

OPIOIDS, SUBSTANCE ABUSE & ADDICTIONS SECTION

Original Research Article

Assessment of Pharmacodynamic Effects Following Oral Administration of Crushed Morphine Sulfate and Naltrexone Hydrochloride Extended-Release Capsules Compared with Crushed Morphine Sulfate Controlled-Release Tablets and Placebo in Nondependent Recreational Opioid Users

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Abstract

Objectives. To compare the pharmacodynamic effects, including self-reports of “drug liking” and “high,” of crushed morphine sulfate and naltrexone hydrochloride extended-release capsules (MSN), crushed morphine sulfate controlled-release (CR) tablets, and placebo in an abuse potential study.

Design. Randomized, double-blind, placebo-controlled, three-way crossover study.

Setting. Single-center.

Subjects. Nondependent recreational opioid users.

Interventions. Orally administered crushed MSN (120-mg morphine sulfate and 4.8-mg naltrexone hydrochloride), crushed 120-mg morphine sulfate CR, and placebo.

Outcome Measures. Subjective ratings (100-point visual analog scales) of positive drug effects (drug liking, high, good effects, take drug again, and overall drug liking), any effects, and negative effects (bad effects, feel sick, nausea, sleepy, and dizzy), along with pupillometry, pharmacokinetic (PK), and safety assessments.

Results. Crushed morphine sulfate CR significantly increased ratings of all positive subjective

measures relative to placebo ($P < 0.0001$). Crushed MSN significantly decreased all positive subjective ratings compared with morphine sulfate CR ($P \leq 0.005$), but significantly increased ratings compared with placebo ($P < 0.03$). Peak pupil diameter was significantly larger for MSN than morphine sulfate ($P < 0.0001$). PK analysis of morphine plasma concentrations indicated that C_{max} was significantly lower and t_{max} significantly longer for crushed MSN compared with crushed morphine sulfate CR. Plasma concentrations of naltrexone and 6- β -naltrexol were present following crushed MSN.

Conclusions. This study demonstrated that when crushed and administered orally to nondependent recreational opioid users, MSN was associated with significantly lower scores on all positive subjective measures including drug liking and high, and significantly less pupil constriction compared with crushed morphine sulfate CR.

Key Words. Abuse Potential; Pharmacodynamic Effects; Opioid; Opioid Antagonist; Morphine; Naltrexone; Controlled-Release

Introduction

In the United States, prescriptions for opioid analgesics have increased substantially over the last 10 years [1], owing in large part to the evolving consensus among pain professionals that opioids are an important option when managing chronic noncancer pain [2,3]. With this increase, there is growing concern over prescription opioid misuse, abuse, and diversion. In 2010, the United States-based National Survey on Drug Use and Health estimated that 5.1 million persons aged ≥ 12 years used pain relievers non-medically in the past month, and 71% had most recently obtained them from a family member or friend [4]. Non-medical use of prescription pain relievers is the second most common form of illicit drug use after marijuana (not including alcohol and tobacco products) [4].

The abuse of prescription opioids has significant societal and economic consequences [5–7]. Over a 10-year period, overdose death rates and substance abuse treatment admissions related to prescription opioids have risen nearly fourfold and sixfold, respectively, in the United States [8]. Emergency department visits attributed to non-medical prescription opioids have likewise increased [9].

The goal of allowing patient accessibility to effective analgesics while minimizing risks of abuse and addiction has prompted the development of new opioid formulations to discourage common methods of tampering associated with opioid abuse and misuse. These formulations incorporate different strategies to deter abuse including physical barriers to limit extraction of active ingredients or chemical barriers with pharmacologically active ingredients to reduce the positive subjective effects of opioids when misused [10,11].

An extended-release (ER) formulation of morphine has been developed that consists of capsules of polymer-coated pellets of morphine, each with a core of sequestered naltrexone, a selective μ -opioid receptor antagonist (MSN; EMBEDA® [morphine sulfate and naltrexone hydrochloride], Pfizer Inc, New York, NY, USA) [12,13]. It has been shown to be efficacious in treating chronic pain [14,15]. The naltrexone remains sequestered when MSN is taken as directed, and plasma levels of naltrexone or its metabolite, 6- β -naltrexol, following oral administration of the intact capsule, are either undetected or negligible [16]. However, when MSN is tampered with (e.g., crushing or chewing), the formulation is designed to release naltrexone to attenuate the effects of morphine. In particular, plasma levels of naltrexone and 6- β -naltrexol following oral administration of crushed MSN pellets are similar to plasma levels following administration of an oral solution of naltrexone [16]. Tampering with ER opioids is common among opioid abusers who are seeking greater psychotropic effects and a faster onset of action [17]. Recent data demonstrate that subjects entering abuse treatment centers reporting abuse of ER morphine show high levels of abuse by intravenous (IV) injection, snorting, and chewing of ER morphine, indicating that tampering with ER morphine is common [18]. In a proof-of-concept study that simulated the IV abuse of crushed MSN, the objective (pupillometry) and subjective (self-reports of high, drug liking) opioid effects were attenuated by the combined treatment of morphine and naltrexone (in the same 25:1 ratio of morphine:naltrexone found in MSN) relative to morphine alone [19].

Human abuse potential testing is a key element in the clinical and safety evaluation of new formulations designed to discourage common methods of tampering associated with opioid abuse and misuse, and regulatory agencies in both Canada and the United States provide recommendations on study design and methodology [20,21]. As outlined in the Food and Drug Administration draft guidance, human abuse potential studies are usually double-blind, double-dummy, placebo- and positive-comparator controlled, and are crossover designs. The abuse potential of the test drug is assessed by comparing responses of the test drug with those of placebo and with those of the positive control. The guidance further states that measures most directly related to likelihood of abuse include ratings of liking and other subject-rated effects (i.e., high), determination of the subject's disposition to take the drug again, and drug identification (subject's ability to categorize the effects of the test drug as similar to those of numerous classes of psychoactive drugs) [21].

A human abuse potential study was conducted previously with MSN. In that randomized, double-blind, placebo- and active-controlled study, nondependent recreational opioid users reported reduced drug liking and euphoria after taking crushed (and dissolved) MSN orally compared with an immediate-release (IR) morphine solution [22]. However, the study did not include an additional comparison with a controlled-release (CR) morphine formulation. For this reason, the current study was undertaken with the

Abuse Potential Study with Morphine/Naltrexone Formulation

primary objective comparing the pharmacodynamic (PD) effects, including self-reports of drug liking and high, following oral administration of crushed MSN with that of crushed morphine sulfate CR tablets in an abuse potential study in nondependent recreational opioid users. The secondary objectives of the study were to determine PD effects of crushed MSN relative to that of placebo, and to compare the pharmacokinetics (PK) and safety of crushed MSN with crushed morphine sulfate CR.

Methods

Study Population

Participants were eligible for study inclusion if they were healthy male or female individuals aged 18–55 years inclusive, with a body mass index of 18.0–33.0 kg/m². Good health was determined by medical history, physical examination, vital signs, clinical laboratory tests, and 12-lead electrocardiogram (ECG). Participants were recreational nonphysically dependent opioid users (as defined by the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition Revision* [DSM-IV-TR] criteria and the naloxone challenge test) who had used opioids for nontherapeutic purposes on at least 10 occasions within the past year and at least once in the 12 weeks prior to screening (visit 1).

Individuals were excluded if they had a history or current diagnosis of substance dependence (excluding nicotine or caffeine) as assessed by the investigator using DSM-IV-TR criteria, or if they had participated in, were participating in, or were seeking treatment for substance-related disorders (excluding caffeine and nicotine). Participants who had a positive urine drug screen (UDS), excluding tetrahydrocannabinol (THC; because of long half-life), at visit 1 or upon admission to the study center at visit 2 were ineligible (however, subjects with an opioid-positive UDS at visit 1 may have been retested once prior to visit 2; if the UDS retest was negative, the subject could proceed to visit 2). Individuals were excluded if they were not willing to refrain from using recreational drugs, including THC, from visit 1 through the end of the study. In addition, individuals were excluded if they had any condition in which an opioid was contraindicated, or had a history of any clinically significant illness, or had a known allergy or history of hypersensitivity to opioids, naltrexone hydrochloride, or similar compounds. Women who were pregnant, lactating, or planning to become pregnant during the course of the study were not eligible.

Study Design

This was a randomized, double-blind, placebo-controlled, three-way crossover study (ALO-01-10-4005; ClinicalTrials.gov NCT01380093) that was conducted under institutional review board approval and a certificate of confidentiality to protect sensitive participant information. The study was conducted in accordance with Good Clinical Practice requirements described in the current revision of the International Conference on Harmonisation

of Technical Requirements of Pharmaceuticals for Human Use Guidelines. All local regulatory requirements were followed, and all participants gave written informed consent prior to entering the study.

The study consisted of five phases: screening, naloxone challenge, drug discrimination, treatment, and follow-up. The screening visit (visit 1), which involved standard medical screening to determine eligibility, took place between 2 and 28 days prior to the naloxone challenge phase. During this visit, consenting subjects had the option to complete the brief Recreational Prescription Opioid Abuse questionnaire that explores behaviors related to prescription opioid abuse [23]. The responses provided were not used to determine subject eligibility, and the data will be published elsewhere. Visit 2 (days 0–3) comprised the naloxone challenge and drug discrimination phases and required a stay in the study center of up to 3 nights. The treatment phase commenced 3–21 days following visit 2 (day 3) and comprised three visits (visits 3–5; treatment periods 1–3), each with a 2-night confined stay. Each treatment period was separated by a minimum of 4 days not to exceed 14 days between dosing. The follow-up visit (visit 6) occurred 3–14 days following the last study drug administration or at the time of early withdrawal.

Naloxone Challenge Phase

A naloxone challenge test was performed on the day of admission to rule out participants who were physically dependent on opioids. Participants received an IV bolus dose of naloxone hydrochloride (0.2 mg), followed by an assessment for signs of withdrawal using the Clinical Opiate Withdrawal Scale (COWS) [24]. If there was no evidence of withdrawal within 30 seconds, defined as a COWS score <5, an additional 0.6-mg bolus dose was injected, and the participant was observed for 5 minutes for signs and symptoms of withdrawal. Participants who did not display signs and symptoms of withdrawal (i.e., had a COWS score <5) entered the drug discrimination phase.

Drug Discrimination Phase

To confirm that participants could safely distinguish between morphine and placebo, participants were randomly assigned to receive either 120 mg of morphine sulfate or placebo in solution (150 mL) administered orally using a crossover design separated by 24 hours. PD and safety assessments were conducted at predose and at 0.5, 1, 1.5, 2, 3, 4, and 5 hours postdose. Participant eligibility for the next phase of the study (treatment phase) was based on the ability of the subject to distinguish morphine from placebo on two subjective drug measures (≥ 15 -point increase for drug liking and ≥ 30 -point increase for high within 2 hours following dosing) and the ability to demonstrate an acceptable placebo response, defined as responses, where 0 = none and 50 = neither like nor dislike (± 10 visual analog scale [VAS] points) on measures of high and drug liking, respectively. Eligibility was also based on tolerability to study treatments (no

episodes of vomiting within 2 hours postdose) and general behavior suggestive that the participant could successfully complete the study.

Treatment and Follow-Up Phase

This phase addressed the study objectives and consisted of three treatment periods, where each dosing was separated by a washout period of at least 4 days but not to exceed 14 days. During each treatment period, participants received a single dose of the following treatments in a randomized, double-blind, crossover fashion: placebo, MSN 120 mg, or morphine sulfate CR 120 mg. The 120-mg dose was chosen to maintain consistency with a previous abuse liability study with MSN [22] and because 120 mg IR morphine sulfate (administered orally in solution) was shown to reliably induce euphoria while inducing only mild side effects [22]. The MSN solution contained 120-mg morphine sulfate/4.8-mg naltrexone hydrochloride and was prepared by manually crushing the contents of 2 × 60 mg/2.4 mg capsules (EMBEDA) using a mortar and pestle for 2 minutes and mixing-in solution (Ocean Spray® Diet Cranberry-Grape, Ocean Spray Cranberries, Inc., Lakeville-Middleboro, MA, USA, an artificially sweetened beverage that was selected to minimize caloric load and impact on gastric emptying time while masking bitterness). The morphine sulfate CR solution was prepared similarly by crushing 2 × 60 mg CR tablets (MS CONTIN®, Purdue Pharma, Stamford, CT, USA) using a mortar and pestle and mixing in solution. Placebo was prepared as a solution containing microcrystalline cellulose. PD, PK, and safety assessments were conducted at predose and up to 24 hours postdose for each treatment. Fasting was required for at least 8 hours before and 2 hours after drug administration in the drug discrimination phase and at each treatment visit.

All participants who received at least one dose of study drug in the treatment phase were requested to return for a follow-up visit (between 3 and 14 days following the last study drug administration or time of early withdrawal), during which final safety assessments were conducted.

PD Assessments

Primary endpoints were drug liking (at the moment) and high using 100-mm VAS. The drug liking VAS was bipolar (0 = strong disliking; 50 = neither like nor dislike; 100 = strong liking), while the high VAS was unipolar (0 = none; 100 = extremely).

Secondary endpoints included 100-mm unipolar VAS items (good drug effects, any drug effects, bad drug effects, feel sick, nausea, sleepy, and dizzy) measuring positive, negative, and any subjective effects. Primary and secondary VAS scores were collected at predose (unless they were directly relevant to the drug effect [e.g., nausea]), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose. Global assessments of take drug again and overall drug liking were also included as VAS secondary endpoints but were only administered 24 hours postdose.

The take drug again VAS is a subjective assessment of the degree to which a subject would desire to take the drug again if given the opportunity: on a bipolar 100-mm scale, a score of 0 = definitely would not, 50 = do not care, and 100 = definitely would. The overall drug liking VAS assesses the participant's global perception of drug liking on a 100-mm scale: a score of 0 = strong disliking, 50 = neither like nor dislike, and 100 = strong liking.

As pupils constrict (miosis) in response to opioids, pupillometry assessment was included as a secondary endpoint to provide an objective measure of opioid pharmacological effects [25]. In a dimly lit room with controlled lighting conditions, participants had pupil diameter (same eye if possible) measured using a pupillometer. Measurements were made at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose.

Principal parameters of interest for PD endpoints included the E_{max} and the effect occurring within 2 hours following dosing, as assessed by the area under the effect curve (AUE_{0-2h}).

PK Assessments

Blood samples were collected for PK determination at selected times prior to and following each dose of study drug in the treatment phase (predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours). Plasma samples were analyzed for morphine, naltrexone, and 6- β -naltrexol concentrations, and plasma concentration-time curves were generated. The plasma PK parameters calculated included the time to maximum observed plasma concentration for each participant (t_{max}); the maximum observed plasma concentration for each participant (C_{max}); and area under the plasma concentration-time curve from time zero (AUC) to a variety of times postdose, including 1 hour (AUC_{0-1h}), 2 hours (AUC_{0-2h}), 4 hours (AUC_{0-4h}), 8 hours (AUC_{0-8h}), 12 hours (AUC_{0-12h}), 24 hours (AUC_{0-24h}), and infinity ($AUC_{0-\infty}$).

Analytical Methods

To determine the plasma concentrations of morphine, naltrexone, and 6- β -naltrexol, 8 mL of blood were drawn at each sampling time point. Samples were collected into 2 × 4 mL ethylenediaminetetraacetic acid Vacutainer® tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) or equivalent, placed on ice, and centrifuged at 3,000 rpm for a period of 10 minutes at 4°C, within 1 hour of sample collection. The plasma was then pipetted into two pre-labeled polypropylene tubes and stored at -20°C ($\pm 5^\circ\text{C}$) until shipped for analysis. The plasma samples were analyzed by Cedra Corporation (Austin, TX, USA) using validated methods. Plasma samples were analyzed for morphine, naltrexone, and 6- β -naltrexol.

Safety Assessments

Adverse events (AEs) and serious adverse events (SAEs) were collected and recorded throughout the study; AEs

were elicited using nonleading questions during the treatment phase at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose. Based on clinical judgment, the investigator made an assessment of intensity (mild, moderate, or severe) and whether there was a reasonable possibility that the pharmacological action of the study drug was responsible for the AE/SAE being reported.

Physical examinations and clinical laboratory tests (chemistry, hematology, and urinalysis) were conducted at screening and follow-up; vital signs (blood pressure, heart rate, respiratory rate, and oxygen saturation of hemoglobin) were collected throughout the study phases and at nominal time points (predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose) during the treatment phase. End tidal CO₂ was measured by capnography during the treatment phase (predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose). Continuous cardiac telemetry (heart rate, cardiac rhythm, and oxygen saturation) was conducted for 5 hours following dosing during the drug discrimination phase and for up to 12 hours following dosing during the treatment phase. ECGs were performed at screening, naloxone challenge, and follow-up.

Statistical Analyses

Approximately 96 individuals were to be screened and qualified in order to enroll 36 participants into the treatment phase and to ensure that at least 24 participants completed the study. Power calculations for select analyses were performed given the completion size of 24 participants. The comparison of MSN vs morphine sulfate CR for drug liking E_{\max} should have power of at least 89%, assuming a mean difference of 15–30 points and a standard deviation (SD) of the paired differences of 15–20 points, based on a paired *t*-test for analysis and a conservative multiple comparison adjustment of $P = 0.025$ (0.05/2). This adjustment accounted for the need for at least one of the principal parameter analyses to reach statistical significance in both of the primary endpoints, drug liking and high, to accept the alternative hypothesis that there was a difference in abuse potential between crushed MSN and crushed morphine sulfate CR. Other endpoints (AUE_{0–2h} for drug liking and E_{\max} and AUE_{0–2h} for high) have demonstrated larger mean differences in previous abuse liability trials [19,26], and thus the power for these analyses was anticipated to be larger. The planned sample size was considered sufficient for both primary endpoints and the two principal parameters (E_{\max} and AUE_{0–2h}).

The evaluable population included all randomized participants who completed all three treatment periods of the treatment phase, who contributed postdose PD data from each period, and who did not have major protocol violations. The safety population was defined within each phase of the study, starting with the naloxone challenge phase, and included all participants who received at least one dose of study drug within that phase.

The principal parameters for the primary endpoints were summarized using descriptive statistics and were ana-

lyzed using a mixed-effect model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence. All statistical tests were conducted using two-tailed significance criteria and performed at the 0.05 significance level. Multiple comparison adjustments were made for all pairwise treatment comparisons of the primary endpoints and principal parameters using the Hochberg method. The percentage change in the principal parameters for the VAS ratings of drug liking, high, and take drug again were calculated using morphine sulfate CR as the reference and were summarized categorically in 10% increments.

Results

Participant Disposition/Demographics

A total of 80 participants were enrolled in the study. Of these, 21 participants were screen failures, and 59 participants entered and completed the naloxone challenge phase and proceeded to the drug discrimination phase. Of these, 23 participants discontinued during the drug discrimination phase; the most common reasons for discontinuation were inability to discriminate between morphine sulfate CR and placebo ($N = 14$), investigator decision ($N = 4$), and postdose vomiting ($N = 3$). Thirty-six participants were randomized into the treatment phase (safety population for this phase), and 33 participants completed the treatment phase (evaluable population); the reasons for discontinuation were noncompliance ($N = 1$) and other ($N = 2$; one participant was unable to attend visit treatment 3 owing to involvement in a car accident and sister being in hospital; second participant had positive urine and serum pregnancy test). The majority of participants in the evaluable population were male (91%), white (97%), and ranged in age from 19 to 40 years with a mean age of 24.2 years (Table 1).

PD Results

The mean VAS scores over time for the primary endpoints, drug liking and high, are shown in Figure 1. The effect of crushed morphine sulfate CR on each measure peaked within 2 hours after dosing and gradually declined to placebo levels by 24 hours postdose. Participants receiving crushed MSN had reduced drug liking and high VAS scores compared with those receiving crushed morphine sulfate CR at all time points, but had higher scores compared with participants receiving placebo.

These results were confirmed statistically based on the principal parameters of interest, E_{\max} , and effect over 2 hours following dosing (AUE_{0–2h}). Study sensitivity was demonstrated in that crushed morphine sulfate CR had significantly higher ratings than placebo on drug liking and high for E_{\max} and AUE_{0–2h} ($P < 0.0001$) (Figure 2). Crushed MSN showed significantly lower scores for both E_{\max} and AUE_{0–2h} compared with crushed morphine sulfate CR ($P < 0.0001$) (Figure 2; Table 2). These values were significantly ($P < 0.001$) greater for crushed MSN compared with placebo, but the treatment differences vs placebo

Table 1 Summary of participant demographics

	Evaluable Population (N = 33)
Age, years	
Mean (SD)	24.2 (3.7)
Median (range)	24.0 (19, 40)
Gender, N (%)	
Male	30 (91)
Female	3 (9)
Ethnicity, N (%)	
Hispanic or Latino	0
Not Hispanic or Latino	33 (100)
Race, N (%)	
Black or African American	1 (3)
White	32 (97)
Body weight, lb	
Mean (SD)	170.2 (29.9)
Median (range)	164.0 (135.0, 257.1)
BMI, kg/m ²	
Mean (SD)	23.9 (3.5)
Median (range)	23.4 (19.1, 33.0)

BMI = body mass index; SD = standard deviation.

were not as great as those observed for morphine sulfate CR vs placebo (Figure 2).

For the secondary positive subjective effects, the mean VAS ratings (E_{\max} and AUC_{0-2h}) for good drug effects, overall drug liking (24 hours postdose), and take drug again (24 hours postdose) were significantly lower for crushed MSN compared with crushed morphine sulfate CR ($P < 0.005$) (Figure 3). VAS ratings following crushed MSN were generally larger than those following placebo, and significant differences were observed for good effects and overall drug liking ($P < 0.03$) but not for take drug again (Figure 3).

The percent change in E_{\max} and AUC_{0-2h} relative to crushed morphine sulfate CR for drug liking and high were calculated. Percent change was summarized categorically into increments of 10%, ranging from at least 10% to 100% reduction. Any increase, no change, and any reduction were also summarized categorically. At least 85% of participants had some degree of reduced drug liking, and 100% of participants had some degree of reduced high after receiving crushed MSN compared with crushed morphine sulfate CR. A similar percent change calculation was conducted for take drug again VAS ratings measured at 24 hours postdose. Relative to crushed morphine sulfate CR, 73% of participants had some degree of reduction in take drug again after receiving crushed MSN.

Mean VAS scores (E_{\max}) for any drug effects and negative subjective effects (bad drug effects, feel sick, nausea, dizzy, and sleepy) are summarized in Table 3. Crushed MSN resulted in significantly lower peak scores on all

measures compared with crushed morphine sulfate CR. Similar results were seen with AUE_{0-2h} except for feel sick and nausea, where crushed MSN did not differ significantly from crushed morphine sulfate CR (data not shown).

Mean pupil diameter during the first 24 hours postdose along with mean peak pupil diameter (E_{\max}) are shown in Figure 4. Peak pupil diameter was significantly smaller for both crushed MSN and crushed morphine sulfate CR compared with placebo ($P < 0.0001$), but was significantly larger for crushed MSN compared with crushed morphine sulfate CR ($P < 0.0001$) (Figure 4). A similar pattern was observed for AUE_{0-2h} (data not shown).

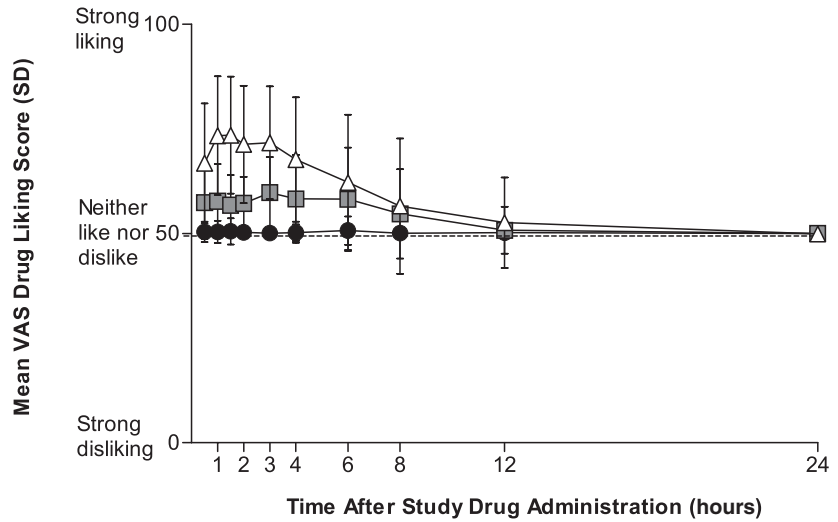
PK Results

Mean plasma concentrations of morphine from predose to 24 hours postdose are shown in Figure 5, while summary parameters are shown in Table 4. Geometric mean ratios for C_{\max} , AUC_{0-1h} , AUC_{0-2h} , AUC_{0-24h} , and $AUC_{0-\infty}$ were significantly different between treatments (P values are shown in Table 4). C_{\max} , AUC_{0-1h} , and AUC_{0-2h} were higher and t_{\max} was shorter for crushed morphine sulfate CR compared with crushed MSN. AUC_{0-24h} and $AUC_{0-\infty}$ were higher for crushed MSN compared with crushed morphine sulfate CR. No statistically significant treatment differences were observed for AUC_{0-4h} , AUC_{0-8h} , or AUC_{0-12h} .

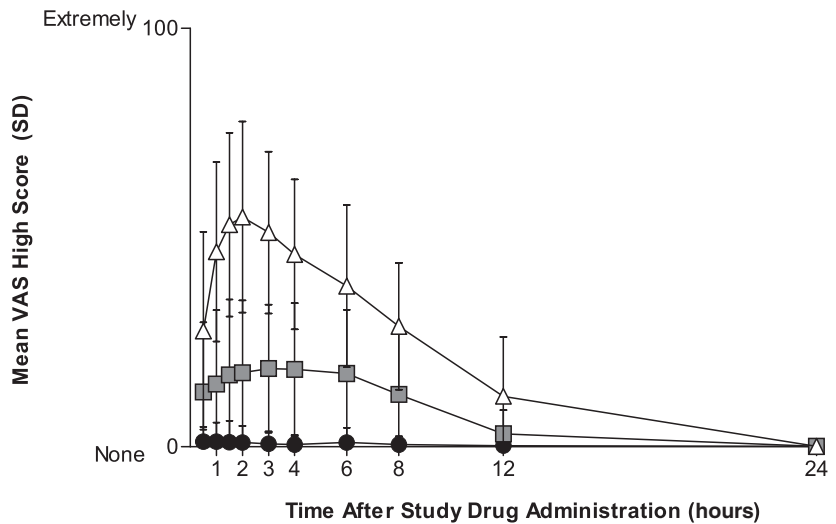
Mean plasma concentrations of naltrexone and 6- β -naltrexol over time in participants treated with crushed MSN are provided in Figure 6. For naltrexone, mean $C_{\max} \pm SD$ was 979 ± 714 pg/mL and mean $t_{\max} \pm SD$ was 0.8 ± 0.3 hours. Mean $AUC \pm SD$ ranged from 619 ± 442 hours·pg/mL (0–1 hours) to $3,160 \pm 1,523$ hours·pg/mL (0–24 hours), and was $3,321 \pm 1,617$ hours·pg/mL for 0 to infinity. For 6- β -naltrexol, mean $C_{\max} \pm SD$ was $6,226 \pm 2,158$ pg/mL and mean $t_{\max} \pm SD$ was 1.0 ± 0.6 hours. Mean $AUC \pm SD$ ranged from $3,935 \pm 1,530$ hours·pg/mL (0–1 hours) to $47,809 \pm 10,184$ hours·pg/mL (0–24 hours), and was $74,932 \pm 25,580$ hours·pg/mL for 0 to infinity.

After receiving crushed morphine sulfate CR, naltrexone and 6- β -naltrexol concentrations were below the limit of quantification for the majority of participants; one participant had a peak concentration of 6- β -naltrexol (10.8 pg/mL) at 8 hours. After receiving placebo, one participant had a peak concentration of naltrexone (12.8 pg/mL) at 24 hours and a peak concentration of 6- β -naltrexol (10.1 pg/mL) at 1 hour; one participant had a peak concentration of 6- β -naltrexol (19.7 pg/mL) at 0.5 hours. Findings of plasma naltrexone and 6- β -naltrexol following dosing of crushed morphine sulfate CR and placebo were unexpected and likely reflect low and clinically unimportant levels associated with previous crushed MSN administration. Because the majority of naltrexone and 6- β -naltrexol levels were undetectable after crushed morphine sulfate CR and placebo, statistical comparisons between crushed MSN and crushed morphine sulfate CR would be uninterpretable.

A. Drug Liking



B. High



- Placebo (N = 33)
- MSN 120 mg crushed (N = 33)
- △ Morphine sulfate CR 120 mg crushed (N = 33)

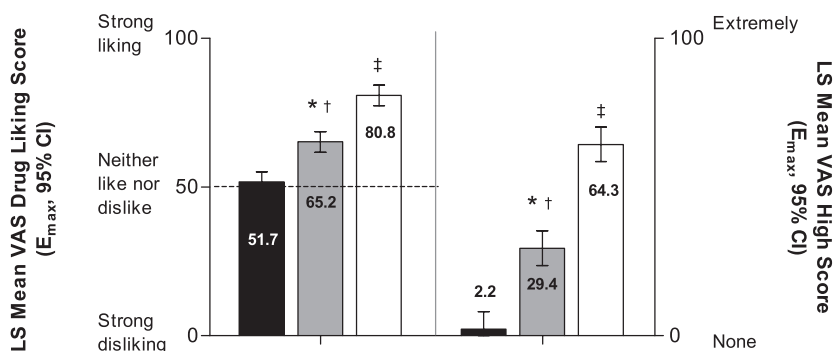
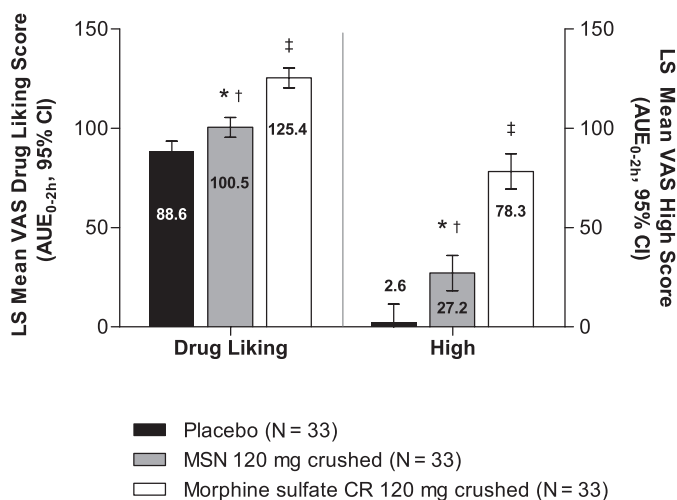
Figure 1 Mean visual analog scale (VAS) scores over time. (A) Drug liking (“Do you like the drug effect you are feeling now?”) and (B) high (“How high are you now?”). N = 32 at the 3 hours postdose time point for drug liking. SD = standard deviation; MSN = extended-release morphine sulfate surrounding a sequestered core of naltrexone hydrochloride; CR = controlled-release.

Safety

In the treatment phase, the AE profiles of crushed MSN and crushed morphine sulfate CR were consistent with that of an opioid-containing drug (Table 5), and most AEs were considered by the investigator to be mild in intensity and related to study drug. More participants reported treatment-emergent AEs (TEAEs) after receiving crushed morphine sulfate CR (N = 28; 85%) than after receiving crushed MSN (N = 11; 31%). The most commonly reported TEAEs (occurring in ≥10% of participants) after receiving crushed morphine sulfate CR were nausea,

vomiting, pruritus, dizziness, and hiccups. Somnolence was the only TEAE reported by ≥10% of participants after receiving crushed MSN.

No clinically important mean changes in vital sign values (blood pressure, respiratory rate, heart rate, and pulse oximetry) from baseline to the various time intervals following treatment administration were observed. Small mean changes from baseline to end of study in hematology and serum chemistry parameters were observed, none of which were considered clinically meaningful. All ECG interpretations at the screening visit and during the

A. E_{max} B. AUE_{0-2h} 

■ Placebo (N = 33)
 ■ MSN 120 mg crushed (N = 33)
 □ Morphine sulfate CR 120 mg crushed (N = 33)

Figure 2 Mean (\pm 95% confidence interval [CI]) visual analog scale (VAS) scores for drug liking (“Do you like the drug effect you are feeling now?”) and high (How high are you now?). (A) Estimates for E_{max} and (B) area under the effect curve from 0 to 2 hours (AUE_{0-2h}) are shown (evaluable population). * $P < 0.0001$, extended-release morphine sulfate surrounding a sequestered core of naltrexone hydrochloride (MSN) vs morphine sulfate controlled-release (CR); † $P < 0.001$, MSN vs placebo; ‡ $P < 0.0001$, morphine sulfate CR vs placebo. Dashed line refers to midpoint on bipolar VAS scale. LS = least squares.

naloxone challenge phase were normal or abnormal, not clinically significant. The mean end tidal CO_2 values demonstrated an opioid treatment effect after crushed MSN and crushed morphine sulfate CR dosing relative to placebo, with the mean increase from baseline greater after crushed morphine sulfate CR than after crushed MSN through 12 hours postdose; however, the mean end tidal CO_2 values remained within normal ranges throughout the study. No subjects had an elevated end tidal CO_2 value (≥ 55 mm Hg).

Discussion

The primary objective of this study was to evaluate the PD effects, including drug liking and high, following oral administration of crushed MSN 120 mg compared with crushed morphine sulfate CR 120 mg in an abuse potential study with nondependent recreational opioid users. Study validity was confirmed in that all positive subjective VAS ratings were significantly higher for morphine sulfate CR compared with placebo. Crushed MSN was associated with significantly lower scores on the primary positive

Table 2 Primary endpoint analyses comparing MSN vs morphine sulfate CR on drug liking and high for both E_{max} and AUE_{0-2h} (evaluable population*)

	LS Mean Difference	95% CI	Adjusted P Value [†]
Drug liking (E_{max})	-15.7	-20.2, -11.1	<0.0001
High (E_{max})	-34.9	-42.1, -27.7	<0.0001
Drug liking (AUE_{0-2h})	-24.9	-31.7, -18.1	<0.0001
High (AUE_{0-2h})	-51.1	-61.2, -41.0	<0.0001

* N = 33.

† P values adjusted using the Hochberg method.

AUE_{0-2h} = area under the effect curve from 0 to 2 hours; CI = confidence interval; CR = controlled-release; E_{max} = maximum effect; LS = least squares; MSN = extended-release morphine sulfate surrounding a sequestered core of naltrexone hydrochloride.

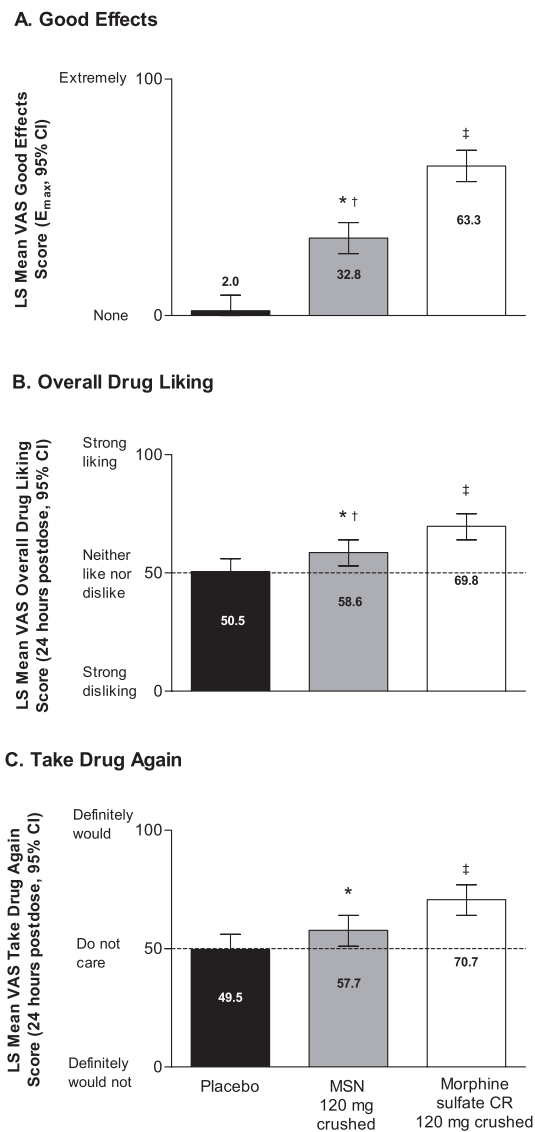


Figure 3 Mean (\pm 95% confidence interval [CI]) visual analog scale (VAS) scores for (A) good effects (“Does the drug have good effects?” measured at E_{max}), (B) overall drug liking (“My overall liking to the drug is . . .” measured at 24 hours postdose), and (C) take drug again (“Would you want to take the drug you just received again if given the opportunity?” measured at 24 hours postdose) (evaluative population). Dashed line refers to midpoint on bipolar scales. * $P \leq 0.005$, extended-release morphine sulfate surrounding a sequestered core of naltrexone hydrochloride (MSN) vs morphine sulfate controlled-release (CR); † $P < 0.03$, MSN vs placebo; ‡ $P < 0.0001$, morphine sulfate CR vs placebo. LS = least squares.

endpoints of drug liking and high, as well as the secondary positive subjective endpoints of good effects, take drug again, and overall drug liking compared with crushed morphine sulfate CR. However, the effects of crushed MSN on these positive measures (with the exception of take drug again) were significantly greater than placebo.

The trends observed for the positive subjective effects were consistent with the objective pupillometry measurements. Mean pupil diameter was smaller with crushed MSN and crushed morphine sulfate CR compared with placebo, but was significantly larger for crushed MSN relative to crushed morphine sulfate CR, indicating attenuated opioid effects with MSN. Together, these data support the hypothesis that tampering with the MSN formulation, such as by crushing, will release naltrexone, which competes with morphine at the μ -opioid receptor, reducing the physiological and behavioral effects of morphine.

Results for the VAS ratings of any drug effects and negative subjective effects (i.e., bad effects, feel sick, nausea, sleepy, and dizzy) showed a similar trend, such that scores were higher for crushed morphine sulfate CR than for crushed MSN. Mean differences between the two treatments were not as great as those observed for positive subjective effect endpoints, possibly because VAS ratings on negative outcomes were relatively low for both treatments. These data indicate that the reduction in drug liking and high in MSN-treated participants was not due to an increase in negative drug effects.

The PK analysis demonstrated time-dependent plasma elevations of naltrexone and its metabolite, 6- β -naltrexol, following treatment with crushed MSN, confirming that naltrexone was released and bioavailable following oral administration. Although both treatments were administered at the same dose and are CR formulations, there were small but significant differences in key PK parameters. C_{max} was statistically significantly lower and t_{max} was statistically significantly longer for crushed MSN relative to crushed morphine sulfate CR. Note that the t_{max} of MSN (0.9 hours) and morphine sulfate CR (0.7 hours) was similar to that of naltrexone (0.8 hours) and shows that peak naltrexone concentrations occur about the same time as the peak morphine concentrations. These differences may be attributed to slight variations in release characteristics when both formulations are crushed. Because the subjective properties of abused drugs are related to speed of absorption and maximal plasma concentrations, the PK differences (albeit small) between crushed MSN and crushed morphine sulfate CR may have contributed to some extent to the reduction in positive subjective effects following MSN. It should be noted from a previous abuse potential study that although orally administered crushed MSN and morphine IR showed similar morphine PK, MSN did show significant reductions on all positive subjective effects relative to morphine IR. This finding was also confirmed with a simulated MSN IV abuse potential study that showed that morphine sulfate coadministered with naltrexone, in the amounts contained

Table 3 LS mean VAS scores (E_{max} , 95% CI[§]) for any drug effects, bad effects, feel sick, nausea, dizzy, and sleepy (evaluable population[¶])

Endpoint	Placebo	MSN Crushed 120 mg	Morphine Sulfate CR Crushed 120 mg	P Values (Unadjusted)
Any drug effects	2.4 (0, 8.1)	29.0 (23.3, 34.8)*†	62.8 (57.1, 68.5)‡	< 0.0001 * < 0.0001 † < 0.0001 ‡
Bad effects	1.0 (0, 5.4)	7.0 (2.6, 11.4)*†	20.7 (16.3, 25.1)‡	< 0.0001 * 0.0215 † < 0.0001 ‡
Feel sick	1.2 (0, 5.3)	5.4 (1.3, 9.5)*†	17.1 (13.0, 21.2)‡	< 0.0001 * 0.0811† < 0.0001 ‡
Nausea	1.4 (0, 5.3)	5.7 (1.8, 9.6)*†	15.7 (11.8, 19.6)‡	< 0.0001 * 0.0529† < 0.0001 ‡
Dizzy	1.1 (0, 5.3)	5.9 (1.6, 10.1)*†	13.9 (9.6, 18.1)‡	0.0018 * 0.0527† < 0.0001 ‡
Sleepy	1.8 (0, 8.3)	27.5 (21.0, 34.0)*†	43.9 (37.4, 50.4)‡	< 0.0001 * < 0.0001 † < 0.0001 ‡

* MSN vs morphine sulfate CR.

† MSN vs placebo.

‡ Morphine sulfate CR vs placebo. Significant effects ($P \leq 0.05$) are in bold.

§ Negative 95% CI lower bounds are set to zero.

¶ N = 33.

CI = confidence interval; CR = controlled-release; E_{max} = maximum effect; LS = least squares; MSN = extended-release morphine sulfate surrounding a sequestered core of naltrexone hydrochloride; VAS = visual analog scale.

in MSN, significantly abated the positive subjective effects compared with IV administration of morphine alone, despite similar morphine PK between the two treatments [19]. This would suggest that the naltrexone in MSN is largely responsible for mitigating the positive and euphoric effects of the coreleased morphine [22]. This is compatible with the peak activity of the agonist and antagonist occurring nearly simultaneously and is compatible with maximum blockage of the agonist effect.

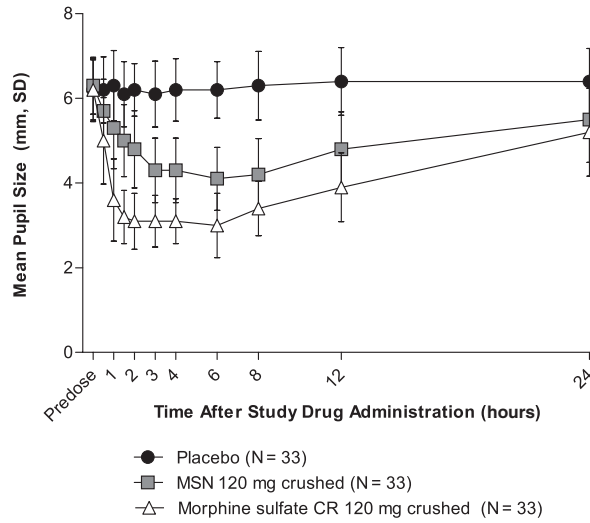
The present data are consistent with findings reported in two previous abuse liability studies [19,22] and extend the findings by including a more relevant positive comparator, a CR formulation of morphine sulfate as well as global assessments of overall drug liking and intent to take drug again. These global endpoints, which also revealed significant differences between treatments, assessed the overall drug experience under drug-free conditions, which may be better predictors of long-term behavior [27].

Crushed MSN had a higher incidence of AEs compared with placebo, but a lower incidence of AEs compared with crushed morphine sulfate CR. Although statistical analyses were not conducted, the data suggest that the release of sequestered naltrexone associated with crushing MSN attenuated the opioid-related adverse effects by antagonizing morphine at the μ opioid receptor. This may have

important safety implications for those who misuse opioids. Signs of respiratory depression were measured in the present study using noninvasive capnography. The increases in end tidal CO_2 concentrations were smaller following ingestion of crushed MSN, suggesting that mitigation of respiratory depression may be possible when higher doses of MSN are crushed and swallowed. The 120-mg dose of morphine in this study did not induce serious respiratory depression, but the pattern of mitigation of the rise of end tidal CO_2 suggests that naltrexone may have a protective effect. Preliminary data from an IV simulation study of morphine and naltrexone (administered in the 25:1 ratio found in MSN) demonstrated that naltrexone administered with morphine significantly reduced signs of respiratory depression (as measured by capnography) relative to morphine alone during the assessment period (i.e., daytime) [28]. Further studies are warranted to determine if the naltrexone in MSN may mitigate the respiratory depressant effects of morphine when MSN is tampered with.

Conclusions drawn from this study are limited due to the relatively small sample size of a homogeneous population (nondependent recreational opioid users). Although guidelines recommend enrolling nondependent recreational opioid users in abuse liability studies, the need to evaluate relevant patient populations exposed to prescription

A. Time course



B. E_{max}

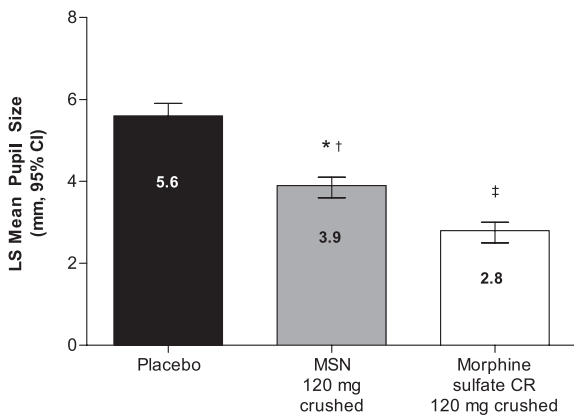


Figure 4 Mean pupil size (diameter, mm): (A) time course and (B) E_{max}. **P* < 0.0001, extended-release morphine sulfate surrounding a sequestered core of naltrexone hydrochloride (MSN) vs morphine sulfate controlled-release (CR); †*P* < 0.0001, MSN vs placebo; ‡*P* < 0.0001, morphine sulfate CR vs placebo. CI = confidence interval; LS = least squares; SD = standard deviation.

opioids has been argued [27]. Study interpretation is also limited in that only one dose of MSN was tested and the effects were studied under fasted conditions. In addition, although the primary PD endpoints used in the present study are well accepted as indicators of abuse potential, demonstration of reduction in misuse, abuse, and diversion with MSN awaits evaluation in real-world epidemiological studies. Only one study to date has examined the relationship between laboratory measures of abuse liability (VAS ratings) and real-world indicators of misuse and

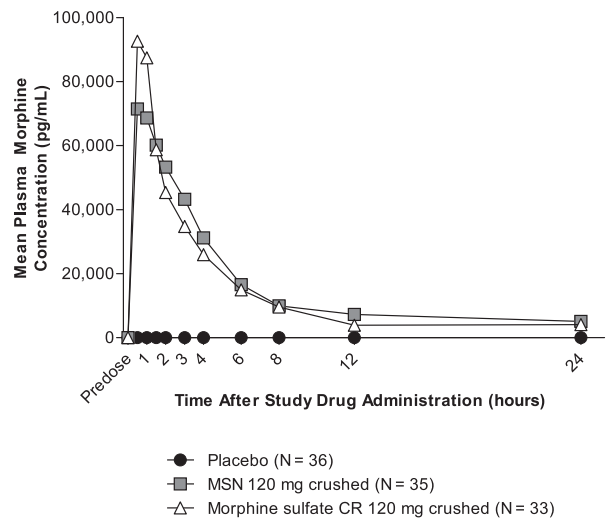


Figure 5 Mean plasma concentrations of morphine over time (safety population). CR = controlled-release; MSN = extended-release morphine sulfate surrounding a sequestered core of naltrexone hydrochloride.

abuse [29]. A retrospective analysis by Eaton et al. [29] suggested that an 8–10-mm difference in the unipolar drug high VAS is clinically important. Additional prospective studies examining the relationship between clinical pharmacology measures of abuse liability and real-life indicators are needed.

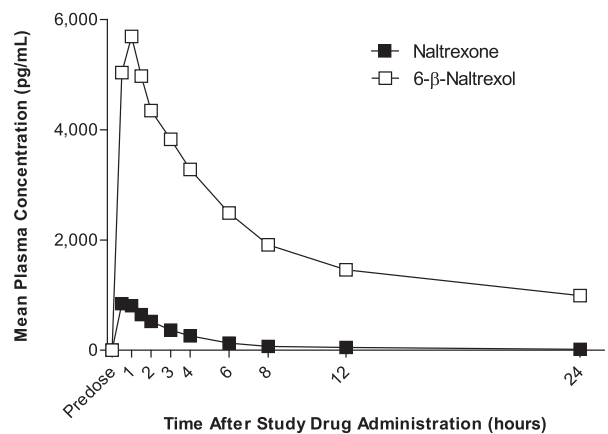


Figure 6 Mean plasma concentrations of naltrexone and 6-β-naltrexol over time following treatment with crushed extended-release morphine sulfate surrounding a sequestered core of naltrexone hydrochloride (MSN) 120 mg (safety population, N = 35).

Table 4 Summary of pharmacokinetic parameters and treatment comparisons for plasma morphine concentrations (safety population)

	MSN Crushed 120 mg N = 35	Morphine Sulfate CR Crushed 120 mg N = 33	P Value for Pairwise Contrast Comparison*
t_{max} , hours			
Mean (SD)	0.9 (0.48)	0.7 (0.25)	0.0181
C_{max} , pg/mL			
Mean (SD)	79,309 (31,556)	103,621 (34,005)	<0.0001
AUC _{0-1h} , hours-pg/mL			
Mean (SD)	52,645 (19,952)	67,920 (24,703)	0.0004
AUC _{0-2h} , hours-pg/mL			
Mean (SD)	112,989 (33,785)	129,721 (39,671)	0.0065
AUC _{0-4h} , hours-pg/mL			
Mean (SD)	197,745 (54,807)	199,442 (60,560)	0.6399
AUC _{0-8h} , hours-pg/mL			
Mean (SD)	269,743 (77,665)	263,270 (76,706)	0.9057
AUC _{0-12h} , hours-pg/mL			
Mean (SD)	303,428 (86,670)	288,324 (81,697)	0.4250
AUC ₀₋₂₄ , hours-pg/mL			
Mean (SD)	376,260 (104,636)	335,357 (91,243)	0.0204
AUC _{0-∞} , hours-pg/mL			
Mean (SD)	551,755 (476,987)	369,270 (98,822)	0.0005

* The analysis was performed on natural log-transformed values for all parameters except t_{max} . A mixed-effect model with fixed effects for sequence, period, and treatment and a random effect for subject nested in sequence were used. Least squares geometric means (except for t_{max} , where LS means were calculated) along with 90% CIs were provided for each treatment. The geometric mean ratios (test/reference) of the natural log-transformed values along with the 90% CIs were calculated for all treatment comparisons.

AUC = area under the plasma concentration–time curve; AUC_{0-∞} = area under the plasma concentration–time curve extrapolated to infinity; C_{max} = maximum observed plasma concentration; CR = controlled-release; MSN = morphine sulfate surrounding an inner core of sequestered naltrexone; SD = standard deviation; t_{max} = time to maximum plasma concentration.

Table 5 Summary of treatment-emergent adverse events in the treatment phase reported by $\geq 5\%$ of participants after any treatment (safety population)

	Placebo N = 36 N (%)	MSN Crushed 120 mg N = 35 N (%)	Morphine Sulfate CR Crushed 120 mg N = 33 N (%)
System Organ Class Preferred Term			
Number of participants with any treatment-emergent AE	3 (8)	11 (31)	28 (85)
Gastrointestinal disorders			
Nausea	1 (3)	3 (9)	15 (45)
Vomiting	0	0	14 (42)
Skin and subcutaneous tissue disorders			
Pruritus	0	2 (6)	12 (36)
Pruritus generalized	0	2 (6)	3 (9)
Nervous system disorders			
Dizziness	0	2 (6)	6 (18)
Somnolence	0	4 (11)	3 (9)
Headache	1 (3)	0	2 (6)
Respiratory, thoracic, and mediastinal disorders			
Hiccups	0	0	5 (15%)

AE = adverse event; CR = controlled-release; MSN = extended-release morphine sulfate surrounding a sequestered core of naltrexone hydrochloride.

Conclusions

MSN contains a sequestered opioid antagonist naltrexone that is coreleased with morphine under conditions of inappropriate use, such as tampering by crushing or chewing, in order to mitigate the effects of morphine. In support of this, the present abuse potential study demonstrated in nondependent recreational opioid users that when crushed and administered orally, MSN was associated with significantly lower scores on all positive subjective measures including drug liking and high, and significantly less pupil constriction compared with morphine sulfate CR.

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