Switching Opioid-Dependent Patients From Methadone to Morphine: Safety, Tolerability, and Methadone Pharmacokinetics

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Abstract

The aim of this study was to switch patientsestablished on methadone opioid substitution therapy (OST) to morphine over 1 week. Subjects established on daily methadone OST (mean dose 60 mg/day) were switched to morphine slow-release capsules, dosed at ₄× the previous total daily methadone dose, for 6 days, then given morphine syrup dosed q3h. All 27 subjects enrolled in this study completed the switch from methadone to morphine. Opioid withdrawal symptoms (OWS) peaked within 12–24 hours of starting morphine, and 24/27 subjects required higher daily morphine doses (mean 5.2× multiple). Pharmacokinetic evaluation showed that 91% of methadone was cleared during this time, with a mean elimination half-life of 59 hours. The most frequent treatment-emergent non-OWS adverse events were headache, nausea, constipation, and neck pain. The method described here appears to be a safe and acceptable approach to switch subjects from methadone to morphine.

Keywords
methadone, morphine, pharmacokinetics, pharmacodynamics, safety, opioid substitution therapy

This paper describes the design, safety, and tolerability of a study for switching patients established on methadone to morphine prior to dosing with noribogaine. Noribogaine is an active metabolite of ibogaine, a naturally occurring psychoactive chemical that may have antiwithdrawal and anticrovling effects for a number of substances.¹ We have reported data from the first-in-patient ascending single-dose clinical trial of noribogaine² in patients established on methadone opioid substitution treatment (OST; the majority of OST in New Zealand involves methadone).³ Prior to dosing with noribogaine, patients were switched from methadone to morphine, an opioid with a shorter elimination half-life. Compared with morphine, onset of withdrawal symptoms after stopping methadone is slower, and duration of withdrawal is prolonged.⁴,⁵ We anticipated that it would be easier to evaluate the effects of noribogaine on opioid withdrawal symptoms using a shorter-half-life opioid. Some ibogaine treatment providers already recommend switching patients from longer- to shorter-half-life opioids prior to ibogaine dosing.⁶,⁷ This paper reports safety, tolerability, and methadone pharmacokinetic data from a study where patients established on methadone OST were switched to morphine over 1 week.

Methods

The study protocol was 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 patients provided written 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 ECG. Patients had DSM-IV⁸ opioid dependence and had no other substance-dependence disorders. This was an

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open-label, uncontrolled study in which patients established on methadone OST were switched to morphine over 7 days prior to blinded noribogaine/placebo dosing. The design was based on an initial pilot study in 5 patients to evaluate study design and rating instruments. Data reported in this paper are from a study in 27 patients who were subsequently dosed with blinded noribogaine or placebo.2

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 with no evidence of acute or serious chronic medical or surgical disorders or conditions determined to be clinically significant at screening.

The study design is shown in Figure 1. Day numbering is based on blinded noribogaine/placebo dosing occurring on day 1. At 8 am on day –8, patients received their usual dose of methadone (Biodone Forte, 5 mg/mL). From day –7 to day –2, participants’ methadone doses were withheld and were replaced with oral sustained release (SR) morphine sulfate capsules (M-Eslon®), dosed 12-hourly as outpatients. The initial daily morphine dose was calculated as 4× the daily methadone dose (based on a local guidance3); however, the SR morphine dose could be increased to 5× if patients reported ongoing significant withdrawal symptoms. Clonidine patches (Catapres TTS-2®, 200 μg/day; Boehringer Ingelheim) were used for symptomatic treatment of residual withdrawal symptoms. On day –1, patients’ SR morphine capsules were replaced with immediate release (IR) morphine syrup (RA-Morph, 5 mg/mL) in an inpatient setting. The daily dose of IR morphine syrup was 50% of the day –2 dose and was administered in 3-hourly divided doses. On day –1, patients demonstrating objective withdrawal symptoms could receive additional 20-mg doses of IR morphine as needed. All patients received a 20-mg dose of IR morphine syrup at 6 am on day 1, prior to 8 am dosing of blinded noribogaine/placebo treatment.2

Patients had 4-hour clinic visits on the mornings of days –8 and –7, and evaluations at 7 am and 7 pm from day –7 evening until clinic admission on day –1. During this time, withdrawal symptoms were evaluated using the subjective, objective, and clinical opioid withdrawal (SOWS, OOWS, and COWS) scales.10,11 Safety evaluations included clinical monitoring, recording of non-OWS adverse events (AEs), safety laboratory tests, vital signs, and 12-lead electrocardiograms (ECG) at clinic visits. Pulse oximetry and capnography were collected 12-hourly using a GE CareScape B650 monitoring system. Pupil diameter in ambient lighting conditions (200 lux) was assessed 12-hourly by pupillometry using a Neuroptics PLR-200 pupillometer.

Blood samples were obtained on day –8 prior to the last methadone dose, at 1, 2, 3, 4 hours postdose, and then daily (at 24, 48, 72, 96, 120, 144, 168, and 192 hours) to measure methadone blood concentrations. Samples were centrifuged and plasma was stored at –70°C until analyzed. Plasma methadone concentrations were determined using a validated, sensitive LC-MSMS method. To 100 μL of human plasma, 50 μL of internal standard solution (196 ng/mL of trihexyphenidyl) and 200 μL of cold acetonitrile were added. Samples were centrifuged, and then 100 μL of supernatant of the sample was added to 100 μL of acetonitrile: BP water (5:95, v/v) containing 10 mM ammonium acetate, pH 6.0. These samples were mixed via vortex and then centrifuged; 20 μL of sample was injected into the LC/MSMS system. The range of quantification for determination of methadone was from 5.0 to 1280.0 ng/mL with a lower limit of quantitation (LLOQ) of 5.0 ng/mL. Urine samples were collected 12-hourly to check for a range of drugs of abuse.

Plasma methadone concentrations above the LLOQ were used to calculate pharmacokinetic parameters using model-independent methods. The maximum plasma concentration (Cmax) and time to maximum plasma concentration (Tmax) were the observed values. Plasma concentration data in the postdistribution phase of the plasma concentration-time plot were fitted using linear regression to the formula ln C = ln C0 – t/Kel, where C0 was the 0-time intercept of the extrapolated terminal phase and Kel was the terminal elimination rate constant. The half-life (t1/2) was determined using the formula t1/2 = 0.693/Kel. The area under the concentration-time curve (AUC) from time 0 to the last determined concentration-time point (t) in the postdistribution phase was calculated using the trapezoidal rule. The area under the curve from the last concentration-time point in the postdistribution phase (Clast) to infinity was calculated from AUClast = Clast/Kel. The concentration used for Clast was the last determined value above the LLOQ at the time point. The total AUC0–∞ was obtained by adding AUClast and the extrapolated AUC0–∞. Noribogaine apparent clearance (CL/F) was determined using the formula CL/F = Dose/AUC0–∞ × 1000, and apparent volume of distribution (Vd/F) was determined using the formula Vd/F = (CL/F)/Kel.

![Figure 1](Image)

**Figure 1.** Study design diagram. QD, once a day; BID, twice a day; IR, Immediate release; CR, Continuous release.
Summary statistics (means, standard deviations, and coefficients of variation) were determined for each dose group for safety laboratory test data, ECG and pharmacokinetic parameters, oximetry, capnography, and pupil diameter. Categorical variables were analyzed using counts and percentages. Time-related changes in OWS scales and pupil diameter were analyzed using modeling. After standardization for each withdrawal measure (to mean 0 and unit standard deviation), changes within and among the 3 measurement types were examined using a single mixed model with random effects for both participants and participant-measurement times along with fixed effects for the measurement type (COWS, SOWS, or OOWS), hour of measurement, and the interaction between these 2 variables.

Model diagnostics included histograms of residuals. For COWS, SOWS, and OOWS, as model residuals were positively skewed, log-transformed versions of these variables prior to standardization (to avoid negative values) were modeled instead (after adding 1 to also avoid 0 values), which produced acceptable model diagnostics. Fitted estimates of means for each source at each time were back-transformed to the original scale (by exponentiating and subtracting 1). Changes within each measurement type between times and between pairs of times, and between measurement types for these, were estimated from the same model and presented as ratios of geometric means. Similar models were constructed to look at pupil diameter following a log-transformation with a random participant effect. Correlations between changes in pupil diameter and changes in each of the withdrawal scales for the time periods of interest were examined using Spearman’s correlation coefficients. Inferential analyses were conducted using Stata 13.1, and 2-sided $P < .05$ was considered statistically significant in all cases.

**Results**

A total of 34 patients were screened, and 27 (21 male, 6 female) were enrolled in and completed this study. Mean age was 41.2 years, mean height was 1.75 m, mean weight was 81.9 kg, and mean BMI was 27.0 kg/m$^2$. Twenty patients were white, 5 were Maori, and 2 other. Mean (SD) methadone dose was 60 (17) mg/day. Mean (SD) duration of methadone OST was 8.8 (8.6) years. Fifteen patients had chronic hepatitis C, 5 had chronic obstructive pulmonary disease, 9 had previous major depressive disorder, and 5 had previous or current anxiety disorders. A table of comorbid conditions and medications for individual patients is available in on-line Supplemental Table S1. There were no dropouts: all patients completed this protocol and received subsequent blinded noribogaine/placebo dosing.$^2$

In regard to methadone pharmacokinetics, the mean methadone plasma concentration-time profile is shown...
in Figure 2A, and individual patient log-linear profiles are shown in Figure 2B. Methadone was rapidly absorbed, with mean (SD) peak concentrations occurring at 3.5 (1.1) hours after oral dosing. The drug was slowly eliminated, with a mean (SD) half-life estimate of 59 (24) hours. Mean (SD) apparent volume of distribution was 723 (634) hours. The decline in mean methadone exposure was calculated as
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\frac{AUC_{192-\infty}}{AUC_{0-\infty}} \times 100. 
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Mean methadone exposure declined by approximately 91% during the washout period prior to noribogaine/placebo dosing, confirming that methadone was largely but not entirely eliminated by the time of blinded noribogaine/placebo dosing.

The mean (SD) initial dose of morphine, started on day –7, was 247 (66) mg/day, representing a 4.1x multiple of the previous mean methadone dose. Twenty-four of 27 participants requested dose increases, typically on the evening of day –7 or on day –6 because of OWS (see Figure 3A). The mean (SD) final morphine dose was 311 (74) mg/day, representing a 5.2x multiple of the previous mean methadone dose. Twenty-one participants also requested clonidine patches, and these requests occurred between days –7 and –1. Mean morphine doses on day –7, mean final morphine doses, and mean and percentage change in morphine doses were not different between patients who received clonidine patches and those who did not (data not shown).

In regard to OWS and pupillometry, mean SOWS, OOWS, and COWS scores from the last methadone dose on day –8 until noribogaine/placebo dosing are shown in Figure 3A. Ratings on all 3 scales increased on day –7, peaking at 8 pm, associated with the first day of taking morphine capsules. Comparison of day –7 with day –8 geometric means showed a statistically significant difference for SOWS (1.95, 95% confidence intervals [CI] 1.11, 3.41, \( P = .02 \)) but not for OOWS (1.39, 95% CI 0.79, 2.44) or COWS (1.52, 95% CI 0.86, 2.66). Ratings on all 3 scales then declined over the next 5 days. When patients were switched to lower doses of morphine syrup on day –1, ratings on all 3 scales again increased slightly. None of the comparisons of day –1 with day –2 ratings were statistically significant for any of the OWS scores. Two hours after methadone dosing on day –8, mean pupil diameter decreased by 0.6 mm (Figure 3B). Comparison of day –7 with day –8 geometric means showed a statistically significant difference (1.33, 95% CI 1.21, 1.47, \( P < .001 \)). Mean pupil diameter tended to diminish between day –7 and day –2 (Pearson’s \( r = -0.68 \)); however, there were further increases on day –1, when lower-dose morphine syrup was started. Comparison of day –1 with day –2 pupil diameter was not statistically significant.

As far as safety is concerned, a total of 40 AEs that were not assessed as OWS were reported by 18 participants. The most common AEs were headache
(10 participants), nausea (3), constipation (3), and neck pain (2). All AEs 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 or changes >60 milliseconds at any time.

Discussion

This main objective for this study was to safely switch patients established on methadone OST to twice-daily morphine in preparation for a blinded single-dose trial of noribogaine or placebo. Key outcomes were safety and tolerability and to minimize dropouts. The approach described in this report appears to be a safe and acceptable design to achieve these outcomes, and there were no dropouts.

We measured methadone washout pharmacokinetics for 2 reasons: to ensure that patients were not continuing to take methadone surreptitiously and to evaluate the extent of elimination over 7 days. The mean elimination half-life in this study was 59 hours, considerably longer than earlier steady-state half-life estimates which ranged between 25 and 34 hours. It should be noted that these earlier values were based on 24-hour sampling intervals, which may account for the underestimations. Over 7 days, methadone exposure (based on the difference between \( \text{AUC}_{\infty} \) minus \( \text{AUC}_{(t)} \)) declined by 91%. If it is important to have no detectable methadone, a longer washout phase (~10 days) might be needed.

The stability of OWS scores and pupil diameter until day –1 indicate that the SR morphine regimen was adequate for relief of opioid withdrawal symptoms. The only statistically significant changes were noted in subjective ratings (SOWS) and pupil diameter between days –8 and –7 but not at other times. We were concerned that if OWS were inadequately controlled, patients might self-medicate with opioids; however, the methadone pharmacokinetics and urine drug screening results suggest that the morphine regimen was adequate for symptom management. Most patients required SR morphine doses that were 5x their established methadone dose, higher than our initial 4x multiple but not dissimilar to the multiple reported in an earlier study. This study also reported transient mild increases in withdrawal symptoms soon after switching from methadone to a slow-release morphine formulation at a 3.5x multiple. In the present study any additional OWS symptoms were managed with clonidine patches. There were no safety issues identified with the morphine regimen.

The limitations of this study should be acknowledged. The study was uncontrolled, with pragmatic endpoints, and was carried out in an outpatient setting. It is likely that there are other approaches for switching patients from methadone to shorter-half-life opioids; however, to date no detailed methods have been published.

In conclusion, we describe a 1-week protocol that allows outpatients to be safely switched from methadone OST to a shorter-half-life alternative, morphine. The protocol appears to be a safe and acceptable approach to achieve these outcomes while minimizing dropouts.

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Conflict of Interest Disclosure

L.F., J.D., 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.

References


Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website.