hr/ml or	96920 ± 741	38797 ± 324	NQ
ng/g [μM • hr]	[292.0 ± 2.2]	[117.9 ± 1.0]	

NQ, not quantifiable
Noribogaine $t_{1/2}$ not quantifiable
* Noncompartmental pharmacokinetic analysis over a 24 hr. period
** Noncompartmental pharmacokinetic analysis over a 2 hr. period
Data represent the average values from individual animals (n = 4) assayed in duplicate.

mg/kg p.o.) in rodents resulted in levels of ibogaine and noribogaine that ranged from 10 to 15 μM and 10 to 12 μM, respectively. The results demonstrate that noribogaine reaches significant concentrations in brain following both routes of administration in rodents. Thus, the concentrations of noribogaine in brain may activate processes that cause the desired effects of suppressing opiate withdrawal signs and diminishing drug craving.

V. Setting and Study Design

We have had the opportunity to describe the clinical experience of a series of patients undergoing opiate detoxification with ibogaine. The study was conducted in a 12 bed freestanding facility in St. Kitts, West Indies. The treatment program had a planned duration of 12 to 14 days and stated goals of: (1) safe physical detoxification from opiates, (2) motivational counseling, and (3) referral to aftercare programs and community support groups (twelve-step programs). Subjects were self-referred for inpatient detoxification from opiates (heroin or

methadone) and met inclusion/exclusion criteria. All individuals were deemed fit and underwent treatment following a physician's review of the history and physical examination. Participants did not have histories of stroke, epilepsy, or axis I psychotic disorders. Results of the electrocardiogram and clinical laboratory testing were within predetermined limits. All subjects signed an informed consent for ibogaine treatment. Overall, the sample of 32 patients was predominately male (69%) and white (82%), with a mean age of 33.6 years and a mean length of addiction of 11.1 years.

All participants met DSM-IV criteria for opioid dependence and had positive urine screens at entry to the study. Participants were assigned to fixed-dose (800 mg; 10 mg/kg) of ibogaine HCl under open-label conditions. Subjects were genotypyed for the CYP2D6 alleles (*2, *4, *5 and wt alleles), as described previously (*13*). On admission, participants were administered the Addiction Severity Index (*14*) and received structured psychiatric evaluations before and after ibogaine treatment (SCID I and II). In cases where the participant's responses were deemed questionable due to intoxication or withdrawal signs, portions of all interviews were repeated later, as necessary. Additional information about substance use history and past/current medical condition(s) was gathered and later cross-referenced for accuracy through a separate comprehensive psychosocial assessment.

VI. Physician Ratings of Withdrawal

Two physicians rated as present or absent 13 physical signs typically associated with opiate withdrawal, based on a 10-minute period of observation (*14,15*). The Objective Opiate Withdrawal Scale (OOWS) data were analyzed from three assessments performed during the period spent in the clinic under medical monitoring, given that those points in relation to ibogaine administration were highly comparable among all patients. The attending physician performed the first assessment following clinic admission an average of 1 hour before ibogaine administration and 12 hours after the last dose of opiate. A psychiatrist without knowledge of the admitting OOWS score performed the second assessment an average of 10 to 12 hours after ibogaine administration and 24 hours after the last opiate dose. The attending physician performed the third assessment 24 hours following ibogaine administration and 36 hours after the last opiate dose. Physician's ratings were subjected to repeated measures analysis of variance (ANOVA) with treatment phase (pre-ibogaine, post-ibogaine, and program discharge) as the within-subjects factor.

VII. Subjects' Self-Report of Withdrawal Symptoms

The Opiate-Symptom Checklist (OP-SCL) was developed for the present study as a subtle assessment of withdrawal symptoms, given that many subjects' verbal reports about withdrawal experience were generally exaggerated, both in number and severity of symptoms. Each of the 13 items that comprises the OP-SCL scale were taken from the Hopkins Symptom Checklist-90, with the criteria for selection based on whether it appeared in two other self-report withdrawal questionnaires, the Addiction Research Center Inventory (*16*) and the Subjective Opiate Withdrawal (*17*) scales. Subjects also completed a series of standardized self-report instruments relating to mood and craving at three different time points during the study within 7 to 10 days after the last dose of opiate. Subjects were asked to provide ratings of their current level of craving for opiates using questions from the Heroin Craving Questionnaire (HCQN-29) (*18*). Self-reported depressive symptoms were determined by the Beck Depression Inventory (BDI) (*19*). Subjects' scores were subjected to repeated measures analyses of variance across treatment phase (pre-ibogaine, post-ibogaine, and discharge) as the within-subjects factor for the total score from the OP-SCL, BDI, and the HCQN-29.

VIII. Acute Detoxification and Behavioral Outcomes

Physical dependence on opiates is characterized by a distinctive pattern of signs and symptoms that make up the naturalistic withdrawal syndrome. The physical dependence produced by an opiate is assessed usually by discontinuation of opioid treatment (spontaneous withdrawal) or by antagonist-precipitated withdrawal. All of the subjects identified opiates as one of the primary reasons for seeking ibogaine treatment and demonstrated active dependence by clinical evaluation, objective observations, and positive urine screen. Physician ratings demonstrate that ibogaine administration brings about a rapid detoxification from heroin and methadone (Figure 3A). The post-ibogaine OOWS rating obtained 10 to 12 hours after ibogaine administration and 24 hours following the last opiate dose was significantly lower than the rating obtained 1 hour prior to ibogaine administration and 12 hours after the last opiate dose. At 24 hours after ibogaine administration and 36 hours after the last opiate dose, the OOWS rating was significantly lower than the pre-ibogaine rating. The blinded post-ibogaine ratings between doctors agreed well item for item and were not significantly different from one another in terms of the mean total OOWS score (mean ± 1 SD, N = 32). These objective measures demonstrate the effects of ibogaine on opiate

withdrawal assessed in this study. Objective signs of opiate withdrawal were rarely seen and none were exacerbated at later time points. The results suggest that ibogaine provided a safe and effective treatment for withdrawal from heroin and methadone. The acute withdrawal syndrome in addicts dependent on heroin begins approximately 8 hours after the last heroin dose, peaks in intensity at 1 to

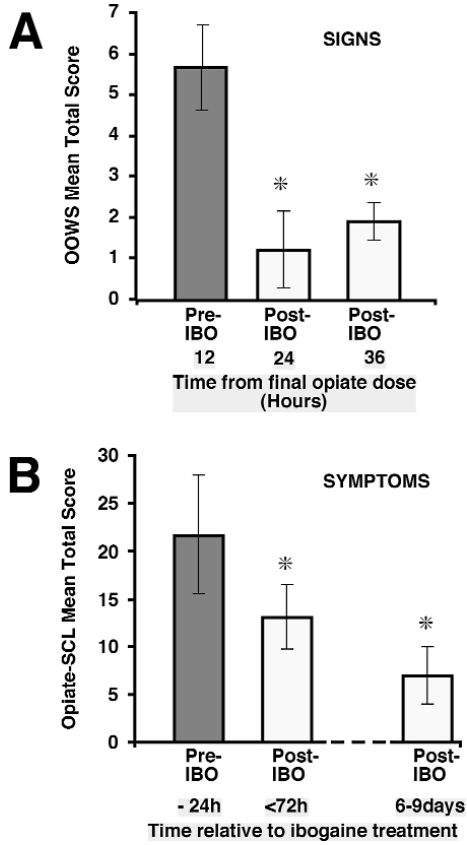


FIGURE 3. SCORES ON THE OBJECTIVE OPIATE WITHDRAWAL SCALE. (a) The effects of single-dose ibogaine treatment on opiate withdrawal signs at three physician-rated assessment times (12, 24, and 36 hours after the last dose of opiate). Average data are shown (mean ± 1 SD, N = 32). *P < .05. (b) The effects of single-dose ibogaine on patients self-report Opiate-Symptom Checklist (OP-SCL). The OP-SCL was developed for the present study as a subtle assessment of patients' subjective complaints based on 13 items selected from the Hopkins Symptom Checklist rated for intensity from 0 to 4. The maximum score attainable for the OP-SCL was 42.
* p < .05.

2 days, and subjective symptoms subside within 7 to 10 days. Self-reports of withdrawal symptoms shortly after recovery from ibogaine treatment (< 72 hours) were significantly decreased from the pre-ibogaine rating obtained 12 hours after the last use of opiates and were comparable to the level of discomfort reported at program discharge approximately one week later (Figure 3B). Thus, for subjects undergoing ibogaine detoxification, all of the subjects were successful during the detoxification process and many were able to maintain abstinence from illicit opiates and methadone over the months following detoxification (data not shown). Perhaps the most important observation was the ability of a single dose of ibogaine to promote a rapid detoxification from methadone without a gradual taper of the opiate. These preliminary observations of ibogaine treatment suggest that methadone withdrawal was not more difficult than heroin withdrawal following ibogaine detoxification. As discussed below, we suggest that the long-acting metabolite noribogaine may account for the efficacy of ibogaine treatment for both heroin and methadone withdrawal.

Craving is thought to be an important symptom contributing to continued drug use by addicts. Opiate-dependent subjects report increased drug craving during the early stages of withdrawal (*20*). We have previously reported that subjects undergoing opiate detoxification reported significantly decreased drug craving for opiates on five measures taken from the HCQN-29 scales at 36 hours posttreatment. These five measures inquired about specific aspects of drug craving, including urges, as well as thoughts about drug of choice or plans to use the drug. Questions are asked also about the positive reinforcing effects of the drug or the expectation of the outcome from using a drug of choice or the alleviation of withdrawal states. Perceived lack of control over drug use was included, since it is a common feature of substance-abuse disorders and is most operative under conditions of active use, relapse, or for subjects at high risk. The results demonstrated that across craving measures, the mean scores remained significantly decreased at program discharge (*10*). BDI scores were also significantly reduced both at program discharge and at 1-month follow-up assessments (*10*). Heroin craving is known to be dramatically reduced depending on the lack of availability of the abused drug in a controlled setting. Thus, more meaningful studies of ibogaine's ability to suppress heroin craving require further investigations done under naturalistic conditions.

IX. Cardiovascular Changes and Side Effects of Ibogaine

Ibogaine has a variety of dose-dependent pharmacological actions, which may not be relevant to its effectiveness for opiate detoxification and diminished drug

cravings, but may influence considerations for safety. However, toxicological studies in primates have demonstrated previously that ibogaine administration at doses recommended for opiate detoxification is safe (*21*). The FDA Phase I Pharmacokinetic and Safety investigations by our group have not advanced in the United States due to a lack of funds to support clinical investigations of ibogaine in patient volunteers. However, we have had the opportunity to obtain additional safety data in drug-dependent subjects under controlled conditions in human studies conducted in St. Kitts, West Indies. For these subjects, baseline screening included a medical evaluation, physical examination, electrocardiogram, blood chemistries, and hematological workup, as well as psychiatric and chemical dependency evaluations. In some cases, more extensive evaluations were done to rule out cardiac risk factors and to exclude subjects for entry to the study. The recognition of the cardiovascular actions of ibogaine date back to the 1950s, when the CIBA Pharmaceutical Company investigated ibogaine as an antihypertensive agent. Ibogaine at doses used for opiate detoxification may lower blood pressure and heart rate when the drug reaches peak concentrations in blood. In contrast, the opiate withdrawal syndrome is associated with increases in pulse, systolic and diastolic blood pressures, and respiratory rate.

Our observations of the safety of ibogaine have not been limited to opiate-dependent subjects. To date, we have evaluated ibogaine's safety in more than 150 drug-dependent subjects that were assigned to one of three fixed-dose treatments under open label conditions: 8, 10, or 12 mg/kg ibogaine. Adverse effects were assessed by clinician side-effect ratings and open-ended query. To date, no significant adverse events were seen under these study conditions. The most frequent side effects observed were nausea and mild tremor and ataxia at early time points after drug administration. Random regression of vital signs (respiration rate, systolic and diastolic blood pressures, and pulse) revealed no significant changes across time or by treatment condition for opiate-dependent subjects. However, a hypotensive response to ibogaine was observed in some cocaine-dependent subjects, which required close monitoring of blood pressure and which was responsive to volume repletion. Comparison of pre- and postdrug effects demonstrated that blood cell count, neurotrophil levels, and sodium and potassium levels were in the normal range. There were no significant changes from baseline seen on liver function tests. No episodes of psychosis or major affective disorder were detected at posttreatment evaluations. Intensive cardiac monitoring demonstrated that no electrocardiographic abnormalities were produced or exaggerated following ibogaine administration in subjects that were not comorbid for any cardiovascular risk factors. These preliminary results demonstrate that single doses of ibogaine were well tolerated in drug-dependent subjects. These preliminary observations are encouraging, but they do not diminish the possibility that ibogaine may have other medical risks not ordinarily associated with opiate withdrawal or with the use of tapering doses of methadone.

However, we anticipate, based on our clinical experience from offshore studies, that any potential adverse cardiovascular responses can be well managed within routine clinical practice.

X. Mechanism of Action

While the precise mechanism(s) underlying the expression of opiate withdrawal signs and symptoms are not fully understood, and may be different between humans and laboratory animals, the cellular and behavioral changes resulting from withdrawal and that have motivational relevance to drug-seeking behavior may involve the same neural circuits as those that participate in opiate dependence. Ibogaine and its active metabolite noribogaine act on a number of different neurotransmitter systems in the brain that may contribute to ibogaine's ability to suppress the autonomic changes, objective signs, and subjective distress associated with opiate withdrawal. However, we have speculated that the actions of noribogaine at mu-opioid receptors may account in part for ibogaine's ability to reduce withdrawal symptoms in opiate-dependent humans (*22*). For example, the desmethyl metabolite noribogaine has been shown to be a full agonist at the mu-opioid receptor (Table 3). This pharmacological activity, coupled with the

TABLE 3.
INHIBITORY POTENCY OF IBOGAINE AND NORIBOGAINE

	Ibogaine		Noribogaine		Pharmacodynamic
	IC_{50}(μM)	nh	IC_{50}(μM)	nh	Action
Serotonergic					
5-HT Transporter (RTI-55)	0.59 ± 0.09	0.8	0.04 ± 0.01	0.76	Reuptake Blocker
Opioidergic					
Mu (DAMGO)	11.0 ± 0. 9	1.0	0.16 ± 0.01	0.99	Agonist
Kappa 1 (U69593)	25.0 ± 0.6	1.1	4.2 ± 0.3	1.05	Partial Agonist (?)
Kappa 2 (IOXY)	23.8 ± 7.1	1.0	92.3 ± 9.2	1.03	Partial Agonist (?)
Glutaminergic					
NMDA (MK-801)	5.2 ± 0.2	0.9	31.4 ± 5.4	1.1	Channel Blocker

The values represent the mean ± SE of the IC_{50} value (μM) from 3-4 independent experiments, each performed in triplicate. nh, Hill slope

long duration of action may produce a self-taper effect in opiate-dependent patients.

The relative contributions of the parent and metabolite to the pharmacodynamic effects have yet to be established with precise certainty. Results from animal studies indicate that opiate withdrawal is associated with hyperactivity of the noradrenergic system and with changes in a variety of other neurotransmitter systems (*23*). Pharmacological agents may have differential effects on different components of opiate withdrawal. In addition to affecting mu-opioid receptors in the brain, noribogaine also has affinity at kappa-opioid receptors and the serotonin transporter (*8*). Indirect serotonergic agonists have been shown to attenuate neuronal opiate withdrawal (*24*). The 5-HT releaser d-fenfluramine and the 5-HT reuptake blockers fluoxetine and sertraline reduce the withdrawal-induced hyperactivity of locus ceruleus neurons. We have demonstrated previously that noribogaine elevates serotonin concentrations in brain by binding to the 5-HT transporter (Table 3) (*8*). Dysphoric mood states associated with opiate withdrawal may be a contributing factor for relapse, since addicts often experience drug craving in conjunction with dysphoric mood states (*20*). An action at the 5-HT transporter may explain the antidepressant effects seen following ibogaine administration in human opiate-dependent patients (*10*). Clinical studies have previously suggested that patients who abused opiates may have been self-medicating their mood disorders, indicating a possible role for endogenous opiates in major depression (*25*). Dysphoria and drug craving reportedly persist in opiate addicts even after detoxfication from opiates has been completed. Thus, noribogaine's effects at multiple opioid receptors and the 5-HT transporter may explain the easy transition following only a single dose of ibogaine in humans following abrupt discontinuation of opiates. These observations suggest that noribogaine may have potential efficacy for use as a rapid opiate detoxification treatment strategy. Recognition of the different components (autonomic changes and the objective signs versus subjective signs, dysphoric mood, and drug craving) may suggest the need for a medication strategy that targets multiple neurotransmitter systems for the treatment of opiate withdrawal and for relapse prevention. The identification of noribogaine's mix of neurotransmitter receptors and neurotransporter binding sites provides additional support for medications targeted to different aspects of the opiate withdrawal syndrome.

Opiate agonist pharmacotherapy with buprenorphine is a new alternative to methadone maintenance for the treatment of opiate dependence (*20*). Noribogaine has some pharmacologic similarities to the mixed agonist-antagonist analgesic buprenorphine. Buprenorphine and noribogaine both act as mu agonists. Compared to buprenorphine's high affinity partial agonist profile, noribogaine has lower receptor affinity, but increased intrinsic activity over buprenorphine as a mu agonist. Behavioral and physiological evidence suggest

that buprenorphine has kappa antagonist effects in addition to its action as a partial mu agonist. Noribogaine binds to kappa receptors, but acts as a partial agonist (Table 3). Both drugs have a long duration of action due to the slow rates of dissociation from opiate receptor sites. Thus, ibogaine's ability to inhibit opiate craving may be accounted for by the mixed mu- and kappa-opioid profile of the active metabolite noribogaine.

XI. Conclusion and Future Directions

Pharmacological treatments for opiate dependence include detoxification agents and maintenance agents. New experimental approaches have also been tried to reduce the time it takes to complete the process of detoxification or to further reduce persisting subjective reports of dysphoria and opiate craving. Ibogaine treatment is a novel approach that has similarities with other detoxification pharmacotherapies, including substitution with a longer-acting opiate (e.g., methadone or buprenorphine). However, ibogaine appears to be a prodrug with the beneficial effects residing in the active metabolite noribogaine. Thus, it would be useful to demonstrate that noribogaine alone is effective in detoxification of heroin-dependent and methadone-maintained patients. If noribogaine alone is safe and effective in open label studies, a randomized, double-blind study comparing noribogaine to clonidine-naltrexone detoxification would be justified. This clinical study would demonstrate whether noribogaine is more effective and has fewer adverse hemodynamic effects. Based on its spectrum of pharmacological activities, we suggest that noribogaine should also be considered as an alternative to methadone maintenance.

A pharmacological approach for the compliance problem has been the development of depot formulations that might be injected as infrequently as once a month. The long-acting pharmacokinetics of noribogaine suggests that the drug may, in fact, persist in the body for weeks to months. Thus, future development of depot noribogaine preparations may provide an optimal therapeutic approach for treating intractable opiate abusers. Another approach would be to combine a noribogaine taper with naltrexone. This approach may provide a means to shorten the time needed to initiate opiate antagonist therapy. Previous studies have also suggested the need for combination pharmacotherapies, such as antidepressants with buprenorphine (*20*). Interestingly, noribogaine has a pharmacological profile that includes actions on both serotonin and opiate systems in the brain. Although not discussed in this report, ibogaine provides an approach for the treatment of abuse of multiple substances including alcohol and cocaine. Many opiate-dependent patients abuse multiple drugs and alcohol. Thus, ibogaine and its

active metabolite noribogaine represent two additional pharmacological treatments for opiate dependence. However, clinical studies are needed to demonstrate whether they will become viable alternatives for treating opiate dependence in the future. It remains to be seen if the politics surrounding this controversial treatment approach will limit the promise for future development of either ibogaine or noribogaine.

Acknowledgments

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