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INVESTIGATION INTO PHARMACOKINETIC PROPERTIES OF ACTIVE ALKALOID IBOGAINE AND ITS METABOLITE NORIBOGAINE

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Abstract: The interest in alkaloid ibogaine found in African plant *Tabernanthe iboga* Baill. has been persisting for several decades. Behavioral, neuroendocrine and neurochemical effects of ibogaine and its active metabolite – noribogaine – were examined, however there are limited pharmacokinetic data in literature and existing data is conflicting. We determined pharmacokinetic parameters of ibogaine and noribogaine not only in plasma, but in organs (heart, liver, spleen, brain, kidney and muscle) of mice after ibogaine and noribogaine intragastrical administration too, because there are no pharmacokinetic studies of internal organs. Circulating plasma levels of ibogaine and noribogaine peaked immediately at 30 min after ibogaine administration, whereas level of noribogaine after noribogaine administration increased slowly to plateau at 4 h. Shorter half-life ($T_{1/2}$) and smaller volume of distribution (Vd) of ibogaine show the faster elimination from plasma, compared with noribogaine. Largest Vd value in plasma calculated for noribogaine after noribogaine administration. Our results demonstrate that noribogaine reaches higher concentration in brain after ibogaine intragastrical administration. Higher concentration and total systemic exposure (AUC_{tot}) of noribogaine in brain could be more efficacious alternative to ibogaine as a medication for the treatment of various types of addiction. High values of AUC_{tot} in heart samples may determine the long elimination from this organ and can lead to cardiovascular abnormalities. Our findings also raise the hypothesis that ibogaine is metabolized not only in the liver, but also in kidney and brain too.

Keywords: ibogaine, noribogaine, pharmacokinetics, *Tabernanthe iboga*

The dangers of addiction are generally well-known, nevertheless people continue to start taking drugs. Dependence on drugs and alcohol is assigned to the most common brain disorders. Almost 50% of all persons who have applied for reliance on drug therapy as the primary drug used opioids. Therefore, researchers are interested in naturally occurring psychoactive alkaloid ibogaine, found in African plant *Tabernanthe iboga* Baill. (Apocynaceae). Psychoactive properties of ibogaine have been known for decades (1).

There are published data that ibogaine can facilitates the symptoms of abstinence (2). In the late 20th century, many scientific researches started to be conducted with an aim to find out the mechanism of action of ibogaine. The pharmacology of ibogaine is quite complex, affecting many different neurotransmitter systems simultaneously. Non-clinical studies have demonstrated that ibogaine reduces craving for cocaine and morphine, attenuates morphine withdrawal symptoms (3). However, the pharmacological targets underlying the physiological and psychological actions of ibogaine are not completely understood (4). The identified antagonistic activity of ibogaine on N-methyl-D-aspartate receptors as well as its agonist activity on opioid receptors can be regarded as a possible mechanism of anti-addictive action (5).

Ibogaine is metabolized by cytochrome P4502D6 (CYP2D6) into active metabolite noribogaine (12-hydroxyibogamine) (6), which can condition the long-term effect of ibogaine (7, 8).

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Although they share similar chemical structures, ibogaine and noribogaine display different binding profiles (9). Although both alkaloids increase extracellular 5-HT in the brain, noribogaine is more potent in this respect (10). Previous study reports, that noribogaine is less toxic (11) and can be safer and causing less undesirable reactions as compared with parent drug (10). However, usually noribogaine is analyzed after administration of ibogaine while we investigated the pharmacokinetic parameters of noribogaine after administration of both – ibogaine, as well as noribogaine.

In previous study (12) we calculated the amounts of tested substances in organs (heart, liver, spleen, brain, kidney and muscle) of mice after ibogaine and noribogaine administration directly into the mice stomach *via* the stomach tube. In present study, we evaluated the main pharmacokinetic parameters of ibogaine and noribogaine in plasma and organs of mice.

EXPERIMENTAL

Animals

The experiments were conducted with non-linear white laboratory mice (20–25 g) of the age of 4 to 6 weeks in compliance with the Law on the Care, Keeping and Use of the Animals of the Republic of Lithuania. The animals were kept in compliance with the requirements of the Good Laboratory Practice (GLP). The experiments were performed in cooperation with the Laboratory of Molecular Neurobiology of the Institute of Neurosciences of the Medical Academy of the Lithuanian University of Health Sciences. Adult male mouse (n = 54) weighing 20-25 g were housed individually in rooms maintained at ~20^{o}C, with a regular light-dark cycle. Water was available in the living cages at all times. Permission for experiments with Laboratory Animals No. 0172 was issued by the State Veterinary Authority of Lithuania.

Chemicals and reagents

Ibogaine hydrochloride, gradient purity eluents and fluorescein sodium salt (internal standard) purchased from manufacturer "Sigma-Aldrich Chemie" (Switzerland) were used for the researches. Noribogaine base was kindly supplied by Reform Italia (Endine, Italia). Ibogaine and noribogaine were stored protected from light. Water purified by Millipore water purification system (Millipore, Bedford, USA) was used for the experiments. Oasis HLB cartridges (30 mg sorbent, size of particles – 30 μm) were supplied by Waters (Milford, USA). Blank human plasma was received from the Division of Haematology of the Clinics of the Lithuanian University of Health Sciences. Heparin sodium salt was purchased from UAB "Labochema LT".

Pharmacokinetic experiments

Mice were randomly assigned to three groups – ibogaine group, noribogaine group and control group. Ibogaine and noribogaine solutions have been prepared *ex tempore* prior to each test by dissolving accurately weighed quantities of the sub-

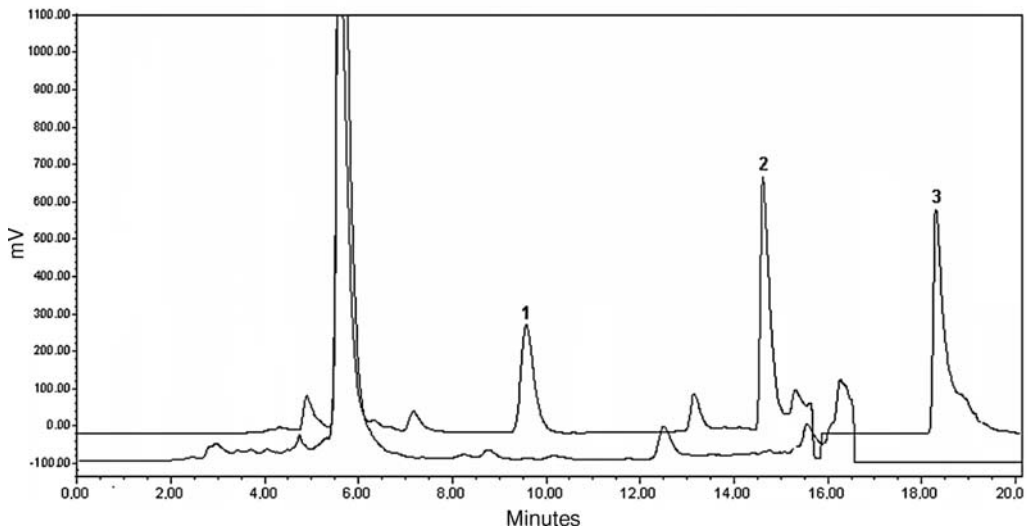

Figure 1. Chromatograms of blank plasma and blank plasma spiked with noribogaine (peak 1), ibogaine (peak 2) and fluoresceine (peak 3)

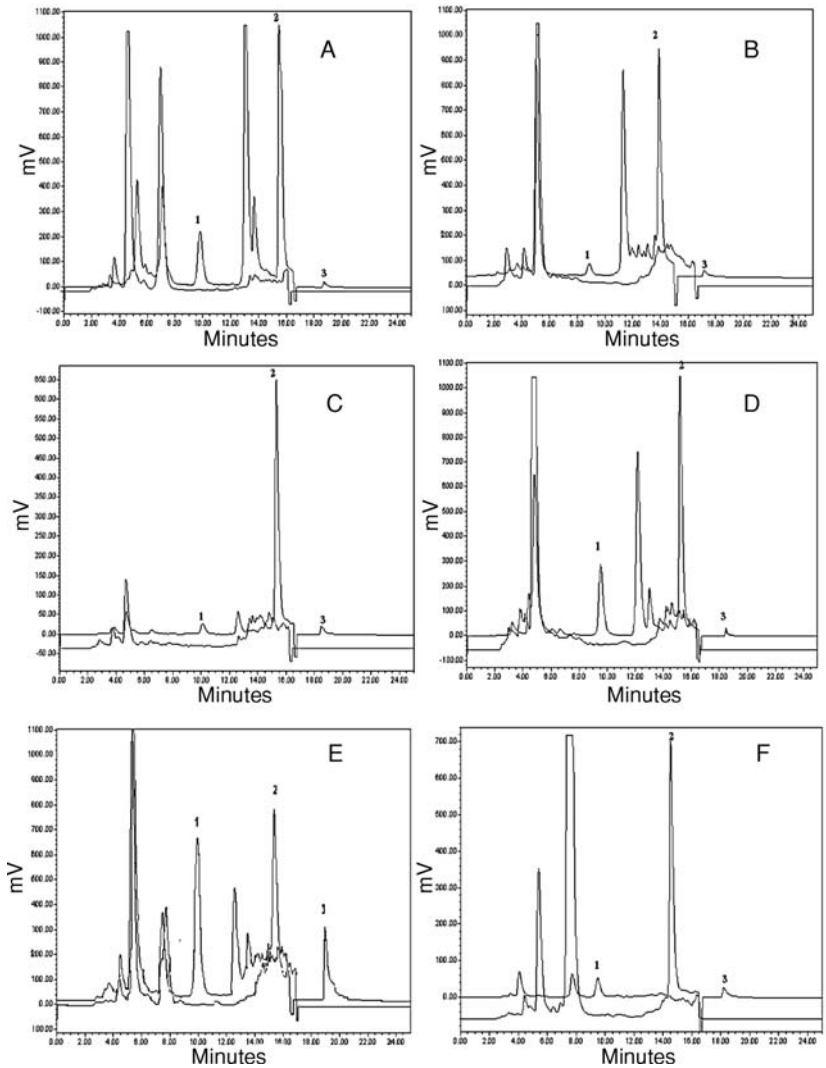

Figure 2. Chromatograms obtained from liver (A), spleen (B), heart (C), kidney (D), brain (E), muscle (F) of tested and control mice. Peak 1 – noribogaine, peak 2 – ibogaine, peak 3 -fluoresceine

stance in deionized water. The volume of solution was recalculated in accordance with the weight of each mouse (e.g., for the mouse of the weight of 25 g – 0.25 mL of prepared solution). Single dose of ibogaine (26.3 mg/kg) and noribogaine (31.5 mg/kg) were administered intragastrically to mice *via* a specially designed stomach tube. Control mice received the same amount of saline. The same method of administration was used.

Animals were dislocated and decapitated 15 min, 30 min, 2 h, 4 h, 6 h, 8 h, 16 h, 24 h, 48 h after the intragastric administration of substance. Three mice were decapitated in each time interval. The blood was collected to centrifugal tube with 25 μL of heparin, centrifuged and collected blood plasma was frozen in the temperature of -40^{o}C. Prepared internal organs (liver, kidney, brain, heart, spleen and muscle) were frozen in the temperature of -40^{o}C until the time of assay by high performance liquid chromatography (HPLC).

Ibogaine and noribogaine concentrations were determinated by HPLC with fluorescence detector. Solid-phase extraction (SPE) was used for the removal of proteins and interfering components. Analytical procedure from plasma and organs and chromatographic analysis were described in previous study (12). The HPLC method validation parameters in our study were specificity, precision

(intermediate precision), linearity and lower limit of quantitation. The specificity of the method was investigated by analyzing three different batches of blank human plasma samples. It shows, that peaks in blank plasma did not impede the identification of the tested materials (Fig. 1).

The same results were obtained analyzing internal organs of tested and control mice (Fig. 2).

RSD were calculated: it was 5.1% for noribogaine and 6.9% for ibogaine. The LLOQs (lower limit of quantitation) were 1.4 ng/mL for ibogaine and 2.15 ng/mL for noribogaine. The correlation coefficients (r) for calibration curves were equal to or better than 0.98 (12).

Pharmacokinetic parameters were calculated by using pharmacokinetic program "Kinetica" (4.0 version, USA). Calculated pharmacokinetic parameters include the following: volume of distribution (Vd), area under curve (AUC), elimination half-life ($T_{1/2}$), maximum concentration (C_{max}). Pharmacokinetic (AUC_{tot}, C_{max}, T_{max}, $T_{1/2}$,) variables were analyzed by non-compartmental model following a trapezoidal rule.

RESULTS

Pharmacokinetic profiles in plasma

Table 1 summarizes the pharmacokinetic parameters for ibogaine and noribogaine after intragastrically administration of ibogaine (26.3 mg//kg) or noribogaine (31.5 mg/kg). Noribogaine was detected in plasma and organs after administration of either ibogaine or noribogaine. The metabolite was detected at the earliest time point (15 min), consistent with first pass metabolism of the parent drug (13).

Figure 3 illustrates the time-concentration profiles for ibogaine and noribogaine in blood plasma. Following intragastric administration circulating levels of ibogaine and noribogaine peaked at 30 min (T_{max}) after ibogaine administration. Noribogaine C_{max} (185 ± 0.02 ng/mL) was much less than that of ibogaine (475 ± 0.05 ng/mL), inconsistent with previous reports (14), giving a noribogaine-to-ibogaine C_{max} ratio of 0.39. These data show, a much smaller fraction of ibogaine is metabolically converted to noribogaine when ibogaine is administered intragas-

Table 1. Basic pharmacokinetic parameters of ibogaine and noribogaine in plasma of mice.

Pharmacokinetic parameters	Ibogaine after ibogaine	Noribogaine after ibogaine	Noribogaine after noribogaine
T_{max}, (h)	0.5 ± 0.015	0.5 ± 0.01	4 ± 0.02
Peak plasma concentration C_{max} (ng/mL)	475 ± 0.05	185 ± 0.02	150 ± 0.02
Elimination half-life $T_{1/2}$ (h)	1.95 ± 0.11	4.42 ± 0.09	6.14 ± 0.21
Volume of distribution Vd (mL/mg)	0.04 ± 0.01	0.20 ± 0.01	0.37 ± 0.05
Clearance CL (mL/h/mg)	0.015 ± 0.00	0.03 ± 0.001	0.04 ± 0.001

Data represent the mean ± SD values from individual animals (n = 3) assayed in duplicate

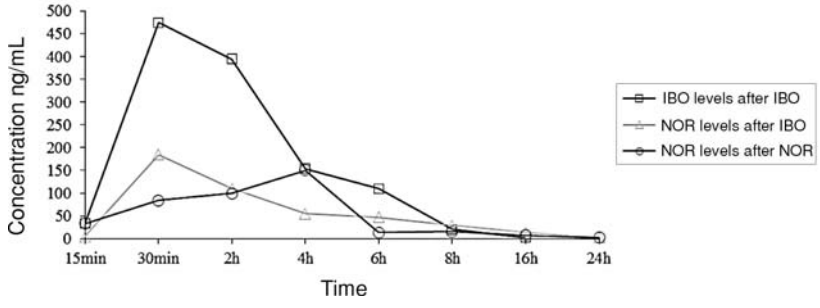

Figure 3. Time-concentration profiles for ibogaine (IBO) and noribogaine (NOR) in plasma of mice after intragastric administration of ibogaine (26.3 mg/kg) or noribogaine (31.5 mg/kg) (n = 3)

Table 2. Basic pharmacokinetic parameters (n = 3) of ibogaine and noribogaine in organs of mice (mean ± SD).

Ibogaine after ibogaine	Spleen	Liver	Heart	Kidney	Brain	Muscle
T_{max}, (h)	4 ± 0.02	0.5 ± 0.015	0.25 ± 0.00	2.0 ±0.1	4.0 ± 0.06	4.0 ± 0.2
C_{max} (ng/mg)	4.88 ± 0.11	2.04 ± 0.11	1.47 ± 0.08	1.25 ± 0.09	0.3 ± 0.02	0.39 ± 0.07
AUC_{tot} (ng×h/mg)	134.54 ± 34.49	10.16 ± 0.64	38.85 ± 5.67	40.37 ± 2.07	3.55 ± 0.31	2.75 ± 0.40

Noribogaine after ibogaine	Spleen	Liver	Heart	Kidney	Brain	Muscle
T_{max}, (h)	4 ± 0.015	0.5 ± 0.00	4 ± 0.2	2 ± 0.01	0.5 ± 0.15	2 ± 0.1
C_{max} (ng/mg)	15.49 ± 0.08	12.05 ± 0.10	0.60 ± 0.08	7.32 ± 0.12	1.95 ± 0.14	1.71 ± 0.09
AUC_{tot} (ng×h/mg)	97.23 ± 0.16	35.55 ± 0.08	9.57 ± 1.34	40.33 ± 0.53	9.48 ± 0.29	9.28 ± 0.54

Noribogaine after noribogaine	Spleen	Liver	Heart	Kidney	Brain	Muscle
T_{max}, (h)	0.5 ± 0.03	2 ± 0.015	4 ± 0.5	0.5 ± 0.00	2.0 ± 0.15	2.0 ± 0.1
C_{max} (ng/mg)	2.23 ± 0.10	15.55 ± 0.09	0.91 ± 0.04	6.04 ± 0.10	4.92 ± 0.11	3.05 ± 0.11
AUC_{tot} (ng×h/mg)	15.29 ± 0.57	97.92 ± 1.44	26.03 ± 1.92	30.26 ± 0.54	24.27 ± 0.58	14.05 ± 0.41

Data represent the mean ± SD values from individual animals (n = 3) assayed in duplicate.

trically. Plasma levels of ibogaine were undetectable 24 h, but plasma levels of noribogaine were 2.5 ± 0.01 ng/mL after intragastrically administration of ibogaine. The mean Vd of ibogaine in plasma was 0.04 ± 0.01 mL/mg body weight and the mean $T_{1/2}$ was 1.95 ± 0.11 h in agreement with previous reports (10, 15). The mean Vd of noribogaine after ibogaine administration was 0.20 ± 0.01 mL/mg and $T_{1/2}$ was 4.42 ± 0.09 h.

Circulating levels of noribogaine increased slowly to a peak (150 ± 0.02 ng/mL) at 4 h (T_{max}) after intragastric administration of noribogaine. Plasma levels of noribogaine decreased rapidly but it was 2.5 ± 0.01 ng/mL 24 h after noribogaine administration. The mean Vd of noribogaine was 0.37 ± 0.05 mL/mg body weight and the mean $T_{1/2}$ was 6.14 ± 0.21 h.

Pharmacokinetic profiles in organs

The main data of pharmacokinetic parameters for ibogaine and noribogaine in organs of mice are presented in Table 2. The results demonstrate that ibogaine and noribogaine are rapidly detected in organs following intragastrically administration of ibogaine or noribogaine. Four hours after intragastrically administration to mice, ibogaine was found in high concentration in spleen (4.88 ± 0.11 ng/mg) and the lower in brain (0.3 ± 0.02 ng/mg). The longest total systemic exposure (AUC_{tot}) was to spleen (134.54 ± 34.49 ng×h/mg) and the smallest – to muscle (2.75 ± 0.40 ng×h/mg) and brain (3.55 ± 0.31 ng×h/mg).

The highest concentration of noribogaine was found in the spleen too (15.49 ± 0.08 ng/mg) after ibogaine administration and in the liver (15.55 ± 0.09 ng/mg) after administration of noribogaine. The lowest levels of noribogaine were in heart after ibogaine or noribogaine administration. The longest total exposure of noribogaine calculated to spleen (97.23 ± 0.16 ng×h/mg) after ibogaine administration and to liver (97.92 ± 1.44 ng×h/mg) after administration of noribogaine. Whereas the smallest were to muscle (9.28 ± 0.54 ng×h/mg), brain (9.48 ± 0.29 ng×h/mg) and heart (9.57 ± 1.34 ng×h/mg) after ibogaine and to muscle (14.05 ± 0.41 ng×h/mg) and spleen (15.29 ± 0.57 ng×h/mg) after noribogaine administration.

DISCUSSION AND CONCLUSIONS

It is known that administration of ibogaine to primates leads to formation of metabolite – noribogaine (7, 8). The circulating time and concentration of metabolite noribogaine depend on route of administration of ibogaine. It is estimated that a substantial fraction of ibogaine is metabolically converted to noribogaine when ibogaine is given *via* the *i.p.* route and much smaller fraction of ibogaine is converted to noribogaine after *i.v.* administration of ibogaine (10). The present results demonstrate, that

noribogaine C_{max} was lower than that of ibogaine after intragastrically administration of ibogaine, inconsistent with previous reports (14, 16). Previous studies have shown that the ratio of noribogaine to ibogaine in the bloodstream is much higher when ibogaine is injected by the *i.p.* route rather than *i.v.* route (10). We observed that the ratio of noribogaine to ibogaine after intragastrically ibogaine administration is higher rather after *i.v.* injection but lower rather *i.p.* injection. Comparing our results with literature data, we can conclude that the peak concentration of noribogaine is achieved faster (T_{max} 0.5 h) when ibogaine is administrated intragastrically rather than the *i.p.* route (T_{max} 2.4 h) or *i.v.* route (T_{max} 2.2 h) (10).

Our results demonstrate that volume of distribution (Vd) of noribogaine reaches a higher values than ibogaine after intragastric administration of either ibogaine or noribogaine. Low values of half-life and Vd of ibogaine show the faster elimination from plasma in agreement with previous reports (17) indicating that long-lasting effect of ibogaine attributable to metabolite (7, 18).

However, a major aim of the present study was to compare the pharmacokinetic properties of noribogaine after administrations of ibogaine and noribogaine. Our results demonstrate that noribogaine achieves higher concentration in a shorter period of time in plasma after administration of ibogaine rather than noribogaine itself inconsistent with report of Zubaran et al. (14). However, peak concentration occurs at 2-3 h and slow elimination of noribogaine was established in previous reports too (19). Noribogaine is less distributed and elimination is faster after administration of ibogaine. Thus, noribogaine may be more potent in the treatment of drug dependence when noribogaine is administered itself rather than ibogaine althouth its absorbtion is longer.

Data presented in the literature show that pharmacokinetic parameters depend on different route of administration and dose of substance. After *i.p.* and *s.c.* injection of ibogaine in rats, the highest level of the substance is achieved in brain and adipose tissue one hour after administration (18). Whereas present results demonstrate high concentration of ibogaine in spleen 4 hours, and in liver 30 min after intragastrical administration.

Present data in brain tissue show that ibogaine and noribogaine penetrate the blood-brain barrier in agreement with previous reports (10, 13, 14). Noribogaine achieves higher concentration in brain tissue compared with ibogaine after ibogaine administration. However, the concentration of noribogaine in brain are greather after administration of noribogaine than of ibogaine. The concentrations of ibogaine and noribogaine have been measured in rat brain following both oral and *i.p.* administrations (40 mg/kg *i.p.*, 50 mg/kg *per os*) (13, 14, 16). The results for concentrations of noribogaine in lower brain regions (cerebellum and brainstem) after administration of ibogaine were lower, compared to ibogaine. However, the concentrations of noribogaine in the higher regions of the brain (cortex and striatum) were higher after intragastric administration of either ibogaine or noribogaine. The concentrations of noribogaine in all regions of brain were much greater after administration of noribogaine than after ibogaine (13, 14).

Literature data show, that ibogaine can lead to serious cardiac-rhythm abnormalities (20-24). So, we compared total systemic exposure in heart to ibogaine and noribogaine. High values of AUC_{tot} allow to agree with these statements. Furthermore, high value of AUC_{tot} of noribogaine suggests, that noribogaine can lead this abnormalities too. Unfortunately, additional experiments are needed to determine effects of noribogaine on the cardiovascular system. Although it is believed that noribogaine constitutes the major cardiac risk after ibogaine intake (17).

Interestingly, concentration of ibogaine and noribogaine increases in spleen, liver and brain, while concentration in blood plasma is already declining. Ibogaine is sequestered in fat (18). Another depot might be the platelets or other blood components, as concentrations of ibogaine were higher in the whole blood than in plasma (25). It could affect the resultss of our study, whereas we tested plasma of mice (which does not contain the platelets), while spleen and liver are tissues of higher blood perfusion (i.e., platelets can affect the results of ibogaine and noribogaine concentrations). Partitioning of the parent drug into brain lipid may serve as a slow release storage "'depot" (13). It can lead to concentration of ibogain eincreasing in the brain even when the concentration in plasma already declines.

We observed that noribogaine C_{max} exceed that of ibogaine in liver, kidney and brain of mice after ibogaine administration. This finding is consistent with the conversion of ibogaine to noribogaine *via* first-pass metabolism in the liver, as previously reported (6, 10, 26). Noribogaine C_{max} (7.32 ± 0.12 ng/mg in kidney, 1.95 ± 0.14 ng/mg in brain) exceeded that of ibogaine (1.25 ± 0.09 ng/mg in kidney, 0.3 ± 0.02 ng/mg in brain) to yield a noribogaine-to-ibogaine C_{max} ratio of 5.86 in kidney and 6.5 in brain. These results confirm the hypothesis

that ibogaine is *o*-demethylated to noribogaine in brain (13) and possibly in kidney. However, more further studies are needed to estimate this.

The present results demonstrate a widespread distribution of ibogaine and noribogaine throughout the body after ibogaine and noribogaine administration. However, some of the results are difficult to explain, for example low values of SD for C_{max} or long absorption of noribogaine after administration of noribogaine. It may be affected by our chosen non-compartment model and low number of animals. Although an increasing number of pharmacokinetic studies of ibogaine and noribogaine are in scientific databases (16, 18, 19, 26, 27), but different results lead us to extend studies using two-compartment or even multi-compartment model and compare the results.

High concentration and AUC_{tot} of noribogaine in brain could be more efficacious alternative to ibogaine as a medication for the treatment of addiction. High values of AUC_{tot} in heart samples may determine the long elimination from this organ. So, further studies, can noribogaine as ibogaine lead to cardiovascular abnormalities, are needed. Noribogaine C_{max} ratio with ibogaine C_{max} in kidney and brain after ibogaine administration may also result in metabolism of alkaloid in these organs.

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