Neurologic, Electroencephalographic and General Medical Observations in Subjects Administered **Ibogaine**

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ABSTRACT

IBOGAINE is a potentially hallucinogenic indole alkaloid with anecdotal antiaddictive properties against multiple drugs of abuse. Medical literature concerning the administration of this substance to humans is sparce. Ibogaine HCL (20-25 mg/kg) was administered orally to five subjects addicted to cocaine and/or opiates. Subjects underwent continuous intensive medical, neurologic and electroencephalographic observation. Movement-induced nausea and vomiting was seen in several subjects, all developed transient ataxia, and several experienced visual hallucinosis. No general medical, EKG or EEG abnormalities were seen. No subjects experienced withdrawal symptoms 24 hours after treatment, and two subjects were free of withdrawal or craving one week after treatment.

INTRODUCTION

Ibogaine (NIH 10567, Endabuse™) is an indole alkaloid derived from the West African bush, *Tabernanthe iboga*. Historically, the crude extract has been used by native tribes in Gabon; in low doses as a stimulant, and in high doses as an hallucinogenic agent utilized in folk rituals (1). Ibogaine has also been utilized in the psychotherapeutic milieu, largely for its abreactive properties (2,3). More recently, anecdotal reports have indicated that ibogaine has potential antiaddictive properties against multiple drugs of abuse, including opiates, stimulants and alcohol (4-9). Drug use is reportedly abruptly terminated without the development of withdrawal symptoms or drug-craving. There is also a body of recent animal research to support such claims (10-16). Pharmacologic studies suggest that ibogaine may act via interactions with the opioid, dopaminergic, serotonergic and/or glutamatergic neurotransmitter systems (13,17-21).

Reports of ibogaine administration to humans have been largely anecdotal and medically unsupervised. The few reports by physicians have utilized lower dosages of ibogaine (300-400 mg) than those reported effective in the interruption of polysubstance abuse (20-25 mg/kg), and descriptions of its effects have concentrated more on the visual imagery induced and the psychodynamic effects of treatment (2,3). The present report is intended to enlarge the small medically supervised literature concerning the acute effects of human treatment with ibogaine, particularly in the setting of chemical dependence. Specific attention was paid to general medical, neurologic and electroencephalographic findings.

METHODS

The present study represented a collaborative effort between the University of Miami, CITA (Centro Internacional para el Tratamiento de Addiciones) and NDA International. Subjects were obtained by private application to NDA

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International for the Endabuse procedure. A total of five subjects were studied. Initial screening evaluations were performed at the University of Miami (subjects 1-3), or the Hospital for Joint Diseases (subjects 4,5). Evaluations consisted of general medical, neurologic and psychiatric examinations. In Panama (Centro Medico Paitilla), further screening was performed, which included EKG, EEG, cranial MRI scan, CBC, SMA-20, urinalysis, HIV and hepatitis serology, alcohol and drug screens. Study exclusions included: seizure disorder, hypertension, cardiac/hepatic/renal disease, or DSM-4 Axis 1 diagnoses. Treatment was conducted by the Panamanian authors at the Centro Medico Paitilla (Panama City) and was approved by the IRB of that institution. Informed consent was obtained from all subjects prior to treatment.

Three subjects (1,2,3) were evaluated neurologically by the primary author in Panama City before, during and immediately after treatment in Panama City. The other two subjects had neurologic and EEG evaluations performed in New York approximately one week before and after treatment, and also had EEGs performed during treatment. Neurologic observations for these subjects were provided by the secondary authors, who were in attendance during treatment in Panama.

The subjects were first administered a 1 mg/kg test dose of ibogaine hydrochloride (OMNICHEM SA, Belgium) orally in capsule form. Patients were attended continuously by nursing and physician staff, and vital signs were performed every 30 minutes. The next day 0.5 mg/kg was administered to rule-out the possibility of a hypersensitivity reaction. On the morning after the second test dose administration, subjects were pretreated with two tablets of domperidone 10 mg, given one hour apart, in hopes of preventing the development of nausea and vomiting. They then received approximately 25 mg/kg of ibogaine hydrochloride orally, with 75% of the dosage given initially, and the remaining 25% one hour later. The subjects then rested in bed in a relatively darkened hospital room with continuous medical monitoring.

Vital signs and EKG were recorded every 30 minutes for four hours, and then hourly for eight hours. Acute symptomatic treatment was provided when necessary, such as the administration of metoclopramide for nausea and vomiting. Neurologic examinations were performed on the first three subjects by the primary author immediately prior to treatment, and 1, 2, 4, 8 and 24 hours after the ingestion of ibogaine. Gross neurologic examinations were performed by the secondary authors for subjects 4 and 5 during treatment, and a comprehensive exam was performed by the primary author one week later in New York. EEG studies were performed immediately pretreatment, as well as four and 24 hours after the ingestion of ibogaine. These were 30 minute EEG studies utilizing a Stellate system with electrodes placed according to the 10-20 system of electrode placement. A certified psychotherapist was in attendance at all times to provide acute counselling as necessary.

RESULTS

Vomiting may occur in up to 30% of those given ibogaine, with or without narcotic dependency, and is movement sensitive (2,3,6). Domperidone was administered in our subjects prophylactically, but three experienced movement-induced vomiting early in the course of treatment and were treated with metoclopramide 10 mg IV. In two of these subjects, since vomiting occurred early, an additional 5 mg/kg of ibogaine was administered orally to assure absorption of the appropriate dose. In the third subject, the dose was readministered as a rectal infusion due to persistent vomiting . As a result of such vomiting, some patients were at points reluctant to rise from bed for a full neurologic evaluation.

In all subjects, baseline neurologic examinations were normal. Signs of transient cerebellar dysfunction developed in all subjects, generally by two hours after ingestion. All neurologic examinations were normal 24 hours after treatment. In all cases, EEGs were normal in the awake or awake and drowsy states, before, during and after treatment.

Visual hallucinosis occurred in two subjects, initially noted within the first two hours after ingestion. The hallucinations were noted only with eyes closed. Notably, subjects remained oriented and

fully responsive, and demonstrated no evidence of psychological or physiologic anxiety, whether or not hallucinosis occurred.

During the study there were no significant general medical or electrocardiographic abnormalities noted.

On the morning after treatment, subjects demonstrated no psychological or physiologic evidence of drug withdrawal, nor was there evidence of craving or drug-seeking behavior. In the case of subjects 4 and 5, there was no evidence of drug withdrawal or craving when seen one week later in New York. Subjects 1 through 3 returned home following treatment and were thus not seen by the authors in follow-up.

DISCUSSION

Overall, ibogaine was well-tolerated, aside from the occurrence of early motion-induced nausea and vomiting in several subjects, which likely reflects acute vestibulocerebellar dysfunction. Thus, subjects treated with ibogaine should remain relatively immobile, and prophylactic treatment with antiemetics seems warranted to ensure effective treatment. There was otherwise no evidence of general systemic side-effects due to ibogaine.

In animal studies of ibogaine, tremor and ataxia are frequent acute effects of treatment (13,22,23), and suggest the presence of transient cerebellar dysfunction. Some concern has been raised by O'Hearn et al., who reported indirect evidence of possible cerebellar Purkinje cell damage in rats given 100 mg/kg of ibogaine (23). However, the ibogaine dosage used in this study was much higher than that used in the Endabuse procedure (20-25 mg/kg). Molinari et al. have replicated these findings at a dose of 100 mg/kg, but have found no evidence of neuropathologic changes at a dose of 40 mg/kg (24). Similarly, Sanchez-Ramos and Mash found no neuropathologic changes in green monkeys given ibogaine 5-25 mg/kg daily for four days (25). In our subjects, ataxia and rare tremor were seen transiently, but there was no clinical evidence of persistent cerebellar dysfunction following treatment.

Past animal research has suggested that high doses of ibogaine may result in seizures (22,26) However, there is also animal data suggesting that ibogaine may have an anticonvulsant effect (27). In rats, ibogaine (10-30 mg/kg intraperitoneal) caused only an increase in EEG rhythmic theta range activity, but there was no report of epileptiform activity being seen (28). In cats, EEG arousal patterns have been described (29). In our subjects, the first humans studied electroencephalographically during ibogaine intoxication, EEGs were normal and there was no clinical or electroencephalographic evidence of seizure activity.

Despite the powerful hallucinogenic properties of ibogaine, all subjects maintained intact reality testing and responsivity during treatment and demonstrated no signs or symptoms of anxiety or thought disorders. In three subjects visual hallucinosis occurred during treatment. Hallucinosis was present only with the subjects eyes closed, as described by Sigg (29,30), and patients were typically reluctant to discuss these at any length. One patient described simple moving geometric spheres, like "asteroids in space," akin to the decription by Sigg of "disks dancing up and down the walls." (30). Another described vivid memories of early childhood, similar to the reactions decribed by Naranjo (2,3). It is notable that at least short-term interruption of drug use was achieved whether or not patients experienced visual hallucinosis. In some subjects who did not experience hallucinosis the heightened awareness of the psychodynamic factors behind their addictions may still have contributed to successful treatment. However, this does not preclude the possibility that the antiaddictive effects of ibogaine may be more closely related to potential neurotransmitter effects rather than psychological abreation. These matters will require further research in order to determine ibogaine's mechanism of action.

In our subjects there were no signs or symptoms of drug withdrawal or craving immediately after treatment. In addition, when examined one week after treatment the two subjects examined at that time remained free of symptoms Though drug testing was not performed at that time, there were no observable signs of recurrent drug use. There was also no reason for

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these subjects to conceal recurrent drug use, as they had sought treatment on their own, at their own expense. The post-treatment period of observation in this study was limited and long-term follow-up will be helpful in assessing the long-term benefits of ibogaine treatment. The authors recognize the methodological weakness of not obtaining post-treatment drug screens and suggest that this be overcome in future research with appropriate evaluations.

The present report represents one of the few medically supervised trials of ibogaine for the interruption of human addiction syndromes, and describes the effects of the highest dosages of ibogaine yet reported in a scientific human study. The results indicate that ibogaine is generally well-tolerated and produces transient cerebellar dysfunction, not unlike that produced by other intoxicants, with no signs of persistent neurologic effects. The absence of withdrawal symptoms or drug craving following treatment supports the anecdotal human reports of ibogaine's efficacy in the treatment of multiple addiction syndromes. Though the number of subjects in this study is small, and the period of follow-up limited, the results suggest that ibogaine does acutely interrupt addictive behavior without untoward consequences, providing a symptom-free window of opportunity that may permit major changes in patients lives, particularly in the presence of an appropriate psychosocial support structure. Such treatment may offer a viable alternative to less effective, more prolonged and costly methods of drug detoxification.•

The present study represented a collaborative effort between the University of Miami, CITA (Centro Internacional para el Tratamiento de Addiciones) and NDA International.

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