

Research Article

Ibogaine Effect on Cocaine Craving and Use in Dependent Patients - A Double-Blind, Placebo-Controlled Pilot Study

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Received: 07-16-2014

Accepted: 07-29-2014

Published: 07-31-2014

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Abstract

Background: Cocaine dependence is a prevalent mental disorder, with unfortunately no specific treatment at the moment. Ibogaine is an extract from an African root, with several evidence pointing to its success in treating several addictive disorders. There are very few human studies evaluating its efficacy in cocaine dependence.

Materials and Methods: A double blind, placebo controlled study was conducted with 20 patients (N=20), split in 2 groups: the ibogaine group received a single dose of 1800 mg of encapsulate ibogaine extract, and the placebo group received a single capsule of sugar powder. All patients were followed for a 24 week period, with biweekly visits to a psychiatric professional, in which a urine sample was collected in order to detect cocaine use. Data analyzes was performed using ANOVA for repeated measures for comparison of data between groups and between members of the same group. Urine samples were compared (positive results) using measure ANOVA statistical tests with the Least Squares Difference for post hoc two group comparisons. Statistical significance was 5% ($P < 0.05$) for all the referred tests.

Results: Statistical significance was observed in the ibogaine group after treatment ($p < 0,0001$), in comparison with baseline (time zero) and with the placebo group at any time of analysis. No such improvement was observed in the placebo group.

Conclusions: Ibogaine is an effective treatment for cocaine dependence, and more studies with larger samples are necessary in order to establish its efficacy and validity.

Keywords: Ibogaine; Cocaine dependence; Double blind trial

Introduction

Cocaine dependence is one of the most prevalent of all addictive disorders, and is at rise in numbers in most populations around the globe. There are currently no consensus in which treatment approach is more indicated for such patients, whether it be counseling, behavioral interventions or pharmacotherapy [1-3].

Cocaine chronic use is directly related to airway lesion formation, pulmonary emphysema and precancerous and cancerous lesions of respiratory tract. It may also have immediate response in the cardiovascular system, with greater chance of myocardial infarction, electrophysiological abnormalities and cardiac arrest [1,2].

Several substances have been postulated as possible

treatment options for cocaine dependence, by controlling craving and abstinence symptoms in the acute stage of drug withdrawal, or by preventing drug relapse in the chronic stage of drug dependence. Although some of the studied medications have shown positive effect in one or both stages of cocaine addiction, they are still considered only moderately successful in treating the condition [4-9].

An effective pharmacological agent, preferably accessible cheap, being able to reduce symptoms in the acute stage of cocaine withdrawal and prevent drug relapse in the chronic stage of dependence would help in rehabilitating patients to normal life.

Ibogaine has been used in several settings in old and modern times. It is a natural alkaloid, extracted from *Tabernanthe iboga*, a plant used in several initiatory rituals in West Central Africa [10, 11]. Evidence of its efficacy in drug dependence was, unfortunately, based almost entirely on anecdotal and personal experiences of physicians in less than ideal clinical environments [12-14]. More evidence has amassed in open label trials and case reports in the last 20 years, however there have been very few double blind, placebo controlled trials conducted with scientific protocol in drug dependent patients, and most of these studies concentrated on heroin and opioid dependence [14-21]. Our goal was to conduct such study, focused on cocaine dependence in a population in Santos, São Paulo, Brazil.

Material and Methods

The study was double blind, placebo controlled, with a total of 20 patients diagnosed with cocaine dependence according to DSM IV criteria [22]. They were sorted in 2 different groups – the ibogaine group (N=10) received a capsule containing dried extract of ibogaine (1800 mg) – extracted from naturally grown *Tabernanthe iboga*, at 75% purity, with excipients in capsules - and the placebo group (N=10), who received a placebo capsule containing sugar powder.

Table 1. Shows pharmacokinetic properties of ibogaine.

Property	Value
Bioavailability	16-71% in males (dose dependent) 7-43% in females (dose-dependent)
Metabolism	CYP2D6 (P450 cytochrome)
Half – Life	7,5 hours
Excretion	Renal and gastrointestinal tracts

Patients were recruited from the Núcleo de Apoio Psicossocial (NAPS) – a municipal institution in Santos, São Paulo, specialized in primary care in mental health. All participants were submitted to an informed consent term, guaranteeing clinical follow-up for a minimal of 6 months, approved by the municipal ethics committee (registration 1569-13).

Inclusion criteria for participants were: male, aged from

18-64 years, any race or ethnic origin, current use of cocaine with self-reported use of cocaine at least once weekly for at least one month preceding study entry, and diagnosis of cocaine dependence, as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR).

Exclusion criteria were current diagnosis of alcohol or other drug abuse or dependence (other than nicotine); significant medical conditions (i.e., major cardiovascular, renal, endocrine, or hepatic disorders), such as abnormal liver function (with laboratory findings of SGOT or SGPT greater than three times normal), hypotension or hypertension, a current cardiac condition, or seizure disorder; lifetime diagnosis of schizophrenia, bipolar disorder, or other psychotic disorders; active suicidality or homicidality; current prescription for psychotropic medication. Hepatic function was determined by serum concentration of total bilirubin and its fractions, albumin and activated prothrombin times, and renal function was estimated according to creatinin and urea plasma concentration, using the Cockcroft-Gault formula.

As ibogaine has several documented side effects (including nausea, temporary ataxia, xerostomia and cardiac conduction abnormalities (prolonged QT syndrome), which is why a baseline electrocardiogram was performed before administration, and compared with other serial exams performed later.

At first, patients were clinically accessed and selected according to inclusion and exclusion criteria. Those considered able (reported at least a 7 day abstinence from cocaine) were sorted into either placebo or ibogaine groups, and received a single dose capsule. The patients were admitted in a general infirmary for the period of 72 hours, undergoing cardiac monitoring every 6 hours (an electrocardiogram was performed every 6 hours), as well as clinical evaluation of somatic symptoms. No other medications (expect for symptomatic for general symptoms such as nausea) were provided. After this period, patients were discharged to outpatient care, for double-weekly consultations with a psychiatrist.

In order to evaluate craving symptoms and abstinence, at beginning of treatment, end of single dose treatment (72 h) and at the end of the 6 months follow-up, the Minnesota Cocaine Craving Scale (MCCS) was applied. It consists of 5 items which correspond to intensity, frequency, duration of craving, changes in relation to previous two weeks and craving response to medication [23].

The BIS11 scale was also applied in the same cutoff points. It is a self-rating questionnaire, 30 Likert-type composed questions, which provides a total score and three sub-scores: attention, nonplanning and motor. Scores vary from 30 to 120 with no established cut-off point. The BIS11 score is a consistent measure of impulsiveness and has proven potential clinical use

impulsiveness and has proven potential clinical use for measuring impulsiveness among selected patient.

Urine samples were collected every two weeks in outpatient care – following protocol of the Acon DOA-754 5-Panel One Step Drug Screen Test card (immunoassay) (cocaine//cannabinoid/opioid/benzodiazepine/ethanol). A positive urine test showed use of cocaine, combined with other drugs or not, at least 60 hours prior to consultation/measurement, and served as an assessment of effectiveness up until the end of the 6 month follow up period. Any find of cocaine use (combined with other drugs), even of substract (cocaethylene) was considered positive.

The percentage of urine positive samples in each group was considered the analyzed parameter, and the reduction in percentage of positive urine samples was considered the primary outcome. Secondary outcome measures included percentage of participants achieving two weeks of abstinence, retention (weeks in treatment).

Data analyzes was performed accordingly: the MCCS and BIS11 scores were compared between the two groups using the ANOVA test for repeated measures at the cutoff points; comparison between the same group at different cutoff points was performed using ANOVA test for repeated measures.

Urine sample results were compared using the chi-square and repeated measure ANOVA statistical tests with the Least Squares Difference for post hoc two group comparisons. Statistical significance was 5% ($P < 0.05$) for all the referred tests.

Results and Discussions

There were no defects from either group during the 6 month evaluation period. There no statistically significant differences from both groups regarding age, demographic, ethnicity or physical comorbitites at first evaluation.

Patients from the ibogaine group experienced several visual hallucinations during the 72 hour period after exposure, mainly in the first 24 hours, of different contents. These varied from sight of small animal and vermin, changes in whether conditions, elements in nature and shadows/appearitions. There were no events of cardiovascular nature, and electrocardiograms remained normal in volunteers from both groups.

There were significant reduction in severity of symptoms at first evaluation and after the 72 hour intervention period in the ibogaine group (MCCS score intensity at time zero = $7,4 \pm 0,70$; intensity at time 72 h = $2,6 \pm 0,84$; $p < 0,0001$, ANOVA test for repeated measures). There was a statistically significant improvement between the ibogaine group at time 72 hours and at 24 weeks analyzes ($p = 0,0047$, t paired test). No such improvement was observed in the pla-

cebo group at any of the studied times of experiment (as seen in table 2).

Table 2. Data of the Minnesota Cocaine Craving Scale (MCCS) and BIS11 test in the ibogaine (N=10) and placebo group (N=10) in three different times.

	Placebo Time zero	Placebo 72 h	Placebo 24 weeks	Ibogaine Time zero	Ibogaine 72 h	Ibogaine 24 weeks
MCCS	$7,3 \pm 0,67^*$	$6,9 \pm 1,1^*$	$6,7 \pm 0,82^*$	$7,4 \pm 0,70^{\alpha}$	$1,3 \pm 0,82^{\alpha}$	$2,6 \pm 0,84^{\alpha}$
BIS11	$4 \pm 5,5$	$6 \pm 2,4$	$4 \pm 5,1$	$5 \pm 2,3$	$6 \pm 5,5$	$6 \pm 3,3$

*ANOVA repeated measures, $p < 0,0001$

α ANOVA test for repeated measures, $p < 0,0001$

When comparing test subjects of different groups at corresponding times, there were no significant differences between ibogaine group and placebo group at start of the experiment ($p=0,37$), though there were differences at 72 hours ($p < 0,0001$, ANOVA test for repeated measures) and 24 weeks ($p < 0,0001$, ANOVA test for repeated measures) between both groups.

The BIS11 test did not show any improvement in either group, when compared by paired or unpaired t Student test.

Urine samples were compared for positive results between both groups, with a lower rate of positive results in the ibogaine group when compared with the placebo group ($F=2,450$; $df=3,12$; $p=0,023$; ANOVA repeated measures) at the total samples collected from the 24 week period, indicating fewer relapses in the ibogaine group (corresponding to 10% of the sample) when compared with the placebo group.

Ibogaine is a drug studied mainly for its activity antagonizing opioid (κ , μ , δ receptors), serotonergic (5-HT_{2A}, 5-HT_{2C}, 5-HT₃ receptors) and glutamatergic receptors (NMDA receptors). It is still unclear how these pharmacodynamic properties affect addictive behavior in cocaine dependents, though studies have appointed the role of glutamate activity inhibition as the main contributor to the substance's success in treating symptoms, lowering neuron mediated excitotoxicity, death and malfunction [28-30].

Conclusion

According to our preliminary results, ibogaine is able to reduce symptoms in an acute stage of cocaine dependence, and reduced drug relapse in the chronic stage of the condition. There are bases for conducting studies with larger samples and for longer periods of time to.

Acknowledgements: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Associação Fundo de Incentivo à Pesquisa (AFIP), Conselho Nacional de Desenvolvimento e Tecnológico (CNPq).

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