Distribution of Ibogaine and Noribogaine in a Man Following a Poisoning Involving Root Bark of the *Tabernanthe iboga* Shrub

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Abstract

In the present paper, we report for the first time the tissue distribution of ibogaine and noribogaine, the main metabolite of ibogaine, in a 48-year-old Caucasian male, with a history of drug abuse, found dead at his home after a poisoning involving the ingestion of root bark from the shrub *Tabernanthe iboga*. Ibogaine and noribogaine were quantified in tissues and fluids using a fully validated liquid chromatography–electrospray mass spectrometry method. Apart from cardiac tissue, ibogaine and noribogaine were identified in all matrices investigated. The highest concentrations were found in spleen, liver, brain, and lung. The tissue/subclavian blood concentration ratios averaged 1.78, 3.75, 1.16, and 4.64 for ibogaine and 0.83, 2.43, 0.90, and 2.69 for noribogaine for spleen, liver, brain, and lung, respectively. Very low concentrations of the two drugs were found in the prostatic tissue. Both ibogaine and noribogaine are secreted in the bile and cross the blood-brain barrier. Four other compounds were detected in most of the studied matrices. One of them was identified as ibogamine. Unfortunately, we were not able to positively identify the other three compounds because of the unavailability of reference substances. Two of them could possibly be attributed to the following oxidation products: iboluteine and desmethoxyiboluteine. The third compound could be ibogaline.

Introduction

Ibogaine is a naturally occurring alkaloid derived from the roots of the rain forest shrub *Tabernanthe iboga*. The root bark has been used for centuries in West Central Africa as a medical and ceremonial agent (1). The main alkaloids in the root bark are ibogaine (~ 80%), ibogaline (~ 15%), and ibogamine (~ 5%) (2). Many of these alkaloids suffer facile autoxidation to yield 9-hydroxy-9*H*-ibogamine, desmethoxyiboluteine, iboluteine, iboquine, and 9-hydroxy-9*H*-ibogaine (3,4). Ibogaine has previously been reported to have central nervous system (CNS) stimulant, anxiogenic, and hallucinogenic properties (5–7). Ibogaine has been used in low doses by the indigenous people of western Africa to combat fatigue, hunger, and thirst and in higher doses as a sacrament in religious rituals. The use of ibogaine for the treatment of drug dependence has been based on anecdotal reports from American and European addict self-help groups, which claim that it decreased the signs of opiate withdrawal and reduced drug craving for cocaine and heroin for extended time periods (8–11). Although ibogaine has diverse effects on the CNS, the pharmacological targets underlying the physiological and psychological actions of ibogaine are not completely understood. In the liver, ibogaine undergoes desmethylation by the action of cytochrome P450 enzymes to its principal metabolite, noribogaine or 12-hydroxyibogamine (12). Noribogaine's pharmacological profile is different from ibogaine's (1,11–18). Ibogaine is more potent than noribogaine in binding to the *N*-methyl-D-aspartic acid receptor in brain tissue (11,13) and as a stimulator of the hypothalamic–pituitary–adrenal axis (13,15). Noribogaine is (*i*) much more potent than ibogaine for binding to μ opioid receptor and is a full μ opioid agonist (10,11,13,16,17); (*ii*) more potent than ibogaine in binding to serotonin transporter and inhibiting reuptake of serotonin (11,13–15,18); and (*iii*) more potent in binding to Kappa 1 and less potent in binding to Kappa 2 opioid receptors. Moreover, ibogaine and noribogaine evoke very different behavioral effects (13–15); ibogaine causes tremors and ataxia, but noribogaine does not (13,14).

Pharmacokinetic data relative to ibogaine in humans are limited (10,16). Following single oral doses of ibogaine (500 to 800 mg) to individual subjects, maximum ibogaine and noribogaine blood concentrations of 30–1250 ng/mL and 700–1200 ng/mL were obtained approximately 2 and 5 h after drug administration, respectively. Thereafter, ibogaine was cleared rapidly from the blood while noribogaine concentrations re-

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mained high. Indeed, concentrations of noribogaine measured at 24 h postdose were in the range of 300–800 ng/mL. Thus, the purported efficacy of ibogaine following single-dose administrations for the treatment of drug dependence may be due in part to the formation of noribogaine (10,16). From blood concentration-time profiles of ibogaine published by Mash et al. (10,16), after an oral dose of 800 mg, the steady state volume of distribution uncorrected for bioavailability was about 13 L/kg, and the half-life of the terminal part of the curves was 4–7 h. Ibogaine is a restricted substance (possession is illegal) in some countries, including the U.S., Switzerland, Denmark, Sweden, and Belgium.

Some analytical methods have been published to quantify ibogaine in biological matrices (19–27); most methods involve a derivatization procedure before analysis. Recently, liquid chromatography–electrospray mass spectrometry (LC–ESI-MS) methods were developed in our laboratory for the simultaneous quantitation of ibogaine and noribogaine in human plasma, whole blood, and urine (28,29). In these papers, extensive stability testing was undertaken using a wide range of storage conditions. These methods were validated according to validation procedures, parameters, and acceptance criteria based on the United States Pharmacopoeia XXIII guidelines and Food and Drug Administration guidance. Moreover, LC–MS- and LC–MS–MS-based procedures are very sensitive to matrix effects. The absence of ion suppression was demonstrated by the method of Matuszewski et al. (30).

In the present paper, we report for the first time the tissue distribution of both ibogaine and noribogaine in a man following an intoxication involving powdered root bark of the *Tabernanthe iboga* shrub. The developed LC–MS methods were found accurate to quantify ibogaine and noribogaine in tissues, bile, stomach contents, blood, and urine. Moreover, under the same chromatographic conditions, four other compounds were detected. One of them has been identified as ibogamine; two compounds could possibly be attributed to desmethoxyiboluteine and iboluteine, oxidation products present in the root of the shrub, *Tabernanthe iboga* (3,4), and the last compound could possibly be ibogaline. But because of the unavailability of reference substances for these three compounds, their structures were not confirmed. We were unable to obtain standards of these substances.

Case Report

A 48-year-old Caucasian male with a history of drug abuse was found dead at his home. Different objects and burned-out parts of plants found at the death scene suggested that some sort of esoteric ritual may have taken place recently. Buprenorphine tablets (0.4 mg), as well as a recent prescription, were found at the scene, but only one tablet was missing. Cannabis resin was also present. A document signed by the deceased, relieving Mr. R. of all responsibility in case of any adverse effects due to the decedent's use of iboga, was also found at the scene.

Blood was collected from the subclavian vein at the scene. The time of death (estimated from livor mortis, rigor mortis, and body temperature) was 6 to 12 h earlier. The autopsy, performed about 48 h later, and histopathology examination of organs and tissues showed massive pulmonary edema with hemorrhagic alveolitis and vascular congestion, consistent with a drug overdose. No other cause of natural death was found. At the time of the autopsy, poisoning through the ingestion of drugs or plants being the main hypothesis, we collected blood from the femoral vein and from the inferior vena cava, urine, stomach contents, bile, and tissues. The vials (with and without sodium fluoride) were kept at 4°C until toxicological analysis, which was carried out within one week.

It emerged from the police investigation that a man originating from Gabon (Africa) was present at the scene during the days preceding the discovery of the body. He is suspected of having provided the deceased with powdered root bark of the *Tabernanthe iboga* shrub, which was mixed with sweet concentrated milk before ingestion. Over approximately 10 h, the victim would have consumed in the region of 18 soup-spoons of the mixture. According to the statement of the Gabonese man, the victim exhibited respiratory problems, difficulties in walking, vomiting, and visual hallucinations following ingestion of the root bark. As a result of the police investigation and forensic data, it was concluded that death occurred approximately 53 h after the last intake of the mixture.

Materials and Methods

Reagents

Ibogaine hydrochloride (molecular weight, 346.9), fluorescein sodium salt (internal standard), and trifluoroacetic acid (TFA) were purchased from Sigma (St. Louis, MO). Small amounts of ibogamine were detected in the ibogaine hydrochloride powder (~ 2–3%). This compound was characterized by LC–MS, and its structure was confirmed by ^1H NMR (data not shown). Noribogaine base (molecular weight, 296.4) was kindly supplied by Reform Italia (Endine, Italy). Ibogaine and noribogaine were stored and protected from light at routine room temperature (20°C). High-performance liquid chromatography-grade acetonitrile, methanol, and acetic acid were obtained from Carlo Erba (Val de Reuil, France). The formate buffer solution (pH 3) consisted of ammonium formate (126 mg/L) in purified water. Ultrapure water was used (Milli-Q device, Millipore, Bedford, MA). Solid-phase extraction (SPE) columns containing 30 mg hydrophilic/lipophilic balance reversed-phase sorbent (*N*-vinylpyrrolidone/divinybenzene copolymer, Oasis HLB cartridges, 30-µm average particle diameter) were purchased from Waters (Saint Quentin, France). The vacuum manifold used for SPE was a Vac Elut 20® from Varian (Les Ulis, France).

For the preparation of calibration curve standards and quality control (QC) samples, whole blood and plasma were obtained from pooled samples collected from healthy volunteers not undergoing drug therapy (Etablissement Français du sang, Montpellier, France). Coagulation was prevented by adding EDTA-sodium salt. The blood was centrifuged at $2000 \times g$ for 10 min to obtain plasma. Human urine was obtained from a healthy volunteer not undergoing drug therapy. The drug-free whole blood, plasma, and urine were stored at −20°C until use.

Stock solutions of ibogaine hydrochloride and the internal standard were prepared by dissolving accurately weighed amounts of the drugs in purified water to give solutions containing 89.5 and 81 mg/L of free-form equivalents of each compound, respectively. A stock solution of noribogaine was prepared in methanol at concentration of 100 mg/L. Stock solutions were stored at 4°C and protected from light. Working solutions were further prepared in light-protected vials extemporaneously. They were obtained by diluting the stock solutions with purified water to obtain 12 working standards ranging from 0.0224 to 44.7 mg/L for ibogaine and 0.025 to 50 mg/L for noribogaine. The stock solution of fluorescein was diluted fourfold (20.25 mg/L) in purified water before use. These solutions were used to prepare calibrators and QC samples.

LC–ESI-MS

Concentrations of ibogaine and noribogaine in the different matrices were determined by a specific LC–ESI-MS method. The LC–MS analysis was performed using an Agilent 1100 quadrupole MS equipped with an ESI interface and a data acquisition station (HPChem software, Agilent Technologies, Les Ulis, France). The MS was coupled to a Hewlett Packard LC system equipped with a quaternary pumping unit, an autosampler, and a diode-array UV detector. Separation of the analytes was performed on a Zorbax eclipse XDB-C8 column (150 × 4.6-mm i.d., 5-µm particle size, Agilent Technologies, Palo Alto, CA). A C_{18} Symmetry column (20 × 3.9-mm i.d., 5-µm particle size, Waters, Paris, France) was used as a guard column. Mobile phase A was 0.02% (v/v) trimethylamine in acetonitrile, and mobile phase B consisted of 2mM formate buffer (pH 3). The gradient started at 15% of phase A and then increased to 35% in 5 min. It increased to 50% in 6.2 min, then to 80% in 3.8 min. The column was then washed for 1 min with 80% of phase A, brought back to the initial conditions over 1 min, and re-equilibrated for 3 min. The flow rate started at 1 mL/min, then decreased to 0.5 mL/min from 1 to 5 min, and remained unchanged for 6.2 min. It increased to 1 mL/min over the next 4.8 min and then remained stable.

Sample pretreatment procedure

The sample pretreatment procedure involved an SPE of the compounds from plasma, whole blood, and urine using Oasis® HLB columns. The 1-mL Waters Oasis HLB cartridges were conditioned with 1 mL of methanol followed by 1 mL of distilled water prior to use. Fluorescein was used as internal standard. During the SPE procedure, protecting the products from light was required (31). The vacuum apparatus was kept under a plastic black cover in order to protect the products from light. The drug/internal standard peak-area ratios were linked via a quadratic equation to concentrations. From QC sample analysis [ibogaine: 2.24, 33.6, and 134.2 ng/mL in plasma and 4.48, 67.2, and 268.4 ng/g (or ng/mL) in whole blood (or urine); noribogaine: 2.5, 37.5, and 150 ng/mL in plasma and 5, 75, and 300 ng/g (or ng/mL) in whole blood (or urine)], precision ranged from 4.3 to 14.8% and accuracy ranged from 89 to 113%. The dilution of the samples had no influence on the performance of the methods. Extraction recoveries were > 70% in plasma and urine, and ≥ 57% in the whole blood. The lower limits of quantitation were 0.89 ng/mL for ibogaine and 1 ng/mL for noribogaine in plasma and 1.78 ng/g (or ng/mL) for ibogaine and 2 ng/g (or ng/mL) for noribogaine in the whole blood (or urine) (28,29).

For quantitative analyses of forensic samples, calibration standards were prepared in drug-free human matrices (plasma, whole blood, or urine). Concentration ranges were 0.89–179 ng/mL for ibogaine and 1–200 ng/mL for noribogaine in plasma and 1.78–358 ng/g (or ng/mL) for ibogaine and 2–400 ng/g (or ng/mL) for noribogaine in whole blood (or urine). Each determination of unknown samples was performed in three to six replicates. QC samples were included at random in each analytical sequence (including calibrators and unknown samples) to verify the accuracy and precision of the analysis (i.e., three QC samples at low, medium, and high concentrations, in duplicate, each 20 processed test samples).

Analytical procedure from blood and urine samples

Preliminary screening analyses were performed from a 250-µg aliquot of blood [i.e., blood from the vena cava and blood from the femoral vein drawn at the autopsy (about 48 h after the death) and blood from the subclavian vein drawn at the scene] and from a 250-µL aliquot of urine using diode-array and MS (scan mode) detection in sequence to identify peaks present on the chromatograms and to verify that each observed peak elutes free from potential interference. In the second step, ibogaine and noribogaine were quantified in all samples by LC–MS. MS data were acquired in single ion monitoring (SIM) mode. For SIM, a 7–10-µg aliquot of blood or a 2-µL aliquot of urine was diluted to 250 µL with drug-free matrix.

The sample pretreatment was as follows: 250 µL of purified water, then 20 µL of the internal standard solution (20.25 mg/L) were added to 250 µL of whole blood. The mixture was mixed with 0.5 mL of water containing 100 mL/L methanol. The methanolic solution was added dropwise, and the mixture was vortex mixed in order to obtain smaller precipitate particles, which avoid significant analyte loss. Thereafter, the mixture was centrifuged (4°C) for 10 min at 17,000 × *g*. The supernatant was then applied onto the conditioned SPE cartridge. The column was rinsed with 2 × 1 mL of purified water and vacuum dried for 2 min. The retained drugs were eluted with 2 × 1 mL of methanol. The eluate fractions were dried under a stream of nitrogen and reconstituted in 100 µL of a mixture of 1 mL/L TFA in water and acetonitrile (85:15, v/v). A 20-µL volume was injected into the system.

To 250 µL of urine, 20 µL of an aqueous internal standard solution (20.25 mg/L) was added. The mixture was carefully shaken then loaded onto the conditioned extraction column. Thereafter, the assay procedure was as described previously.

Analytical procedure from tissue samples

An aliquot of about 300–400 mg of each tissue sample (heart, liver, kidney, prostate, lung, brain, spleen, and muscle) was removed. Each sample was washed twice for 30 s in 0.9% sodium chloride to limit blood contamination, dried on gauze, and then powdered under liquid nitrogen. For the screening analysis, an aliquot of 150–200 mg, depending on the tissue, was accurately weighed in a polypropylene tube, then carefully vortex mixed for 20 s with 300 µL of blank human plasma. The mixture was incubated at 4°C for 12 h to allow a steady-state between the matrix components, and then 0.5 mL of water containing 100 mL/L acetic acid was added. The mixture was vortex mixed and then centrifuged at 4°C for 20 min (1450 × *g*). The supernatant was loaded onto the conditioned extraction column. Thereafter, the assay procedure was as described previously.

For quantitative analyses of ibogaine and noribogaine in each tissue sample using LC–MS (SIM mode), only a few milligrams of each tissue were required for the quantitation of the two drugs because of the very high drug concentrations observed in the preliminary screening step. Thus, the concentrations of ibogaine and noribogaine were determined against a calibration curve performed in blank human plasma. An aliquot of 3–10 mg, depending on the tissue, was accurately weighed in a polypropylene tube, vortex mixed for 20 s with 490 µL of blank human plasma, and 20 µL of the internal standard solution (20.25 mg/L of fluorescein) was added. The mixture was incubated at 4°C for 12 h to allow a steady-state between the matrix components. Thereafter, the assay procedure was as described in the screening analysis.

Analytical procedure from bile and stomach contents

After 10 min centrifugation at 5000 × *g* (4°C), which removed all particles, an aliquot of 250 µL of the supernatant was used for the screening analysis. To quantify ibogaine and noribogaine, a 5-µL aliquot of bile or a 50-µL aliquot of stomach contents, obtained after centrifugation, was diluted to 250 µL with whole blood or plasma, respectively. Thereafter, the assay procedure was as described previously. Calibration standards were prepared in drug-free human whole blood to quantify the two drugs in bile or in plasma to quantify the two drugs in stomach contents.

Results

Mass Spectra

Noribogaine, ibogaine, and fluorescein were characterized by the protonated molecules $[M+H]^+$ at *m/z* 297.2, 311.1, and 333, respectively (Figure 1). Fragment ions were observed at *m/z* 122.2 and 174 for ibogaine (Figure 1A) and *m/z* 122.2 and 160 for noribogaine (Figure 1B). The fragmentation patterns are presented in Figure 1 (3).

Results of the screening analysis

Figures 2A and 2B show the mass spectra (full scan) obtained from lung and blood from vena cava using a 200- or 250-mg aliquot of each matrix, respectively. The screening analysis, using the analytical conditions described previously, revealed the presence of six compounds at retention times of 6.0 min (C1), 6.8 min (C2), 9.0 min (C3), 9.6 min (C4), 10.2 min (C5), and 10.8 min (C6). The purity of these peaks was confirmed from diode-array and MS spectra. Additional peaks at retention

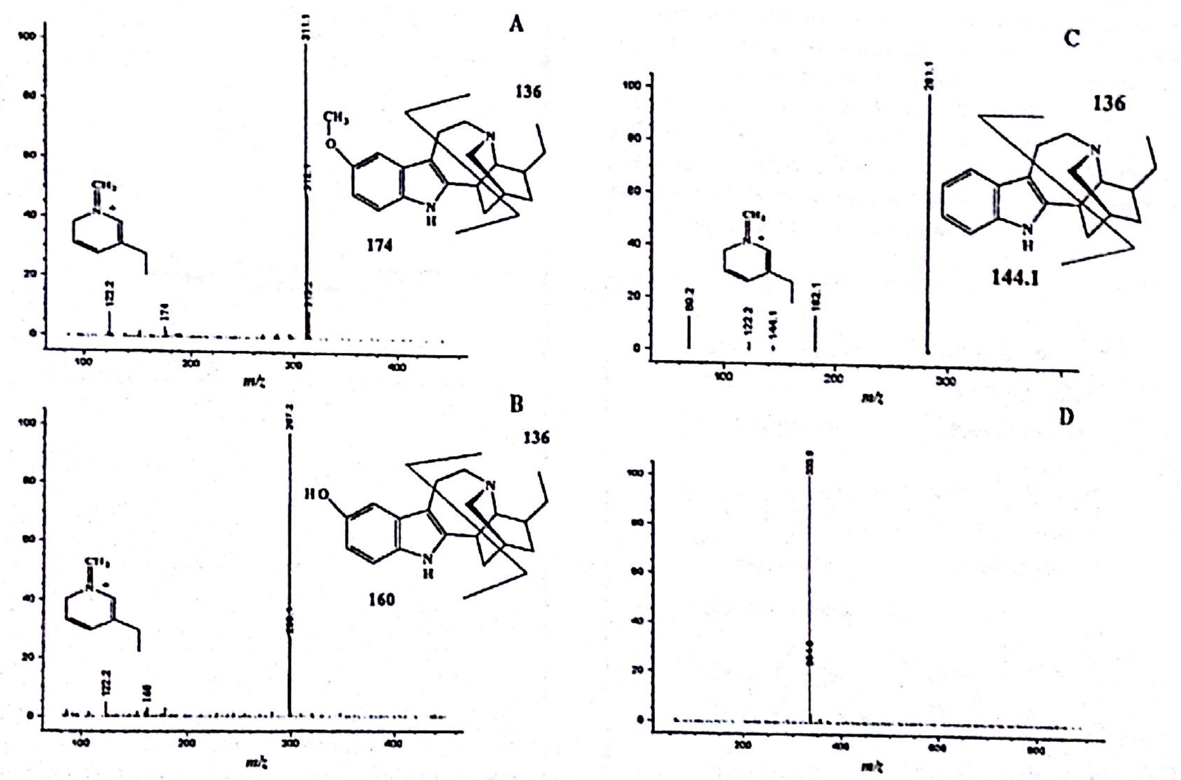

Figure 1. Mass spectra of ibogaine (A), noribogaine (B), ibogamine (C), and fluorescein (D).

times of 2.1 and 4.2 min are endogenous compounds from the matrix. No compounds were detected in the cardiac tissue (Figure 2C). From this chromatogram, we can see that by using the previously described pretreatment procedure, each analyte was well resolved from the human matrix endogenous peaks and from the internal standard. According to the mass spectra obtained from the references, peak C2 was noribogaine and peak C5 was ibogaine. Compound C6 was identified as being ibogamine, but because of the lack of a pure substance, this compound was estimated as described later for C1, C3, and C4. Noribogaine, ibogaine, and ibogamine were characterized by the protonated molecules $[M+H]^+$ at m/z 297.2, 311.1, and 281.1, respectively. A fragment ion was obtained at m/z 122.2 for the three compounds. Additional fragment ions were obtained at m/z 174 for ibogaine (Figure 1A), m/z 160 for noribogaine (Figure 1B), and m/z 144.1 for ibogamine (Figure 1C). Unfortunately, we were unable to positively identify the other three compounds. Two of them could possibly be attributed to desmethoxyiboluteine (C1, $[M+H]^+$ at m/z 313) and iboluteine (C4, $[M+H]^+$ at m/z 327), oxidation products present in the root of shrub *Tabernanthe iboga* (3,4). The third compound could possibly be ibogaline (C3, $[M+H]^+$ at m/z 341) (Figure 2). Fragment ions were obtained at m/z 122.2 and 150.1 for iboluteine and desmethoxyiboluteine, characteristic of the iboluteine moiety (32), and at m/z 122.2 and 204.1 for ibogaline. These mass spectra were in accordance with the results published by Clivio et al. (32). Structures of these compounds are given in Figure 3. However, because of the lack of reference substances available for these compounds, their structures were not confirmed. They were estimated in percentage with regard to the peak area corresponding to ibogaine using the following equation:

[Peak area of C1, C3, or C4/peak area of ibogaine] × 100 Eq. 1

The six compounds were detected in blood, urine, lung, liver, spleen, and stomach contents. C1 and C3 were never detected in muscle, brain, and kidney. In prostatic tissue and bile, only ibogaine and noribogaine were detected.

In all matrices investigated, mean chromatographic peak areas of C1, C3, and C6 represented approximately 15%, 25%, and 16.5% of that of ibogaine, respectively. Concerning the compound C4, very low levels were detected in the spleen (< 2%). Higher concentrations were observed in the lung, liver, kidney, blood, urine, and stomach contents, with the peak area of C4 representing approximately 40% of that of ibogaine. In the brain, the peak area of C4 was similar to that of ibogaine (ratio = 0.96).

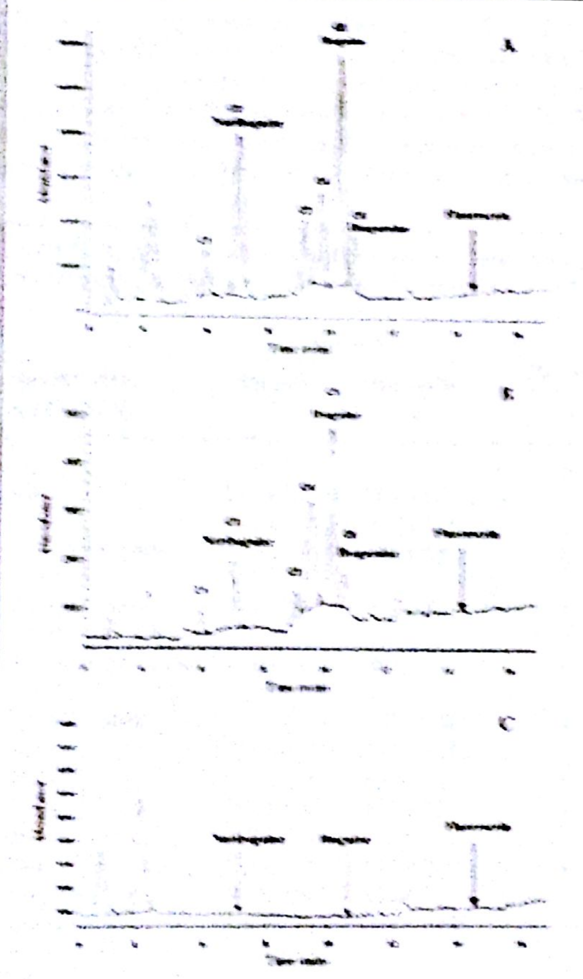

Figure 2. Typical chromatograms (scan mode) obtained from lung (A), blood from vena cava (B), and heart (C) using an aliquot of 200–250 mg of each matrix. Peak C2 = noribogaine; peak C5 = ibogaine; and peak C6 = ibogamine.

Concentrations of ibogaine and noribogaine in the different matrices

Results are presented in Table I. The highest ibogaine and noribogaine tissue concentrations were observed in the spleen, liver, brain, and lung. The tissue/subclavian blood concentration ratios averaged 1.78, 3.75, 1.16, and 4.64 ibogaine and 0.53, 2.43, 0.90, and 2.69 noribogaine, for spleen, liver, brain, and lung, respectively. Very low concentrations of both ibogaine and noribogaine were found in the prostate tissue; the tissue/blood concentration ratios were lower than 0.1.

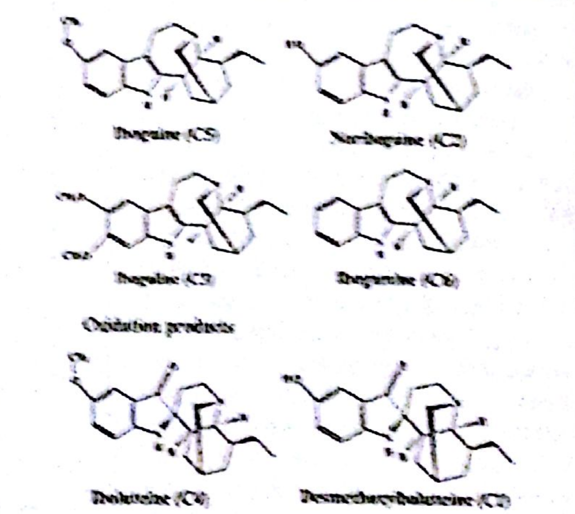

Figure 3. Structures of the different compounds detected in the body.

Conclusions

Despite thorough investigation, including autopsy, histopathology, and toxicological analysis, no other cause of death could be established. The victim was considered to have died from "pulmonary edema due to drug overdose by ingestion of *Tabernanthe iboga* root bark". The manner of death was defined as "accidental". Little is known about the pharmacokinetics of ibogaine in humans, and there are no other well-documented fatal cases reported in the literature. We are, therefore, unable to explain the true connection between iboga alkaloid ingestion and the pulmonary edema.

In the present study, we reported in detail and, for the first time, the tissue distribution of both ibogaine and noribogaine in a man after a poisoning case involving the root bark of *Tabernanthe iboga*. Ibogaine and noribogaine were quantified in blood and urine using previously validated LC–ESI-MS methods (28,29). These methods were applied in the quantitation of these two drugs in tissues (heart, liver, kidney, prostate, lung, brain, spleen, and muscle), bile, and stomach contents. Apart from cardiac tissue, ibogaine and noribogaine were identified in all matrices investigated. In this paper, we proposed structures for ibogaine and noribogaine LC–ESI-MS fragmentation products; these results agree with those published by Taylor (3), who reported a fragmentation pattern for ibogaine, which differs from that presented by Bogusz et al. (27). The highest concentrations were found in spleen, liver, brain, and lung. The tissue/subclavian blood concentration ratios averaged 1.78, 3.75, 1.16, and 4.64 for ibogaine and 0.83, 2.43, 0.90, and 2.69 for noribogaine for spleen, liver, brain, and lung, respectively. Very low concentrations of the two drugs were found in the prostate tissue. Both ibogaine and noribogaine are secreted in the bile and cross the blood-brain barrier. In the blood, concentrations of ibogaine and noribogaine were 5–20-fold greater than those reported by Mash et al. (16) after a single oral dose of 800 mg of ibogaine in humans. The highest concentrations were found in the blood sample drawn at the death scene. Four other compounds were identified in most of the studied matrices. One of them was identified as ibogamine; unfortunately, we were unable to positively identify the other three compounds. Two of them could possibly be attributed to iboluteine (C4) and desmethoxyiboluteine (C1), oxidation products present in the root of shrub *Tabernanthe iboga* (3,4). The mass spectra obtained for these two compounds were similar to those reported in the literature (3,30). Moreover, the C1 and C4 compounds have similar retention times and mass spectra to those observed for the oxidation products formed after the exposure of ibogaine and noribogaine solutions to daylight (data not shown). Therefore, as ibogaine is light-sensitive (3), iboluteine could be formed spontaneously during preparation of the mixture from powdered root bark. Moreover, according to Taylor (3), many of the iboga alkaloids easily undergo autoxidation. Therefore, the isolation of iboluteine from the biological matrices cannot by itself be taken as proof of its natural occurrence in roots. In addition, it is possible that part of these oxidation products could be formed after death.

Table I. Results of the Sceening Analysis and Concentrations of Ibogaine and Noribogaine in Fluids and Tissues of the Body (n = 3–6)[*]

Concentration (µg/g or µg/mL)	Mean ± SD[†] Ibogaine C5	Mean ± SD[†] Noribogaine C2	(Percent[‡]) C1	(Percent[‡]) C3	(Percent[‡]) C4	Ibogamine C6
			(15)	(25)	(< 2–100)	(16.5)
Bile	21.3 ± 5.6	11.2 ± 1.7	–	–	–	–
Urine	83.3 ± 8.45	21.5 ± 3.42	+	+	+ (40)	+
Blood from femoral vein[§]	5.4 ± 1.4	5.6 ± 0.9	+	+	+ (40)	+
Blood from vena cava[§]	6.6 ± 0.6	15.5 ± 0.7	+	+	+ (40)	+
Blood from sub-clavian vein[#]	10.8 ± 0.4	20.8 ± 3.0	+	+	+ (40)	+
Stomach contents	2.91 ± 0.155	1.23 ± 0.105	+	+	+ (40)	+
Prostate	0.556 ± 0.234	0.579 ± 0.103	–	–	–	–
Kidney	7.06 ± 1.46	4.93 ± 1.42	–	–	+ (40)	+
Spleen	19.2 ± 4.70	17.3 ± 3.33	+	+	+ (< 2)	+
Liver	40.5 ± 3.38	50.5 ± 3.63	+	+	+ (40)	+
Brain	12.5 ± 0.26	18.7 ± 0.47	–	–	+ (100)	+
Lung	50.1 ± 4.90	55.9 ± 5.24	+	+	+ (40)	+
Muscle	7.66 ± 1.75	3.41 ± 0.405	–	–	+ (9.6)	+

[*] n = number of replicates.
[†] SD = standard deviation.
[‡] Calculated from [Peak area of C1, C3, C4, or C6/peak area of ibogaine] × 100.
[§] Drawn the day of autopsy.
[#] Drawn at the death scene; (–) absence; (+) presence. C1, C3, and C4 could be desmethoxyiboluteine, ibogaline, and iboluteine, respectively.

The differences in the concentrations of ibogaine and noribogaine in blood drawn at the scene and blood taken at the autopsy may indicate that degradation (oxidation) of these two drugs occurred after death. The oxidation products were not secreted in the bile, and only C4 crosses the blood-brain barrier, attaining similar concentrations to those of ibogaine. The third compound could possibly be ibogaline (C3), known to be one of the most important iboga alkaloids (quantitatively) after ibogaine in the roots of *Tabernanthe iboga* (2). Our results indicate that this compound did not cross the brain barrier and was not secreted in bile. Attempts to obtain standards of these substances proved unsuccessful.

The present results demonstrate a widespread distribution of ibogaine and noribogaine throughout the body. Particularly noteworthy are the high concentrations of these two drugs in liver, lung, spleen, and brain. Taking into account (*i*) the rapid decrease in ibogaine concentrations ($t_{1/2}$ = 4–7 h) and the very slow decrease in noribogaine concentrations (10,16), (*ii*) the high concentrations of ibogaine found in the blood drawn at the death scene (10.8 µg/mL), and (*iii*) the parent drug/metabolite blood concentration ratios (~ 0.5), we can speculate that the victim could have consumed the mixture made from root bark of the *Tabernanthe iboga* shrub for a longer period of time than 10 h (as written in the police report). The survival time could have been 8–12 h after the last intake.

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