An analytical study of iboga alkaloids contained in *Tabernanthe iboga*-derived products offered by ibogaine treatment providers

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Abstract

Background: Therapeutic properties of ibogaine in the treatment of addiction are attracting both clinicians and patients to its use. Since ibogaine is not an authorized medicine, the quality of these products is not always known, increasing the probability of adverse reactions. **Objective:** This study collects different types of *iboga*-derived samples from treatment providers, vendors and online buyers to analyse their content. **Methods:** Analysis of *iboga* products (n = 16) was performed using gas chromatography and mass spectrometry methods (GC/MS). Products included *Iboga* root bark, Total Alkaloids (TA), Purified Total Alkaloids (PTA HCl), ibogaine hydrochloride (ibogaine HCl) and one *Voacanga africana* root bark. **Results:** The content of ibogaine was highly variable, ranging from 0.6% to 11.2% for products sold as iboga root bark, from 8.2% to 32.9% for products sold as TA, 73.7% for one sample sold as PTA and from 61.5% to 73.4% for products sold as ibogaine HCl. One sample did not show any *iboga* alkaloids. Other alkaloids and unknown substances were found in almost all samples. **Discussion:** The purity of iboga products is highly variable. These results should be taken into consideration by suppliers and users, especially regarding correct dosing to avoid overdose, as well as potential interactions with other substances.

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Keywords: *Tabernanthe iboga*, ibogaine, sample analysis, addiction treatment, harm reduction.

Introduction

Ibogaine is a psychoactive alkaloid with hallucinogenic properties present in the root bark of *Tabernanthe iboga*, a tropical plant traditionally used in rites of passage and ethnomedicine in African countries such as Congo and Gabon[1]. Its anti-addictive properties were discovered serendipitously in the sixties by Howard Lotsof, who at that time was a heroin user and noticed that after using ibogaine his craving for heroin was significantly reduced. Since then, thousands of people have been treated with ibogaine to address drug dependence and/or for personal growth[2].

Pre-clinical research has demonstrated the anti-addictive properties of ibogaine in different animal species with reductions in self-administered morphine, cocaine, (meth)-amphetamines, alcohol and nicotine[3]. Ibogaine was also found to reduce or eliminate drug craving and withdrawal in humans in several case series and in clinical settings, but randomized trials are lacking[4-7].

Indeed, the number of ibogaine clinics and ibogaine treatment providers has been increasing during the last few years. In 2008 it was estimated that 3,414 people used ibogaine, approximately a fourfold increase relative to the estimation of 857 from five years before[8]. From those 3,414 subjects, 68% used ibogaine for the treatment of drug addiction. In New Zealand, Australia and South Africa, ibogaine can be prescribed for the treatment of drug addiction (the legal status of ibogaine around the world can be found at: https://www.ibogainealliance.org/ibogaine/law/). Most of the *iboga* that is

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used in ibogaine clinics comes from Gabon, where unlicensed *iboga* exportation is forbidden. The lack of a regulated market results in a lack of quality control and patients may therefore be consuming ibogaine with unknown concentrations of active ingredients.

While ibogaine clinics are spreading around the world, accidents and fatalities have been increasing. By 2015 22 ibogaine-related deaths were reported[9,10]. Although ibogaine is considered a safe treatment when conducted under medical supervision[11], many ibogaine providers offer ibogaine treatments outside of a medically controlled setting (for example, in hotel rooms). Furthermore, the purity of the ibogaine or *iboga* extracts used by treatment providers or self-administered by patients is frequently unknown, and. many clinics and private providers buy *iboga*/ibogaine from web-based suppliers without any quality control. This can increase the risks of adverse reactions and/or fatalities.

In one of the fatalities, the hypotensional substance reserpine[12] was found in the blood of a man who died after ingesting ibogaine in Slovenia in 2011[13]. Reserpine might potentiate the hypotensional effects of ibogaine, increasing the risks of cardiovascular toxicity. Furthermore, both reserpine and ibogaine are metabolized by CYP-2D6[14] and this specific drug interaction could increase the blood levels of ibogaine, increasing the risk of overdose. This is especially relevant when most of the time the concentration of *iboga* alkaloids in ibogaine samples is unknown. Because the ibogaine sample involved in the fatality was not analysed, it is unknown if it contained reserpine or if the person used any other herbal or pharmaceutical product containing it. In the same year, reserpine was found in ibogaine samples analysed in Slovenia[12]. Forensic analyses after ibogaine fatalities regularly show the presence of other drugs in the body[15].

Therefore, we performed this study to gain more insight into the purity and content of *iboga* samples available on the market, and to evaluate the claims made by the vendors about the characteristics of their products.

Methods

Sample collection

An advertisement was released through the website, newsletter and blog of the ICEERS Foundation (a non-profit organization that investigates the ethnobotany and therapeutic properties of iboga, ayahuasca, and cannabis) in July of 2013 (http://news.iceers.org/2013/07/scientific-study-analysis-of-iboga/) asking treatment providers, vendors and buyers to send samples for analysis. We requested information about (A) the type of material (root bark, *iboga* extract, ibogaine hydrochloride (HCl), etc.); (B) the source (company, vendor, country, etc.); (C) date of purchase; (D) the expected percentage of ibogaine; (E) any information about abnormal effects experienced, potency, etc.; and (F) any additional information considered relevant. Requested samples could include: (A) pulverized root bark; (B) total alkaloids (TA) (solid extracts containing the alkaloids present in the root bark); (C) purified total alkaloids (PTA) (solid extracts containing the semi-purified alkaloids in salt form); and (D) "pure" ibogaine HCl.

Samples preparation for GC/MS

GC/MS qualitative and quantitative analysis was carried by Energy Control, a Spanish non-governmental organization with extensive experience in drug analysis. Their methodology for the GC/MS analysis has been previously reported[16].

The samples were prepared by dissolving 5.0 mg of each sample in 5.0 mL of methanol in glass vials. All vials were vortexed for 1 minute and then sonicated for 15 minutes.

The substances were determined with gas chromatography coupled with mass spectrometry (Agilent 7890B gas chromatograph coupled to a 5977A quadrupole mass spectrometer detector; (Agilent; Santa Clara, CA, USA) at the Municipal Institute for Medical Research in Barcelona (IMIM – Hospital del Mar). The gas chromatograph was fitted with a G4513A auto-sampler injector. Samples were injected in split mode into a 30 meter, 0.25 mm i.d., 0.25 mm film thickness 5% phenylmethylsilicone column (HP-5MS, Agilent Technologies). The oven temperature was initially maintained at 90 ºC for 2 min and programmed to reach 320 ºC at 20 ºC per min. It was finally maintained at 320 ºC for 9.5 min. The total run time was 21.5 min. Insert liners packed with silanized glass wool were used. The injector and the interface were operated at 280 ºC. Helium was used as carrier gas at a flow rate of 1 mL/min. The mass spectrometer was operated in electron impact ionization mode at 70 eV. To confirm the mass spectra, two libraries were used: the Searchable Mass Spectral Library NIST/EPA/NIH Mass Spectral Library, Data Version: NIST 14 and the Searchable Mass Spectral Library Version 2.3 (http://www.swgdrug.org/ms.htm). A GC/MS comparison of the samples with the analytical standards of ibogaine, ibogamine, and voacangine was also performed. Ibogaine and voacangine were provided by Phytostan Inc., Montreal, Quebec. Analysis certificates of Phytostan Inc. alkaloids have been performed by the laboratory of Martin Kuehne, Department of Chemistru, University of Vermont, Burlington, Vermont, verifying the high purities of those alkaloids[15]. Ibogamine was provided by REFORM Italia srd.

Data analysis

The moles of ibogaine HCl in the Phytostan reference sample per unit of signal intensity for the ibogaine peak were calculated based on the injected mass. The moles of each detected component in a sample were then calculated based on its signal intensity relative to that of the Phytostan sample times the moles in the Phytostan sample. The mass of each component was calculated using its molecular weight, accounting for salt form. The mass percent of each component was then obtained by dividing the mass of each component by the mass injected for the sample.

Results

Table 1 shows all the information gathered from the received samples.

Source

We received 17 samples from five different known vendors during 2013. Samples were submitted from nine different countries with date purchases from 2006 to 2013. One of the 17 samples was excluded due to suspected contamination during handling.

Samples

The 16 remaining samples used were: iboga root bark (n = 6), iboga TA extract (n = 5), iboga PTA HCl (n = 1), ibogaine HCl (n = 3), and *Voacanga africana* root bark (n = 1). Of the six samples of iboga root bark, one was sold as coming from a supplier in Cameroon.

Alkaloid content

We were able to identify and quantify up to five different alkaloids from the samples (see Table 1).

Table 2 shows means and ranges of iboga alkaloids found in the analysed samples.

The alkaloid identification profile of the samples was similar for all products, except for one sample which did not contain any iboga alkaloid. The quantity of ibogaine was highly variable among the samples of each type of product and also among different types of products. High variability was especially worrying for the case of samples labelled as TA, which had the largest ibogaine variation. High variation in the content of ibogaine HCl samples was also found, possibly because some were actually PTA HCl based on all

Table 1. Description of the samples

Material	Date of Purchase	Country	Form	Color	Expected ibogaine concentration	Quantitative analysis (GC/MS)
Iboga Root bark	Unknown	Australia	Powder	Light brown	--	A: 0,6%
Iboga Root bark	2006	Netherlands	Fine chopped bark	Brown	--	All unknown substances
Iboga Root bark	17/10/2012	New Zealand	Powder	Light brown	2-4%	A: 11.2% C: 0.7%
Iboga Root bark	11/04/2012	Canada	Powder	Brown	--	A: 2.1% C: 0,3%
Iboga Root bark	11/04/2012	Mexico	Powder	Light brown	--	A: 9.9% B: 0.1% C: 0.6%
Iboga Root bark	03/04/2013	Germany	Chopped bark	Brown	--	A: 7.1% B: 1.5% C: 2.3% D: 0.2%
Iboga extract-PTA	11/04/2012	South Africa	Powder	Light brown	80%	A: 73.7% B: 4.7% C: 6.1%
Iboga extract-TA	Unknown	Australia	Powder	Brown	--	A: 9.1% B: 2.3% C: 0.6% D: 0.2% E: 0.1%
Iboga extract-TA	07/04/2010	South Africa	Powder	Brown	40%	A: 32.9% B: 0.2% C: 2.1% D: 0.4% E: 0.3%
Iboga extract-TA	16/05/2012	New Zealand	Sticky raisin	Dark brown	35% (sold as 35% of ibogaine)	A: 25.4% B: 0.5% C: 16.4% D: 0.6% E: 0.6%
Iboga extract-TA	16/08/2012	New Zealand	Pressed Powder	Dark brown	Less than 5% (sold as 35% of ibogaine)	A: 13.3% B: 0.2% C: 1.6% D: 0.1% E: 0.1%
Iboga extract-TA	11/10/2012	New Zealand	Powder	Dark brown	Less than 10% (sold as 35% of ibogaine)	A: 8.2% B: 0.2% C: 0.8% D: 0.1% E: 0.1%
Iboga extract-TA	07/05/2013	Hawai USA	Powder	Light brown	--	A: 61.6% B: 7.2% C: 7.1%
Voacanga africana Root bark	03/04/2013	Spain	Pieces of bark	Brown	5-10% carbometoxi-ibogaina (voacangine)	A: 0.6% D: 2.1%
Ibogaine HCL	Unknown	Australia	Powder	White	--	A: 73.4% C: 2.1%
Ibogaine HCL	07/05/2013	Hawai USA	Powder	White	--	A: 65.9% C: 8.7%

Note. A: ibogaine; B: ibogaline; C: ibogamine; D: iboleutine; E: voacangine.

Table 2. Alkaloid summary

	Iboga Root Bark (n = 6)			TA (n = 5)			Ibogaine HCl (n = 3)			PTA HCl (n = 1)			*V. africana* (n = 1)		
	N	Ave.	Range	N	Ave.	Range	N	Ave.	Range	N	Ave.	Range	N	Ave.	Range
Ibogaine	5	6.2%	0.6%-11.2%	5	17.8%	8.2%-32.9%	3	67.0%	61.6%-73.4%	1	73.7%	--	1	0.6%	--
Ibogaline	2	0.8%	0.1%-1.5%	5	0.69%%	0.2%-2.3%	1	7.2%	--	1	4.7%	--	0	--	--
Ibogamine	4	0.98%	0.3%-2.3%	5	4.3%	0.6%-16.4%	3	5.9%	2.1%-8.7%	1	6.1%	--	0	--	--
Voacangine	1	0.2%	--	5	0.25%	0.1%-0.6%	0	--	--	0	--	--	1	2.1%	--
Iboleutine	0	--	--	5	0.27%	0.1%-0.6%	0	--	--	0	--	--	0	--	--

of them containing ibogamine and/or ibogaline in amounts similar to those for PTA HCl.

The expected concentrations of ibogaine in the samples (which were rated by the senders) were below our results in two cases, with a large difference in iboga root bark from Cameroon, which had almost three times more ibogaine than expected. The remaining samples rated by the senders were above our results, with the largest discrepancy observed in the *V. africana* sample, which was expected to have a concentration of 5%-10% of voacangine but showed less than 2.1%.

We also found unknown substances in several samples which we were unable to identify.

Discussion and conclusions

This is the first report analysing iboga products from on-line suppliers. Results show a large diversity of iboga alkaloid content in all the different products (iboga root bark, iboga extracts and ibogaine HCl). This is especially meaningful for the ibogaine HCl samples, which are supposed to be purified. However, some ibogaine samples that have been used for scientific purposes in the past showed traces of ibogamine or ibogaline, even when the concentration of ibogaine was between 95% and 99.6%[17]. Traces of ibogamine or ibogaline are to be expected in ibogaine isolated from the Tabernanthe iboga plant. During the analysis we also found substances other than iboga alkaloids in three of the samples, although we could not identify them. As noted above, we also found one sample that did not contain any iboga alkaloid. Also, two other samples contained less than 1% ibogaine. Low or zero concentrations of ibogaine should be of high concern. A recent report of a product sold as iboga bark was found to be Rauvolfia powder, which did not contain any iboga alkaloids and caused the death of the subject who used it thinking it was iboga root bark[18].

The most relevant implication from these results is that ibogaine users are often not able to know the quality and purity of the purchased products when they come from on-line suppliers. Since many users and treatment providers obtain iboga/ibogaine for the treatment of addiction, they increase the potential risk of suffering side effects or adverse situations when they buy material of unknown quality from on-line suppliers. These adverse situations can include overdoses and fatalities[15,19].

The contents of alkaloids in the iboga plant have a large variation and depend on many variables such as subspecies, growing environment, harvesting time, conservation of the samples, etc. Our results could be a reflection of the variability of alkaloid concentrations in iboga-derived products and its relationship with dosing difficulties. Important cardiovascular effects are observed at doses often used in drug-detoxification. Ibogaine needs to be provided in low doses to ensure safety[20] and because the variability within iboga products can be a source of serious adverse reactions, this is an issue that should be taken into account by practitioners.

Given the high variability of ibogaine concentrations in iboga-derived products, both users and providers should be careful during dose calculations. At the same time, harm reduction programs should include qualitative and quantitative drug analysis to avoid overdosing and related fatalities. Since this 2013 analysis, the manufacture of high-purity ibogaine HCl from *Voacanga africana* bark has increased, offering treatment providers with a another way to avoid the quality issues inherent in using bark or crude alkaloids for treatment.

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Contributors: JCB and BDL conceived of the study and collected the samples. JCB wrote the first draft of the manuscript. IF and MMV performed the analysis of the products. IF, MMV and CWJ interpreted the chemical analysis. BDL, ASC, DFG, RGD, JECH, MAAC and CWJ contributed to data interpretation and literature review. All authors contributed to and have approved the final manuscript.

Conflict of interest

No conflict declared.

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