Original Article

Ascending Single-Dose, Double-Blind, Placebo-Controlled Safety Study of Noribogaine in Opioid-Dependent Patients

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Abstract

Ibogaine is a psychoactive substance that may reduce opioid withdrawal symptoms. This was the first clinical trial of noribogaine, ibogaine's active metabolite, in patients established on methadone opioid substitution therapy (OST). In this randomized, double-blind, placebo-controlled single ascending-dose study, we evaluated the safety, tolerability, and pharmacokinetics of noribogaine in 27 patients seeking to discontinue methadone OST who had been switched to morphine during the previous week. Noribogaine doses were 60, 120, or 180 mg (n = 6/dose level) or matching placebo (n = 3/dose level). Noribogaine was well tolerated. The most frequent treatment-emergent adverse events were non-euphoric changes in light perception ~1 hour postdose, headache, and nausea. Noribogaine had dose-linear increases for AUC and C_{max} and was slowly eliminated (mean $t_{1/2}$ range, 24–30 hours). There was a concentration-dependent increase in QTcI (0.17 ms/ng/mL), with the largest observed mean effect of ~16, 28, and 42 milliseconds in the 60-, 120-, and 180-mg groups, respectively. Noribogaine showed a nonstatistically significant trend toward decreased total score in opioid withdrawal ratings, most notably at the 120-mg dose; however, the study design may have confounded evaluations of time to resumption of OST. Future exposure-controlled multiple-dose noribogaine studies are planned that will address these safety and design issues.

Keywords

noribogaine, first-in-patient, pharmacokinetics, opioid withdrawal, QTc

Ibogaine is one of several indole alkaloids present in the root bark of *Tabernanthe iboga*, a West African rainforest shrub. Ritual eating of root bark is sacramental in the Bwiti religion (eg, in young men undergoing adult initiation rituals), where it has psychedelic effects.[1] Since 1962, ibogaine has been reported to improve opioid withdrawal symptoms and opioid cravings, based on lay reports and case series.[2] To date, ibogaine has not been evaluated in randomized controlled trials. Its mechanism of action is unclear. Subsequent research has identified ibogaine as being rapidly converted oxidatively to an active metabolite, noribogaine,[3] which is eliminated much more slowly than ibogaine and thus might contribute to its antiwithdrawal and anticraving effects.[4] Noribogaine is cleared via a number of oxidation, sulfation, and glucuronidation pathways (data on file, DemeRx). We recently reported on the safety, tolerability, pharmacokinetics, and pharmacodynamics of single 3- to 60-mg doses of noribogaine administered to healthy volunteers.[5]

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The objectives of the present study were to evaluate the safety and tolerability, pharmacokinetics, and pharmacodynamics of single-dose noribogaine in patients seeking to discontinue methadone opioid substitution treatment (OST).

Methods

The protocol and consent forms for this study were approved by the Southern Health and Disabilities Ethics Committee (13/STH/100), and the study was registered with the Australian New Zealand Clinical Trial Registry (ACTRN12613001064796). All testing occurred at the Zentech Clinical Trials Unit in Dunedin, New Zealand. This was an ascending single-dose, placebo-controlled, randomized, double-blind, parallel-group study in 27 patients established on methadone OST aged 18 years or older. Patient inclusion criteria included being established on methadone OST at 25–80 mg/day for at least 30 days prior to screening, being aged 18 years or older, and having no evidence of acute or serious chronic medical or surgical disorders or conditions determined to be clinically significant at screening. 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 electrocardiogram (ECG). There were 3 ascending-dose levels (60, 120, and 240 mg). The upper dose was selected based on an analysis of unpublished safety and pharmacokinetic data (Dr Deborah Mash; data on file, DemeRx). During review of blinded safety data after the first 2 dose groups, including ECG interval measurements from safety ECGs, QT prolongation was observed in the 120-mg group, leading to a recommendation to reduce the next dose escalation to 180 mg, which was endorsed by the study's independent Data Safety Monitoring Board (DSMB). 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 the DSMB.

In the week before noribogaine/placebo dosing, methadone was replaced by oral controlled-release morphine capsules (M-Eslon) for 6 days, followed by 1 day of oral immediate-release morphine (this is described in more detail elsewhere[6]). After an overnight fast of at least 10 hours, the last morphine dose was given at 6 AM on day 1, and at ~8 AM blinded noribogaine or placebo capsules were administered with 240 mL of water. Participants did not receive food until at least 5 hours postdose. Participants were confined to the study site from 24 hours prior to noribogaine/placebo dosing until 72 hours postdose, and there were subsequent outpatient and telephone assessments until 35 days postdose. Participants who requested resumption of OST were given morphine (if this occurred within 24 hours of noribogaine/placebo dosing) or methadone (later than 24 hours). Participants restarted on OST were released to the care of the local OST clinical service after discharge from the study site.

Blood was obtained for pharmacokinetic assessments predose and then 0.5, 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12, 16, 24, 36, 48, 60, 72, 96, 120, and 144 hours postdose. Samples were centrifuged and plasma stored at -70°C until analyzed.

Pharmacodynamic assessments sensitive to mu-opioid-agonist effects, and withdrawal included pupillometry, 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 6 hours after dosing and thereafter 12, 24, 48, and 72 hours postdosing. Additional oximetry data were collected at 120, 168, and 216 hours. Pupil diameter in ambient lighting conditions (200 lux) was assessed by pupillometry using a Neuroptics PLR-200 pupillometer predose, and 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours postdosing. Opioid withdrawal was evaluated in several ways: time to resumption of OST, measured from the time of the last dose of oral morphine at 6 AM on day 1 until the time at which morphine/methadone was next taken; and Subjective, Objective, and Clinical Opioid Withdrawal Scales (SOWS, OOWS, and COWS) ratings,[7,8] taken predose and 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 144 hours postdose, at time of OST resumption, and 2 hours thereafter.

Safety evaluations included physical examinations, recording of adverse events (AEs), safety laboratory tests, vital signs, ECG telemetry from -2 to 6 hours after dosing, 12-lead safety ECGs, and continuous ECG recordings. Safety ECGs were recorded with GE Carescape B650 equipment on day 1 prior to dosing of blinded, randomized study treatment (placebo or noribogaine) and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72 96, 120, and 144 hours postdosing. ECGs were reviewed on site by the investigator for safety monitoring, and machine-generated interval data were collected. Continuous ECG recordings were performed on the day of study treatment (day 1) and the day before (day -1), using Global Instrumentation (Manlius, New York) M12R Holter recorders. Continuous 12-lead digital ECG data were stored onto SD memory cards and were analyzed by the central ECG laboratory (iCardiac Technologies, Rochester, New York). Up to 10 replicate ECGs were extracted from the continuous recording at the following times, when subjects were resting: predose

and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 12, 16, and 24 hours postdose and corresponding clock times on day -1. ECG intervals were measured by the high-precision QT technique, as previously described.[9]

Plasma noribogaine concentrations were determined using a validated, sensitive liquid chromatography–tandem mass spectrometry 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 → 122.3, and for the internal standard noribogaine-d_4 m/z 301.1 → 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 quantitation (LLOQ) was 0.50 ng/mL noribogaine. The calibration curve was between 0.50 and 256.00 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. For binary flow, initial concentration was 8% mobile phase B; then held at 8% mobile phase B for 0.5 minutes and linear rise to 90% mobile phase B over 1.5 minutes; held at 90% mobile phase B for 1 minute and then dropped back to 8% mobile phase B over 0.01 minutes. Equilibrate system for 3 minutes. Total run time was 6 minutes. Within- and between-day assay precision was <9%, and within- and between-day assay accuracy was <9%.

Noribogaine concentrations above the lower limit of quantication 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 is the zero-time intercept of the extrapolated terminal phase and Kel is the terminal elimination rate constant. The half-life ($t_{1/2}$) was determined using the formula $t_{1/2} = 0.693/\text{Kel}$. 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 $AUC_{t\text{-}\infty} = C_{tf}/\text{Kel}$. The concentration used for C_{tf} was the last determined value above the LLOQ at that 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 $\text{CL/F} = \text{dose}/AUC_{0-\infty} \times 1000$, and apparent volume of distribution (V_d/F) was determined using the formula $V_d/F = (\text{CL/F})/\text{Kel}$.

Summary statistics (means, standard deviations, and coefficients of variation) were determined for each dose group for safety laboratory test data, safety ECGs, pharmacokinetic parameters, and pharmacodynamic variables including time to OST resumption. Categorical variables were analyzed using counts and percentages. Dose-proportionality of AUC and C_{max} was assessed using linear regression. For purposes of safety monitoring on site, 12-lead ECGs were evaluated categorically for QTcF > 500 milliseconds and change from baseline (ΔQTcF) > 60 milliseconds.

QTcF and an individualized heart rate correction method (QTcI) were used for QT assessment, and the cardiodynamic ECGs were extracted on the day of dosing (day 1) and the day before (day -1). QTcI was derived from all QT/RR pairs during the full 24-hour baseline day (day -1) for each subject to calculate that subject's individual correction formula. Based on all QT/RR pairs from each subject, QTcI was derived from a linear regression model: $\log(\text{QT}) = \log(a) + b \times \log(\text{RR})$. The coefficient of log(RR) for each subject, b_i, was then used to calculate QTcI for each subject as follows: $\text{QTcI} = \text{QT}/\text{RR}^{bi}$. To evaluate which of the 2 QTc methods (QTcF and QTcI) best removed the heart rate dependence of the QT interval, the relationship between QTcF and QTcI and the RR interval was investigated using on-treatment data (noribogaine and placebo) by linear regression modeling: $\text{QTc} = a + b \times \text{RR}$. The RR coefficient for each subject, b_i, was then used to calculate the average sum of squared slopes for each of the different QT-RR correction methods, as proposed by the Food and Drug Administration's Interdisciplinary Review Team for QT studies.[10] The correction method that resulted in the slope closest to zero (for on-treatment data) was then used as the primary end point. The change-from-baseline QTc (ΔQTc) was subjected to a linear mixed-effects model with fitting terms for time (categorical), treatment (noribogaine 60, 120, and 180 mg and placebo), and time-by-treatment interaction. Subject was included as a random effect for the intercept. Subjects dosed with placebo were analyzed as a pooled group.

The relationship between plasma concentrations of noribogaine and the placebo-corrected ΔQTcI (ΔΔQTcI) was quantified using a linear mixed-effects modeling approach, using the formula $\Delta\Delta\text{QTcI}_{ij} = \text{intercept}_i + \text{slope}_i \cdot \text{Conc}_{ij} + \varepsilon_{ij}$, where $\Delta\Delta\text{QTcI}_{ij}$ is the

time-matched, placebo-corrected change-from-baseline QTcI for subject i at time j with concentration $Conc_{ij}$. The residual ε_{ij} is assumed to be identical, independent, normally distributed with mean 0 and variance σ^2. Three exposure–response models were considered: (1) a linear model with an intercept, (2) a linear model with mean intercept fixed to 0 (with variability), and (3) a linear model with no intercept. Time-matched concentration was included in the model as a covariate and subject as a random effect for both intercept and slope, whenever applicable. The normal Q-Q plots of the random effects and the within-subject errors were used to investigate the normality of the random effects and the within-subject errors, respectively. A plot of standardized residuals versus fitted values was used to examine departure from model assumptions. A final assessment of the adequacy of the linear mixed-effects model was provided by a goodness-of-fit plot (ie, the observed concentration decile-ΔΔ QTcI plot).[10]

Results

Thirty-four subjects were screened, and 27 (21 male, 6 female) were enrolled in and completed the study. Mean age was 41.2 years, mean height was 1.75 m, mean weight was 81.9 kg, and mean body mass index was 27.0 kg/m^2. Twenty subjects were white, 5 were Maori, and 2 were other. Comorbid diagnoses and concomitant medications are listed elsewhere.[6]

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 3.0–4.4 hours (range, 1–8 hours) across dose groups. Fluctuations in individual distribution-phase concentration–time profiles suggest the possibility of enterohepatic recirculation. Both C_{max} and AUC increased linearly with dose. The drug was slowly eliminated, with mean plasma elimination half-life of approximately 24–30 hours across dose groups. Apparent volume of distribution was extensive (means ranging from 1032 to 2106 L across dose groups).

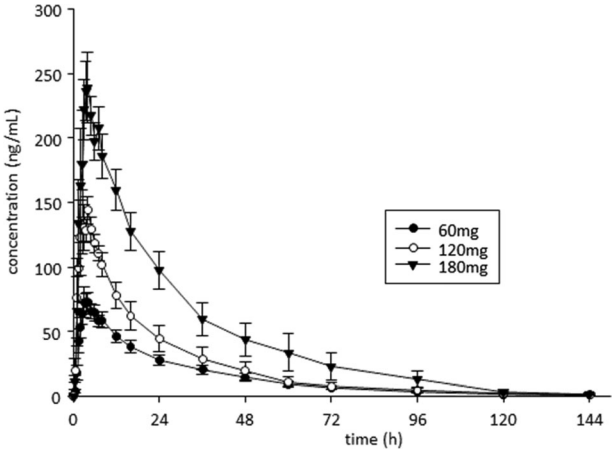

Figure 1. Mean (SEM) noribogaine concentration–time profiles after single oral dosing with 60-, 120-, or 180-mg doses.

Pharmacodynamics

For time to resumption of OST, mean time between the last dose of morphine (given 2 hours prior to dosing of blinded study medication) and time to resumption of OST by treatment arm are shown in Table 2, upper panel. When time to OST resumption was analyzed by cohort (Table 2, lower panel), placebo results for each cohort were very similar to those of the corresponding active arm (Pearson's $r = 0.993$).

Opioid withdrawal symptoms (OWS) were evaluated using the COWS, OOWS, and SOWS.[7,8] Increases in all 3 scales were observed 1–2 hours prior to resumption of OST (Figure 2A–C). Following resumption of OST, ratings for all scales decreased within 1–3 hours.

Pupillometry showed that in the 2 hours prior to resumption of OST, mean pupil diameter increased by 0.47 mm (range across groups, 0.3–0.64 mm). Changes in pupil diameter over time did not differ between treatment groups (Figure 2D).

Table 1. Mean (SD) Plasma Noribogaine Pharmacokinetic Parameters for All Dose Groups

PK Parameter	60 mg (n = 6), Mean (SD)	120 mg (n = 6), Mean (SD)	180 mg (n = 6), Mean (SD)
$AUC_{0-\infty}$ (ng·h/mL)	2060.3 (609.4)	3280.5 (1581.4)	6887.7 (3488.9)
AUC_{0-216} (ng·h/mL)	2018.0 (613.9)	3226.4 (1544.3)	6523.3 (2909.8)
C_{max} (ng/mL)	81.6 (23.8)	172.8 (32.1)	267.9 (46.9)
T_{max} (h)	3.6 (0.9)	3.0 (1.2)	4.4 (1.8)
$t_{1/2}$ (h)	29.3 (7.3)	30.5 (9.1)	23.9 (5.5)
V_d/F (L)	1440.7 (854.0)	2106.4 (1644.5)	1032.2 (365.3)
CL/F (L/h)	32.1 (12.4)	44.7 (21.4)	31.5 (13.1)

Table 2. Mean (SD) Time to Resumption of OST by Treatment Arm (Upper) or by Cohort (Lower)

Time to Resumption of OST (h)	Placebo (n = 9)	60 mg (n = 6)	120 mg (n = 6)	180 mg (n = 6)
Mean (SD)	13.9 (7.4)	8.6 (3.7)	22.5 (10.3)	11.4 (5.0)

	Cohort 1		Cohort 2		Cohort 3	
	Placebo (n = 3)	60 mg (n = 6)	Placebo (n = 3)	120 mg (n = 6)	Placebo (n = 3)	180 mg (n = 6)
Mean (SD)	9.0 (3.1)	8.6 (3.7)	20.5 (9.6)	22.5 (10.3)	12.1 (3.3)	11.4 (5.0)

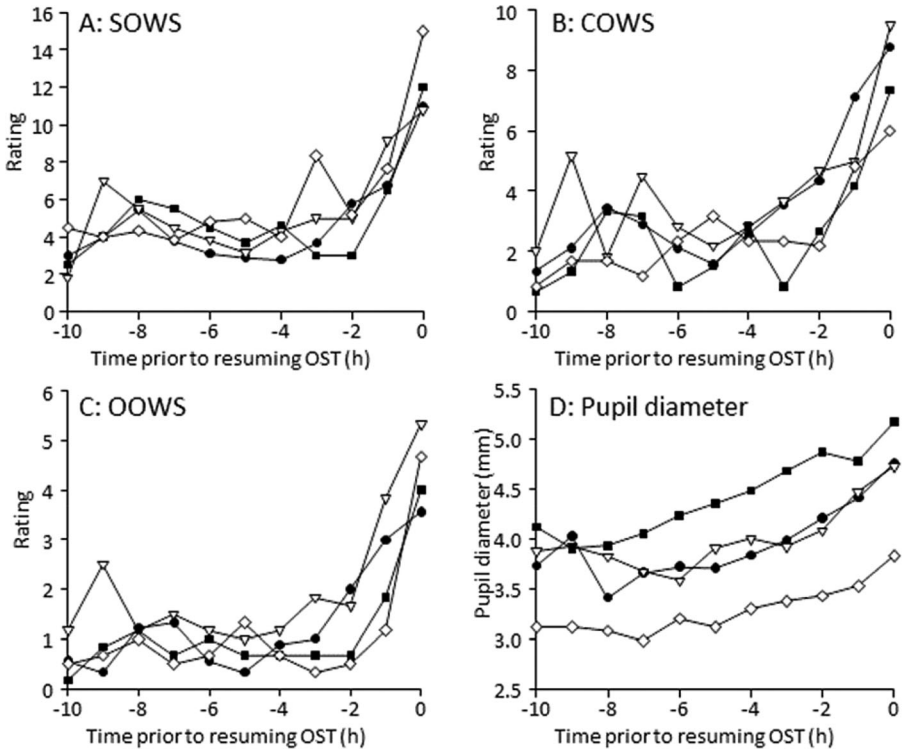

Figure 2. Changes in opioid withdrawal symptoms and pupil diameter, relative to time of restarting OST (0 hours = time of restarting OST). (A) SOWS; (B) COWS; (C) OOWS; (D) pupil diameter. ●, Placebo; ▽, noribogaine 60 mg; ■, noribogaine 120 mg; ◊, noribogaine 180 mg.

Electrocardiographic Effects

Mean ΔQTcI by time and by treatment group on day 1 is shown in Figure 3A. The mean slope for QTcI derived from the full 24-hour baseline (day -1) was larger (0.40) compared with QTcF (0.33). QTcI was chosen as the primary end point because the average sum of squared slopes was somewhat lower for this correction than for QTcF when averaged across all treatments (0.00503 vs 0.00795). Noribogaine caused a clear, statistically significant dose- and concentration-dependent effect on the QTc interval, with the largest mean effect (ΔΔQTcI) of 16 milliseconds at 4 hours in the 60-mg group, 28 milliseconds at 3 hours in the 120-mg group, and 42 milliseconds at 3 hours in the 180-mg group. The effect on ΔΔQTcF was comparable. In the 180-mg group, 1 subject had a QTcI value exceeding 480 milliseconds at 1 time, and 1 subject had QTcI > 500 milliseconds at 4 points. One subject each in the 120- and 180-mg groups had a ΔQTcI > 60 milliseconds at 1 point.

An exposure linear response model with an intercept provided the best fit of the data. When the actually observed ΔQTc values (mean, 90%CI) were plotted against the model predicted values, it could be seen that the model fit the data well (Figure 3B). The mean slope of the noribogaine/plasma concentration relationship was 0.17 milliseconds per ng/mL (90%CI, 0.14 to 0.20 milliseconds). Using the model, a QTcI effect (ΔΔQTcI) of 30 milliseconds (90%CI, 26 to 35 milliseconds) and 42 milliseconds (90%CI, 36 to

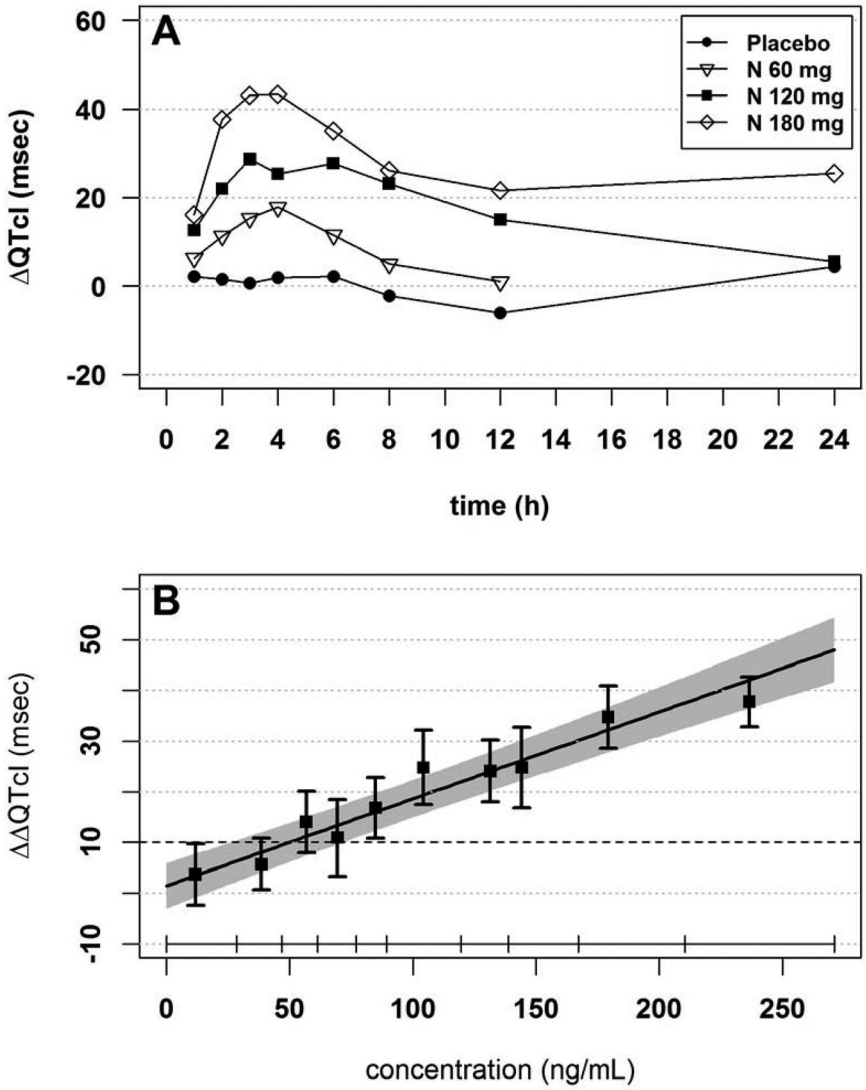

Figure 3. (A) Change-from-baseline mean QTcI (ΔQTcI) by time-by-treatment group. (B) Exposure-response relationship between noribogaine plasma levels and ΔΔQTcI using the linear model that provided the best fit to the data. The mean and 90%CI of the predicted QTc effect (ΔΔQTcI) using the linear model is shown as the black line with the gray-shaded area. To demonstrate how the model captured the observed data (goodness of fit), the actually observed QTc values are shown as vertical bars (mean ΔΔQTcI, 90%CI) plotted for each plasma concentration decile (horizontal bar inserted at the bottom). It can be seen that the model captured the data appropriately, that is, the observed mean values are, with 1 exception, within the confidence limits of the predicted values.

48 milliseconds) could be projected at the observed geometric mean C_{max} of 168 and 238 ng/mL after a single dose of 120- and 180-mg noribogaine, respectively.

There were small observed effects on heart rate and PR interval across dosing groups with no clear dose-related trends. However, a reduction in the heart rate was observed in the highest-dose group (180 mg), in which the placebo-corrected change-from-baseline heart rate reached -11 bpm 6 hours after dosing.

Safety

A total of 78 adverse events (AEs) were reported by 22 participants (Table 2). The most common AEs were visual impairment, headache, and nausea. Visual impairment was the term used to describe noneuphoric changes in light perception of mild intensity, often as a sense that the light in the room was brighter than usual. Some of the actual terms reported by participants were: "the light seems different — brighter," "colors seem brighter," and "bright lights." This occurred within 1 hour of dosing and decreased or disappeared by 2.5–3 hours postdosing and was most commonly reported in the 120- and 180-mg dose groups (Table 3). There were no hallucinations reported. Three AEs were rated as severe (nausea, vomiting, and headache); all others were rated as mild-moderate in intensity. There

Table 3. Most Commonly Reported Adverse Events by Individual, by Dose Group

AE	Placebo (n = 9)	60 mg (n = 6)	120 mg (n = 6)	180 mg (n = 6)
Headache	5	4	2	2
Visual impairment	2	2	5	4
Nausea	1	0	2	2

were no deaths or serious AEs. All AEs 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 changes in ophthalmological or other physical examinations.

Discussion

There are a number of important findings from this first study of noribogaine administered to patients established on OST. Single doses of 60 to 180 mg noribogaine were well tolerated. Noribogaine caused dose- and concentration-dependent QTc prolongation, which reached clinically concerning levels in the higher-dose groups. Noribogaine was rapidly absorbed and slowly eliminated and had a large volume of distribution. Mean noribogaine AUC and C_{max} increased linearly with dose. Visual changes involving change in light perception were reported shortly after dosing. The 120-mg dose group experienced the longest times to OST, which were supported with the lowest OWS scores.

The most notable safety finding was that noribogaine increased QTc in a dose- and concentration-related manner. The mean effect on QTcI was 28 milliseconds in the 120-mg dose group and 42 milliseconds in the 180-mg group, changes that would be clinically concerning in a clinical setting and would require ECG monitoring in subsequent clinical trials.[11] Such ECG monitoring should be designed to quickly identify subjects with pronounced QT prolongation to enable dose adjustment or discontinuation. Exposure response (ER) analysis was consistent with the observed QT prolongation in the by-time-point analysis across dose groups; ER analysis can therefore be used to predict the QT effect in future clinical trials to optimize the benefit/risk of noribogaine treatment in opioid-dependent subjects seeking treatment. It should also be noted that the QT effect of the single noribogaine dose diminished with declining plasma levels and, importantly, before the QT effect of methadone, which was initiated 24 hours later in most subjects, became apparent. Noribogaine interacts with hERG channels with a reported IC_{50} of 5 μM (~1500 ng/mL; DemeRx, data on file), a value not dissimilar to that reported for ibogaine (3.9 μM).[12] The safety margin between hERG IC_{50} and the mean C_{max} after a single dose of 180 mg (267.9 ng/mL) is 5.6-fold; therefore, the finding of QTc prolongation at much lower concentrations was unexpected. It is possible that the relatively pronounced QT effect of noribogaine is a result of interactions with cardiac ion channels other than iKr, analogous to those reported for ibogaine.[13] Ibogaine is rapidly converted to noribogaine in humans with peak noribogaine levels of 18.7 ng/mL after an oral dose of 20 mg in CYP2D6 extensive metabolizers,[14] and we would predict that an ibogaine dose of 286 mg would lead to noribogaine C_{max} values comparable to those observed in patients receiving 180 mg noribogaine. Ibogaine doses used in opioid addiction treatment are considerably higher than this,[15] and our findings therefore strongly suggest that patients receiving ibogaine in any clinical setting should receive careful ECG monitoring. As also recently recommended by others,[16] a careful benefit/risk assessment should be made for each subject, and risk factors associated with torsades de pointes should be clarified before ibogaine administration.

Tolerability was generally good, with nausea, headache, and visual changes the most common side effects reported. There were no noribogaine-related changes noted in physical examinations, vital signs, or safety laboratory tests at any of the doses tested. Visual changes involving change in light perception were reported shortly after dosing, mainly by subjects dosed with 120–180 mg. These changes only occurred during the drug absorption phase, being first reported ~1 hour after dosing, and had disappeared by 2.5–3 hours. No hallucinations or dream-like states were reported. In contrast higher ibogaine doses produced symptoms including light sensitivity and closed-eyed dream-like states for 4–8 hours.[15]

This study's pharmacokinetic findings are similar to those reported in the initial healthy volunteer study.[5] Noribogaine was rapidly absorbed and slowly eliminated, with dose-linear increases in AUC and C_{max}. Individual concentration–time profiles were indicative of enterohepatic recirculation, and volume of distribution was extensive, which may have contributed to noribogaine's prolonged elimination phase. Compared with the healthy volunteer study,[5] in the present study T_{max} was delayed by 1–2 hours, and, by comparison, C_{max} in the 60-mg group was lower, presumably because of predose morphine slowing gastric emptying.

We evaluated opioid withdrawal symptoms with pupillometry and 1 subjective and 2 objective rating scales and also recorded the time at which participants requested to restart OST. The typical OWS profile was for ratings to increase over 1–2 hours

prior to OST resumption. Likewise, pupil diameter increased by 1 mm overall, with a ~0.5-mm increase in 2 hours prior to OST resumption. These changes appear to be quantitatively similar to the acute changes reported in morphine-treated subjects undergoing naloxone withdrawal.[17] Nearly identical times to OST resumption were observed for individuals receiving placebo versus active drug within each cohort (Table 2, lower panel). One possible explanation is the awareness that subjects in the same cohort were restarting OST may have influenced subjects' decisions about when they would restart. The study's safety and pharmacokinetic end points necessitated that subjects be housed and observed in a single ward, and restarting of OST would have been obvious to other participants, and this may have confounded any evaluation of dose–response for time to restarting OST.

The potential shortcomings of this study should be acknowledged. As mentioned above, aspects of study design may have confounded evaluation of time to restarting OST. It is possible that repeated doses of noribogaine are required to achieve prolonged reduction of withdrawal symptoms, and the present single-dose design would not have been sufficient. The numbers of study participants was small, and the study is likely to have been underpowered to identify uncommon or subtle safety findings.

In conclusion, this study's main safety finding was noribogaine produced a dose- and concentration-dependent increase in QTcI. The level of QT prolongation observed at higher plasma levels warrants careful consideration and ECG monitoring in subsequent clinical trials to enable early identification of subjects with pronounced QT prolongation. Pharmacodynamically, noribogaine produced changes in light perception associated with ascending concentrations, particularly at higher doses. The lack of statistically significant dose-related changes in OWRS or time to OST resumption could be a result of aspects of the study design, with confinement of active and placebo-treated patients in the same research ward. Only single doses of study medication were administered, and it is likely that multiple doses administered over a longer period would be needed to properly evaluate activity against OWS. Future exposure-controlled multiple-dose noribogaine studies are planned that will address these safety and design issues.

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Declaration of Conflicting Interests

L.F., J.D., B.D., M.Z., R.C.S., and J.H. were paid consultants of DemeRx. H.W. is an employee of DemeRx. F.L., N.H., and C.T.H. are employees of Zenith Technologies.

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