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Ascending-Dose Study of Noribogaine in Healthy Volunteers: Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability

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Abstract

Noribogaine is the active metabolite of the naturally occurring psychoactive substance ibogaine, and may help suppress withdrawal symptoms in opioid-dependent subjects. The objectives of this Phase I study were to assess the safety, tolerability, pharmacokinetic, and pharmacodynamic profiles of noribogaine. In this ascending single-dose, placebo-controlled, randomized, double-blind, parallel-group study in 36 healthy drug-free male volunteers, 4 cohorts (n = 9) received oral doses of 3, 10, 30, or 60 mg or matching placebo, with intensive safety and pharmacokinetic assessments out to 216 hours, along with pharmacodynamic assessments sensitive to the effects of mu-opioid agonists. Noribogaine was rapidly absorbed, with peak concentrations occurring 2–3 hours after oral dosing, and showed dose-linear increases of area under the concentration–time curve (AUC) and C_{max} between 3 and 60 mg. The drug was slowly eliminated, with mean half-life estimates of 28–49 hours across dose groups. Apparent volume of distribution was high (mean 1417–3086 L across dose groups). No safety or tolerability issues were identified in any cohort. No mu-opioid agonist pharmacodynamic effects were noted in pupillometry or cold-pressor testing. Single oral doses of noribogaine 3–60 mg were safe and well tolerated in healthy volunteers.

Keywords

noribogaine, first-in-man, pharmacokinetics, pharmacodynamics, safety

Ibogaine is a naturally occurring psychoactive chemical from the roots of the *Tabernanthe iboga* plant. It has been used for centuries in low doses to help combat hunger, thirst, and fatigue, and in high doses to provoke dream-like hallucinations for spiritual rituals.[1,2] In 1962, a group of lay drug experimenters found that single high doses of ibogaine prevented withdrawal symptoms in heroin-dependent subjects, and could facilitate abstinence in previously opioid-dependent subjects via reduced drug craving.[3,4] Subsequent research identified that ibogaine was rapidly converted into an active metabolite, noribogaine,[5] which was eliminated much more slowly than ibogaine, and thus might contribute to the anti-withdrawal and anti-craving effects.[6] Although there are potency differences, ibogaine and noribogaine have similar pharmacologies, interacting with N-methyl-D-aspartate (NMDA) and opioid receptors and serotonin transporters.[4] Noribogaine may have advantages over ibogaine in terms of acute stress effects[6] and acute toxicity in mice.[7] As the first step in a program to evaluate the role of noribogaine in managing symptoms of opioid withdrawal, this is a report of an ascending dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single doses of noribogaine administered to healthy volunteers.

Methods

The objectives of this study were to evaluate the safety and tolerability, pharmacokinetics, and pharmacodynamics of noribogaine in healthy volunteers. The protocol for this study was approved by the Lower South Regional Ethics Committee (LRS/12/06/015), and the study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12612000821897). This was an ascending single-dose, placebo-controlled, randomized double blind, parallel group study in 36 healthy drug-free male volunteers aged between 18 and 55 years, performed

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at the Zenith Technology Clinical Trials Unit. All subjects provided signed informed consent prior to enrollment, and were assessed as suitable to participate based on review of medical history, physical examination, safety laboratory tests, vital signs, and electrocardiograms (ECG). There were 4 ascending dose levels (3, 10, 30, and 60 mg). The lowest dose was selected based on preclinical safety studies and the 2005 FDA Dose selection guidance.[8] Within each dose level, 6 participants were randomized to receive noribogaine and 3 to receive placebo, based on a computer-generated random code. Dosing began with the lowest noribogaine dose, and subsequent cohorts received the next highest dose after the blinded safety, tolerability, and pharmacokinetics of the completed cohort were reviewed and dose-escalation approved by an independent Data Safety Monitoring Board. Blinded study drug was administered as a capsule with 240 mL of water after an overnight fast of at least 10 hours. Participants did not receive any food until at least 5 hours post-dose. Participants were confined to the study site from 12 hours prior to drug administration, until 72 hours post-dose, and there were subsequent outpatient assessments until 216 hours post-dose.

Blood was obtained for pharmacokinetic assessments pre-dose and then at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 14, 18, 24, 30, 36, 48, 60, 72, 96, 120, 168, and 216 hours post-dose. Samples were centrifuged and plasma stored at −70 °C until analyzed. Block, 24-hour urine collections were obtained following study drug administration for the 30 and 60 mg cohorts. Aliquots were frozen at −20 °C until analyzed.

Because of noribogaine's expected mu-opioid agonist pharmacology, pharmacodynamic assessments sensitive to mu-agonist effects were selected to assess exposure–response relationships, including pupillometry, cold-pressor testing, oximetry, and capnography. Pulse oximetry and capnography data were collected continuously using a GE Carescape B650 monitoring system from 2 hours prior to dosing and until six hours after dosing, and thereafter at 12, 24, 48, and 72 hours post-dosing. Additional oximetry data were collected at 120, 168, and 216 hours. Pupillary miosis was assessed by pupillometry. Dark-adapted pupil diameter was measured in triplicate using a Neuroptics PLR-200 pupillometer under standardized light intensity (<5 lux) pre-dose, and at 2, 4, 6, 12, 24, 48, 72, 96, 120, 168, and 216 hours post-dosing. Cold-pressor testing, to assess analgesic effects, was conducted in 1 °C water according to the method of Mitchell et al[9] pre-dose, 6, 24, 48, 72, and 216 hours post-dosing.

Safety evaluations included clinical monitoring, recording of adverse events (AEs), safety laboratory tests, vital signs, ECG telemetry from −2 h to 6 h after dosing, and 12-lead ECGs pre-dose and at 1, 2, 4, 6, 12, 24, 48, 72, 120, and 216 hours post-dosing after 5 minute rest.

There were 2 validated LCMSMS chromatography methods and 4 sample preparation methods for the assays of noribogaine and noribogaine glucuronide in plasma and urine.

Noribogaine Capsules (3 and 10 mg Doses)

Plasma noribogaine concentrations were determined using a validated, sensitive LCMSMS method. Sample preparation involved double extraction of basified plasma samples with tert-butyl methyl ether, drying the samples under a stream of nitrogen and reconstitution of sample with acetonitrile:B.P. water (5:95, v/v) containing 0.1% (v/v) formic acid. The compounds were separated by a 150 × 2.0 mm Luna 5 μm C18 column and detected with a triple–quadrupole API 4000 or 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogaine-d_4 was used as the internal standard. The precursor-product ion transition values for noribogaine were m/z 297.6 to 122.3, and for the internal standard noribogaine-d_4 m/z 301.1 to 122.2. Analyst® software was used for data acquisition and processing. The ratio of the peak area of noribogaine to the internal standard noribogaine-d_4 was used for calibration and measurement of the unknown concentration of noribogaine. The lower limit of quantification (LLOQ) was 0.025 ng/mL noribogaine. The calibration curve was between 0.025 and 25.600 ng/mL noribogaine. Mobile phase A was acetonitrile:B.P. water (5:95, v/v) containing 0.1% (v/v) formic acid, and mobile phase B was acetonitrile:B.P. water (95:5, v/v) containing 0.1% (v/v) formic acid. Total run time was 6 minutes. Binary flow: Initial concentration was 8% mobile phase B; hold at 8% mobile phase B for 0.5 minutes and linear rise to 90% mobile phase B over 1.5 minutes; hold at 90% mobile phase B for 1 minute and then drop back to 8% mobile phase B over 0.01 minute. Equilibrate system for 3 minutes. Total run time was 6 minutes. The within- and between-day assay precision was <9%, and the within- and between-day assay accuracy was <9%.

Noribogaine Capsules (30 and 60 mg Doses)

Plasma noribogaine concentrations were determined using a validated, sensitive LCMSMS method. Sample preparation involved deproteinization of plasma samples with acetonitrile and dilution of sample with 0.1% (v/v) formic acid. The compounds were separated by a 150 × 2.0 mm Luna 5 μm C18 column and detected with a triple–quadrupole API 4000 or 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogaine-d_4 was used as the internal standard. The precursor-product ion transition values for noribogaine were m/z 297.6 to 122.3, and for the internal standard noribogaine-d_4 m/z 301.1 to 122.2. Analyst® software was used for data acquisition and processing. The ratio of the peak area of

noribogaine to the internal standard noribogaine-d_4 was used for calibration and measurement of the unknown concentration of noribogaine. The LLOQ was 0.50 ng/mL noribogaine. The calibration curve was between 0.50 and 256.00 ng/mL noribogaine. Mobile phase was the same as method A, and binary flow was also the same as method A. The within- and between-day assay precision was <9%, and the within- and between-day assay accuracy was <9%.

Plasma Noribogaine Glucuronide Assay (30 and 60 mg Doses)

Plasma noribogaine glucuronide concentrations were determined in the 30 mg and 60 mg dose groups using a validated sensitive LCMSMS method. Sample preparation involved deproteinization of plasma samples with acetonitrile, drying the samples under a stream of nitrogen and reconstitution of sample with acetonitrile:B.P. water (5:95, v/v) containing 0.1% (v/v) formic acid. The compounds were separated by a 150 × 2.0 mm Luna 5 μm C18 column and detected with a triple–quadrupole API 4000 or 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogaine-d_4 was used as the internal standard. The precursor-product ion transition values for noribogaine glucuronide were m/z 472.8 to 297.3, and for the internal standard noribogaine-d_4 m/z 301.1 to 122.2. Analyst® software was used for data acquisition and processing. The ratio of the peak area of noribogaine glucuronide to the internal standard noribogaine-d_4 was used for calibration and measurement of the unknown concentration of noribogaine glucuronide. The LLOQ was 0.050 ng/mL noribogaine glucuronide. The calibration curve was between 0.050 and 6.400 ng/mL noribogaine glucuronide. Mobile phase was the same as method A. Binary flow: Initial concentration was 6% mobile phase B; hold at 6% mobile phase B for 0.5 minutes and linear rise to 90% mobile phase B over 2 minutes; hold at 90% mobile phase B for 1 minute and then drop back to 6% mobile phase B over 0.01 minute. Equilibrate system for 3.5 minutes. Total run time was 7 minutes. The within- and between-day assay precision was <11%, and the within- and between-day assay accuracy was <10%.

Urine Noribogaine and Noribogaine Glucuronide Assay (for 30 and 60 mg Doses)

Urine noribogaine and noribogaine glucuronide concentrations were determined in the 30 and 60 mg dose groups using a validated sensitive LCMSMS method. Sample preparation involved deproteinization of urine samples with acetonitrile and dilution of the sample with 0.1% (v/v) formic acid. The compounds were separated by a 150 × 2.0 mm Luna 5 μm C18 column and detected with a triple–quadrupole API 5000 mass spectrometer using electrospray ionization in positive mode and multiple reaction monitoring. Noribogaine-d_4 was used as the internal standard. The precursor-product ion transition values for noribogaine were m/z 297.6 to 122.3, noribogaine glucuronide m/z 472.8 to 297.3, and for the internal standard noribogaine-d_4 m/z 301.1 to 122.2. Analyst® software was used for data acquisition and processing. The ratios of the peak area of noribogaine and noribogaine glucuronide to the internal standard noribogaine-d_4 were used for calibration and measurement of the unknown concentration of noribogaine and its glucuronide. Assay LLOQ was 20.0 ng/mL for noribogaine and 2.0 ng/mL for noribogaine glucuronide. The calibration curve was between 20.0 and 5120.0 ng/mL noribogaine, and 2.0–512.0 ng/mL noribogaine glucuronide. Mobile phases were as described in method A, and binary flow as in method C. The within- and between-day assay precision was <13%, and within- and between-day assay accuracy was <12%.

Noribogaine and noribogaine glucuronide concentrations above the limit of quantification were used to calculate pharmacokinetic parameters using model-independent methods. The maximum plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}) were the observed values. Plasma concentration data in the post-distribution phase of the plasma concentration–time plot were fitted using linear regression to the formula $\ln C = \ln C_o - t.Kel$, where C_o was the zero-time intercept of the extrapolated terminal phase and Kel was the terminal elimination rate constant. The half-life ($t_{1/2}$) was determined using the formula $t_{1/2} = 0.693/Kel$. The area under the concentration–time curve (AUC) from time zero to the last determined concentration–time point (tf) in the post-distribution phase was calculated using the trapezoidal rule. The area under the curve from the last concentration–time point in the post-distribution phase (C_{tf}) to time infinity was calculated from $AUC_{t-\infty} = C_{tf}/Kel$. The concentration used for C_{tf} was the last determined value above the LLOQ at the time point. The total $AUC_{0-\infty}$ was obtained by adding AUC_{tf} and $AUC_{t-\infty}$. Noribogaine apparent clearance (CL/F) was determined using the formula $CL/F = Dose/AUC_{0-\infty} \times 1{,}000$, and apparent volume of distribution (Vd/F) was determined using the formula $Vd/F = (CL/F)/Kel$. Total urine noribogaine was the sum of both analytes.

Summary statistics (means, standard deviations, and coefficients of variation) were determined for each dose group for safety laboratory test data, ECG and pharmacokinetic parameters, and pharmacodynamic variables. Categorical variables were analyzed using counts and percentages. Dose proportionality of AUC and C_{max} was assessed using linear regression. The effect of dose on pharmacodynamic parameter values over time was assessed using two-factor analysis of variance (ANOVA). Pairwise comparisons (with Tukey–Kramer adjustment) between each dose group to the placebo were conducted at

each time point using the least-squares estimates obtained from the ANOVA, using SAS Proc Mixed (SAS ver 6.0).

Results

Thirty-six healthy male volunteers were enrolled in and completed the study. Mean (SD) age was 22.0 (3.3) years, mean (SD) height was 1.82 (0.08) m, and mean (SD) weight was 78.0 (9.2) kg. Twenty-six subjects were Caucasian, 3 were Asian, 1 Maori, 1 Pacific Islander, and 5 Other.

Pharmacokinetics

Mean plasma concentration–time plots of noribogaine are shown in Figure 1, and mean pharmacokinetic parameters are shown in Table 1. Noribogaine was rapidly absorbed, with the mean time to peak concentrations occurring at approximately 2–3 hours after oral dosing. Fluctuations in individual distribution-phase concentration–time profiles suggest the possibility of enterohepatic recirculation (see highlighted individual 4–8 hour profiles in Figure 1, inset). Both C_{max} and AUC increased linearly with dose (Table 1, upper panel). The drug was slowly eliminated, with mean plasma elimination half-lives of approximately 28–49 hours across dose groups. Volume of distribution was extensive (means ranging from 1417 to 3086 L across dose groups). Mean plasma noribogaine glucuronide concentration–time plots for the 30 and 60 mg dose groups are shown in Figure 2, and mean pharmacokinetic parameters are shown in Table 1, lower panel. Noribogaine glucuronide was detected in all subjects by 0.75 hours, and the mean time to peak concentrations was about 3–4 hours after oral noribogaine dosing, approximately one hour later than noribogaine T_{max}. Plasma noribogaine glucuronide was slowly eliminated, with mean half-life estimates of 21–23 hours. The ratio of the mean noribogaine glucuronide C_{max} and AUC relative to respective means for noribogaine was 3–4% for both dose groups. Mean total urine noribogaine elimination values were 1.16 mg and 0.82 mg for the 30 mg and 60 mg dose groups, respectively, representing 3.9% and 1.4% of the doses administered.

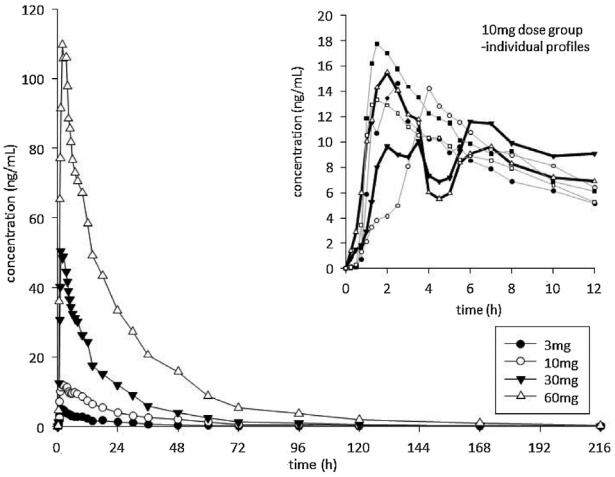

Figure 1. Mean noribogaine concentration–time profiles after single oral dosing with 3, 10, 30, or 60 mg doses. Inset: Individual concentration–time profiles from 0 to 12 hours after a 10 mg dose.

Pharmacodynamics

No between-dose group differences in pupil diameter were detected over time. After adjusting for baseline differences, comparison of each dose group with placebo by ANOVA showed no statistically significant differences ($P > .9$). In particular, there was no evidence of noribogaine-induced pupillary constriction.

There was also no evidence of noribogaine-related analgesic effect in the cold-pressor test. This was assessed in two ways: duration of hand immersion in ice water, and visual analog scale (VAS) pain scores upon hand removal from the water bath. For time to hand removal, after adjusting for baseline differences, comparison of each dose group with placebo by ANOVA showed no statistically significant differences ($P > .9$). Similarly, for VAS pain scores, after adjusting for baseline differences, comparison of each dose group with placebo by ANOVA showed no statistically significant differences ($P = .17$).

Safety

A total of 13 treatment emergent adverse events were reported by 7 participants (Table 2). Six adverse events were reported by 3 participants in the placebo group, 5 adverse events were reported by 2 subjects in the 3 mg dose group, and 1 adverse event was reported by single subjects in the 10 mg and 30 mg dose groups, respectively. The most common adverse events were headache (4 reports) and epistaxis (2 reports). All adverse events were of mild or moderate intensity, and all resolved prior to study completion. There were no changes in vital signs or safety laboratory tests of note. In particular, there were no changes in oximetry or capnography, or changes in respiratory rate. There were no QTcF values >500 milliseconds at any time. One subject dosed with 10 mg noribogaine had a single increase in QTcF of >60 milliseconds at 24 hours post-dosing.

Discussion

To our knowledge, this was the first study of noribogaine administered to humans. Noribogaine doses from 3 to 60 mg were safe and well tolerated. Noribogaine was rapidly absorbed, slowly eliminated, and had a large volume of distribution. Mean noribogaine AUC and C_{max} increased linearly with dose over the range examined. No evidence of noribogaine-related mu-agonist activity was

Table 1. Mean (SD) Plasma Noribogaine Pharmacokinetic Parameters for All Dose Groups, and Mean (SD) Plasma Noribogaine Glucuronide Pharmacokinetic Parameters for the 30 and 60 mg Dose Groups

Noribogaine	3 mg (n = 6)(Mean [SD])	10 mg (n = 6)(Mean [SD])	30 mg (n = 6)(Mean [SD])	60 mg (n = 6)(Mean [SD])
$AUC_{0-\infty}$ (ng h/mL)	74.2 (13.1)	254.5 (78.9)	700.4 (223.3)	1962.2 (726.5)
C_{max} (ng/mL)	5.2 (1.4)	14.5 (2.1)	55.9 (14.8)	116.0 (22.5)
T_{max} (hours)	1.9 (0.6)	2.9 (1.8)	1.8 (0.6)	2.4 (0.6)
$t_{1/2}$ (hours)	40.9 (8.7)	49.2 (11.5)	27.6 (7.0)	29.1 (9.3)
Vd/F (L)	2485.1 (801.5)	3085.8 (1197.0)	1850.8 (707.9)	1416.8 (670.1)
CL/F (L/h)	41.4 (7.0)	42.3 (12.0)	46.9 (16.4)	34.0 (11.4)
Noribogaine glucuronide				
$AUC_{0-\infty}$ (ng h/mL)	–	–	25.8 (9.3)	67.1 (21.9)
C_{max} (ng/mL)	–	–	1.8 (0.6)	4.1 (1.2)
T_{max} (hours)	–	–	3.0 (0.6)	3.8 (1.2)
$t_{1/2}$ (hours)	–	–	20.6 (4.9)	23.1 (3.0)

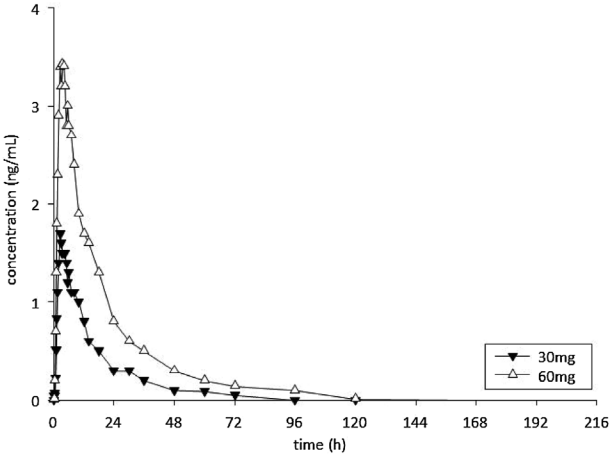

Figure 2. Mean plasma noribogaine glucuronide concentration–time profiles after single oral 30 or 60 mg doses.

noted in pharmacodynamic assessments sensitive to effects of mu-opioid agonists.

Both ibogaine and noribogaine interact most potently with the serotonin transporter, with lower affinities for mu- and kappa-opioid receptors and NMDA glutamatergic receptors.[1,4] Noribogaine is an antagonist of the serotonin transporter (SERT; Ki = 0.04 nM),[9] and prior to the study we anticipated adverse effects such as nausea and insomnia might be seen at higher doses. However, these adverse effects were not reported, nor were there other adverse events that appeared to be associated with noribogaine. Uniquely, noribogaine interacts noncompetitively with SERT, in contrast to (eg) the competitive inhibitor cocaine, to produce an inward-facing conformation of the transporter.[10] Although it is possible that the absence of typical serotonergic side effects is dose related (ie that these might occur at doses >60 mg), it is possible that the unique pharmacology of noribogaine at SERT also affects its clinical tolerability.

Table 2. Reported Adverse Events by Dose Group and by Severity

Dose (mg)	Mild	Moderate	Severe
Placebo	Blepharitis	Epistaxis	–
	Bruising		
	Dry skin		
	Eye pain, nonspecific		
	Infection at cannula site		
3	Back pain	Headache	–
	Dizziness		
	Epistaxis		
	Headache		
10	Headache	–	–
30	Headache	–	–
60	–	–	–

Noribogaine has low micromolar affinity for mu-opioid receptors.[11] Originally this interaction was reported to be agonist activity[12]; however, a very recent publication has identified this to reflect either antagonism or weak partial agonism in a number of in vitro models.[13] Our negative pharmacodynamic findings would be consistent with a lack of mu-agonist activity for noribogaine at dose up to 60 mg. In contrast, the pharmacodynamic effect of the mu-agonist morphine is seen at doses of 8 mg on pupillary constriction,[14] and at 10 mg for longer time to hand removal from an ice water bath in male subjects.[15] Respiratory rate, oximetry, and capnography, which are also affected by mu-agonists, were also unchanged by noribogaine up to 60 mg.

There were no noribogaine-related changes noted in vital signs or safety laboratory tests at any of the doses tested. Noribogaine has been reported to interact with hERG channels (ED50 = 5 μM; Demerx, data on file). Noribogaine has a molecular weight of 296 Da, so the reported IC50 value corresponds to a concentration of ~1,500 ng/mL, approximately 13-fold higher than the mean C_{max} values at 60 mg.

Published data on the human pharmacokinetics of noribogaine are limited to a report of 24 hour whole blood data, as a metabolite, from patients dosed with ibogaine.[4] Our study shows that noribogaine is rapidly absorbed and slowly eliminated, with dose-linear increases in AUC and C_{max}. The prolonged elimination could reflect a number of

processes: enterohepatic circulation (see inset, Figure 1), a high volume of distribution reflecting its lipophilicity (predicted logP = 3.880),[16] and likely slow metabolic clearance mechanisms. In this study, the proportion of plasma noribogaine glucuronide relative to parent was very small (3–4% for AUC and C_{max}), consistent with the in vitro metabolic data. We also found that renal clearance of noribogaine and its glucuronide was very low, comprising 1.4–3.9% of the dose administered.

In conclusion, single 3–60 mg noribogaine doses were safe and well tolerated in healthy male volunteers. Noribogaine was rapidly absorbed and slowly eliminated, with dose-linear increases in AUC and C_{max}. There was no evidence of mu-opioid agonist effects at doses up to 60 mg in a number of sensitive pharmacodynamic tests. The results of this study support the further development of noribogaine as a treatment for drug dependence.

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Declaration of Conflicting Interests

This research was funded by Demerx Inc. Dr Friedhoff is a paid consultant of Demerx.

Author Contributions

Study design: PG, NH, CTH, FL, LF; ethics and regulatory submission: ML, NH, CTH, PG; Principal Investigator: PG; data collection: PG, NH; study monitoring: ML; data analysis: FL; data review and interpretation: all authors.

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