Relative Oral Bioavailability of Morphine and Naltrexone Derived From Crushed Morphine Sulfate and Naltrexone Hydrochloride Extended-Release Capsules Versus Intact Product and Versus Naltrexone Solution: A Single-Dose, Randomized-Sequence, Open-Label, Three-Way Crossover Trial in Healthy Volunteers

Franklin K. Johnson, MS[1]; Jeffrey G. Stark, PhD[2]; Frederick A. Bieberdorf, MD[2†]; and Joe Stauffer, DO, MBA[1,3]

[1]Alpharma Pharmaceuticals LLC, a wholly owned subsidiary of King Pharmaceuticals, Inc., Bridgewater, New Jersey; [2]CEDRA Clinical Research, LLC, Austin, Texas; and [3]The Johns Hopkins University School of Medicine, Baltimore, Maryland

ABSTRACT

Background: Morphine sulfate/sequestered naltrexone hydrochloride (HCl) (MS-sNT) extended-release fixed-dose combination capsules, approved by the US Food and Drug Administration (FDA) in August 2009 for chronic moderate to severe pain, contain extended-release morphine pellets with a sequestered core of the opioid antagonist naltrexone. MS-sNT was designed so that if the product is tampered with by crushing, the naltrexone becomes bioavailable to mitigate morphine-induced subjective effects, rendering the product less attractive for tampering.

Objectives: The primary aim of this study was to compare the oral bioavailability of naltrexone and its metabolite 6-β-naltrexol, derived from crushed pellets from MS-sNT capsules, to naltrexone solution. This study also assessed the relative bioavailability of morphine from crushed pellets from MS-sNT capsules and that from the whole, intact product.

Methods: This single-dose, randomized-sequence, open-label, 3-period, 3-treatment crossover trial was conducted in healthy volunteers. Adults admitted to the study center underwent a 10-hour overnight fast before study drug administration. Each subject received all 3 of the following treatments, 1 per session, separated by a 14-day washout: tampered pellets (crushed for ≥2 minutes with a mortar and pestle) from a 60-mg MS-sNT capsule (60 mg morphine/2.4 mg naltrexone); 60-mg whole, intact MS-sNT capsule; and oral naltrexone HCl (2.4 mg) solution. Plasma concentrations of naltrexone and 6-β-naltrexol were measured 0 to 168 hours after administration. Morphine pharmacokinetics of crushed and whole pellets were determined 0 to 72 hours after administration. The analysis of relative bioavailability was based on conventional FDA criteria for assuming bioequivalence; that is, 90% CIs for ratios of geometric means (natural logarithm [ln]-transformed C_{max} and AUC) fell within the range of 80% to 125%. Subjects underwent physical examinations, clinical laboratory tests, and ECG at screening and study discharge and were monitored for adverse events (AEs) throughout the study.

Results: Of the 24 subjects enrolled in the study, 23 completed it. Most subjects were white (79%) and male (63%); the mean (SD) age was 39.3 (11.2) years and the mean weight was 77.6 (13.5) kg (range, 55.0–102.5 kg). Plasma C_{max} and AUC_{0-t} of naltrexone after the administration of crushed pellets of MS-sNT (579 pg/mL and 1811 h · pg/mL, respectively) and naltrexone solution (584 pg/mL and 1954 h · pg/mL) were not significantly different; 90% CIs were 83.8% to 116% and 83.3% to 102%, meeting the regulatory

†Deceased.

Partial findings from this study were presented in poster form at: 109th and 110th Annual Meetings of the American Society for Clinical Pharmacology and Therapeutics, April 2–5, 2008, Orlando, Florida, and March 18–21, 2009, National Harbor, Maryland; and 27th Annual Scientific Meeting of the American Pain Society, May 8–10, 2008, Tampa, Florida.

Accepted for publication March 12, 2010.
doi:10.1016/j.clinthera.2010.05.011
0149-2918/$ - see front matter

© 2010 Excerpta Medica Inc. All rights reserved.

requirements for assuming bioequivalence in this study population. Plasma naltrexone concentration was below the lower limit of quantitation (4.0 pg/mL) in 23 of 24 subjects (96%) after whole MS-sNT administration. Morphine AUC_{0-t} was not significantly different whether MS-sNT was crushed (163 h · ng/mL) or administered whole (174 h · ng/mL), but C_{max} was numerically higher (24.5 vs 7.7 ng/mL) and T_{max} was numerically shorter (2.00 vs 7.03 hours) with MS-sNT crushed versus whole. The most commonly reported AEs were nausea (8/23 [35%], 10/24 [42%], and 3/23 [13%] subjects in the crushed, whole, and naltrexone groups, respectively) and emesis (6 [26%], 7 [29%], and 2 [9%]).

Conclusions: In this single-dose study, when pellets from MS-sNT were crushed, naltrexone appeared to be completely released and available to mitigate morphine-induced effects. When MS-sNT was administered whole, morphine was released in an extended-release fashion while naltrexone remained sequestered. (*Clin Ther.* 2010;32:1149–1164) © 2010 Excerpta Medica Inc.

Key words: abuse, morphine, naltrexone, opioid, tampering.

INTRODUCTION

Opioids have been used throughout recorded history for medicinal purposes and remain an important class of analgesic agents.[1–4] Immediate-release opioid formulations provide effective pain relief, with a time to onset of 15 to 20 minutes.[5] However, their plasma $t_{1/2}$ of ~3 to 4 hours[6] necessitates frequent dosing to maintain adequate pain control.[5] Oral extended-release opioid formulations were developed to provide clinically effective analgesia with once- or twice-daily dosing.[7] Unexpectedly, illicit use of these extended-release opioid formulations increased proportionally with their legitimate medical use.[8–10] To attain the desired euphoric effect, opioid abusers are likely to tamper with extended-release opioid formulations to provide immediate release of much of the loaded supply of opioid within the formulation.[2,6,11]

Public awareness of the increase in illicit use of prescription opioids and the impact of this abuse on society have resulted in a greater reluctance among physicians and their patients to use opioids for effective pain management.[8,10,12,13] Thus, there is a need for extended-release opioid formulations that are effective in reducing pain but more difficult to tamper with and/or abuse.[2,8,14]

Naltrexone* is an orally available competitive opioid receptor antagonist with high affinity for opioid receptors.[15–19] Naltrexone was approved by the US Food and Drug Administration (FDA) in 1994 for the blockade of the pharmacologic effects of opioids and for the treatment of alcohol dependence.[20] Clinically, it has been reported to block the euphoric effects of opioids[16,20] and to minimize opioid effects.[16,17,19] Naltrexone has been associated with few reported adverse events (AEs), the most common (6%–21%) being gastrointestinal symptoms, such as nausea (21%).[16,18,19,21] Naltrexone has been reported to block the pharmacologic effects of morphine in healthy, opioid-naive volunteers administered oral doses of controlled-release morphine sulfate of up to 200 mg. In these studies, 100-mg doses of naltrexone were administered at 24 hours before, at the same time as, and at 24 hours after the administration of 60 mg (n = 24)[22] or 200 mg (n = 24)[23] controlled-release morphine sulfate. The findings from these studies suggest the utility of naltrexone blockade in opioid-naive volunteers administered high oral doses of morphine.

On oral administration, naltrexone is nearly completely (>96%) absorbed from the gastrointestinal tract.[24] Naltrexone undergoes rapid and extensive first-pass metabolism to its primary metabolite, 6-β-naltrexol, limiting the amount of unchanged naltrexone reaching the systemic circulation, with an estimated naltrexone oral bioavailability of 5% to 60%.[15,16,18,21,25,26] The 6-β-naltrexol metabolite is an opioid receptor antagonist ~12- to 50-fold less potent than the parent molecule.[25] Because as much as 95% of naltrexone is subject to first-pass metabolic conversion to 6-β-naltrexol, plasma concentrations of the metabolite are orders of magnitude greater than that of the parent molecule.[16,21,24,25] Thus, pharmacokinetic studies measure plasma naltrexone and 6-β-naltrexol concentrations.

The strategy of sequestering naltrexone within an extended-release morphine formulation has been developed. This proprietary formulation, morphine sulfate/sequestered naltrexone hydrochloride (HCl) (MS-sNT) extended-release fixed-dose combination capsules†[27] for oral use, was approved by the FDA in August 2009[28] for the management of chronic moderate to severe pain. These gelatin capsules contain polymer-

*Trademark: Revia® (DuPont Pharma, Wilmington, Delaware).
†Trademark: Embeda® (Alpharma Pharmaceuticals LLC, a wholly owned subsidiary of King Pharmaceuticals, Inc., Bridgewater, New Jersey).

coated extended-release morphine sulfate pellets. Embedded in each pellet is a sequestered core of naltrexone. When administered as intended (whole capsule or intact pellets sprinkled on applesauce and consumed without chewing), the extended-release properties of the formulation are maintained to provide analgesic effects of morphine while the sequestered core of naltrexone remains intact. If MS-sNT pellets are tampered with by crushing, the sequestered naltrexone core becomes disrupted, rendering the opioid antagonist bioavailable to mitigate the pharmacologic effects of the morphine that is concurrently released.

When MS-sNT is tampered with by crushing, sufficient naltrexone must be released to be available to mitigate the effects of morphine. This relative bioavailability study was designed to assess the pharmacokinetics of naltrexone, 6-β-naltrexol, and morphine if MS-sNT should be tampered with by crushing and administered orally. The study was designed to determine how much of the naltrexone sequestered within the MS-sNT capsule would be released on crushing to provide supportive information for the New Drug Application submitted to the FDA. Comparisons were made to intact MS-sNT administered orally and to an equivalent dose of oral naltrexone HCl solution.

SUBJECTS AND METHODS

This single-dose, randomized-sequence, open-label, 3-period, 3-treatment crossover study was conducted at CEDRA Clinical Research, LLC, Austin, Texas, between February 12, 2007, and March 19, 2007. The protocol was approved by IntegReview Ethical Review Board, Austin, Texas, an independent institutional review board chosen by CEDRA. This study was conducted before the publication of the 2008 revision to the Declaration of Helsinki and therefore does not have a study registration number.

Inclusion Criteria

Healthy men and women between the ages of 18 and 55 years were recruited by advertising and from the study center's database. Serology tests, including hepatitis B virus, hepatitis C virus, and HIV, were conducted at screening and at discharge. Urine samples were tested for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, and opioids) in all potential subjects, and urinary pregnancy tests were conducted in all of the women. Potential subjects were excluded if they had any abnormal finding on physical examination, medical history taking, or clinical laboratory analysis, or if they had any condition that could jeopardize their safety or the validity of the study results. Other major exclusion criteria were adverse or allergic reactions or intolerance to morphine or naltrexone, use of over-the-counter medications within 7 days before the administration of the first dose of study drug, use of prescription medications (except hormonal contraceptive or hormone replacement therapy) within 14 days before the administration of the first dose of study drug, tobacco use within 60 days before the administration of the first dose of study drug, treatment for drug or alcohol abuse in the past 5 years, treatment of or positive test result for HIV, or positive urine drug screen for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, or opioids.

Women who were pregnant or breastfeeding were ineligible. Women of childbearing potential were required to use approved contraceptive methods. Subjects were required to provide written informed consent before the initiation of any study-specific procedure.

The research coordinator provided instructions to the subjects when they were admitted to the facility concerning the reporting of any AEs they might have experienced at any time during the study from consent until resolution. A script was followed to review all events that would occur in-house.

Study Drug Administration

Before study treatment, each subject was admitted to the study center and underwent a 10-hour overnight fast. Subjects were randomized to a treatment sequence, using a schedule prepared by the clinical site's biostatistician using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina), as follows: subjects were assigned numbers in an ascending order based on successful completion of the screening process. Then each subject was assigned a treatment sequence based on a randomization schedule prepared by the CEDRA biostatistics personnel and provided to the research center. Subjects received each of the 3 single-dose treatments, 1 per study period, administered with 240 mL of apple juice at room temperature, as follows:

1. Crushed pellets from a 60-mg MS-sNT capsule (60 mg morphine/2.4 mg sequestered naltrexone) (lot no. PI-1594; expiration, October 2008). Just before administration, pellets of MS-sNT were ground using a mortar and pestle for ≥2 minutes.

A small amount (~90 mL) of a commercial brand of apple juice was poured into the mortar, stirred, and poured into a dosing cup. This step was repeated twice, using a total of 180 mL of apple juice. The subjects consumed all of the crushed MS-sNT–apple juice mixture, and the dosing cup was rinsed 3 times, each time with 20 mL of apple juice.

2. A 60-mg whole, intact MS-sNT capsule (lot no. PI-1594; expiration, October 2008).
3. Oral naltrexone HCl (2.4 mg) solution, prepared on the morning of administration by drawing 2.4 mg of naltrexone solution (Professional Compounding Association of America; lot no. C115850; expiration, June 1, 2009) into a 3-mL syringe for oral administration.

All doses were administered by qualified research personnel. The protocol required that all subjects remain in the study research center for the duration of each treatment period and return to the study site for all outpatient visits. Subjects fasted for 4 hours after the administration of each dose of study drug; water was allowed ad libitum except for 1 hour before through 1 hour after study drug administration. Subjects received the same diet while at the study site. Meals were provided at 4 and 10 hours after drug administration and at standard mealtimes thereafter. Subjects were required to refrain from any consumption of alcohol, caffeine, and foods and beverages containing xanthine or grapefruit, as well as from strenuous exercise for 48 hours before the administration of the first dose of study drug until study discharge. Each study period was preceded by a washout time of ≥14 days.

Pharmacokinetic Assessments

For pharmacokinetic analysis, blood samples (3 mL for morphine and 6 mL for naltrexone and 6-β-naltrexol) were collected into tubes containing EDTA as a preservative (Vacutainer, Becton, Dickinson and Company, Franklin Lakes, New Jersey) at 0 (baseline), 2, 4, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 12, 18, 24, 30, 36, 48, and 72 hours after administration for morphine determination, and at 0 (baseline), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168 hours after administration for naltrexone and 6-β-naltrexol determinations. Samples for pharmacokinetic analysis were collected via direct venipuncture without catheters. After collection, samples were centrifuged at 3000 rpm for 10 minutes (1811*g*) at 4°C. Plasma samples were transferred into appropriately labeled polypropylene screw-cap tubes and stored at ≤–20°C within 1 hour of collection until analysis.

All frozen pharmacokinetic samples were packed with appropriate documentation and on sufficient dry ice for shipment to a central laboratory at CEDRA. Internal and calibration standards and controls were prepared at the analysis center. Morphine, naltrexone, and 6-β-naltrexol concentrations were measured using validated bioanalytic methods (LC-MS/MS). EDTA plasma samples were assayed for morphine using a validated analytic method over the range of 0.200 to 60 ng/mL for morphine (based on analysis of 0.25 mL EDTA human plasma) (data on file, Determination of Morphine, Morphine 3-β-glucuronide, and Morphine-6-β-glucuronide in EDTA Human Plasma by LC-MS/MSC, CEDRA document control no. 11-100-V4, 2005). Plasma samples containing morphine internal standard (morphine D6 [Cerilliant Corporation, Round Rock, Texas] prepared at 100 µg/mL in methanol) were diluted with acid and extracted via solid-phase extraction. The eluent from this extraction was evaporated and reconstituted, and an aliquot of the reconstituted extract was injected onto a Sciex API 4000 LC-MS/MS (Applied Biosystems Inc., Foster City, California) in positive-ion electrospray mode equipped with a silica HPLC column. The peak area of the morphine ion product was measured against the peak area of the morphine D_6 internal standard product ion.

Quantitation was conducted using separate weighted linear least squares regression analysis generated from calibration standards prepared immediately before each run. The assay was linear over the range 0.200 to 60 ng/mL for morphine. Precision and accuracy were confirmed and there were no interferences observed at morphine retention time. Morphine recovery ranged from 65.7% to 81.1%. Plasma concentrations of the 2 major metabolites of morphine, morphine-3-glucuronide and morphine-6-glucuronide, were not measured in this study. These metabolites have been found to have a plasma concentration–time profile similar to that of morphine (data on file, King Pharmaceuticals study no. ALO-01-07-101, 2007).

The analysis for naltrexone over the range of 4.00 to 500 pg/mL and 6-β-naltrexol over the range of 10.0 to 4000 pg/mL (0.5 mL EDTA human plasma) was conducted based on validated methods (data on file, CEDRA, document control no. 11-758-V3, Determina-

tion of 6β-Naltrexol in EDTA Human Plasma by LC-MS/MS, 2003; and CEDRA, document control no. 11-891-V2, Determination of Naltrexone and 6β-Naltrexol in EDTA Human Plasma by LC-MS/MS, 2005), as follows: internal standards (naltrexone D_3 and 6-β-naltrexol-D_3 HCl [Cerilliant Corporation]) were added to the plasma samples, which were then extracted with an organic solvent mixture under alkaline conditions. Following centrifugation, the upper organic layer was removed and further cleansed using liquid–liquid extraction. The extract was dried, reconstituted, and then injected onto the LC-MS/MS system as described previously.

Quantitation was performed in a manner similar to that described for morphine by the addition of 20 μL of calibration standards for naltrexone and 6-β-naltrexol (Sigma-Aldrich Corporation, St. Louis, Missouri, and Mallinckrodt Baker, Inc., Phillipsburg, New Jersey, respectively) to 0.5 mL of plasma to yield the required concentration ranges. Precision and accuracy were established. The assay was linear over the range of 4.00 to 500 pg/mL for naltrexone and 10.00 to 4000 pg/mL for 6-β-naltrexol. No interference, except from naloxone, was noted at the retention times of naltrexone and 6-β-naltrexol.

A more sensitive analysis for 6-β-naltrexol was conducted over the range of 0.25 to 10 pg/mL (1.0 mL EDTA human plasma). In this assay, human EDTA plasma containing 6-β-naltrexol and the internal standard was extracted with an organic solvent mixture and reconstituted as described previously. An aliquot of the reconstituted extract was injected onto the LC-MS/MS system and quantified as described previously by adding 20 μL of spiking solution of calibration standards at final concentrations of 0.25 to 10 pg/mL to 1 mL of plasma. This assay was found to be linear over the range of 0.25 to 10 pg/mL for 6-β-naltrexol. The average recovery of 6-β-naltrexol ranged from 40.2% to 45.3%. No interference was observed at the retention time of 6-β-naltrexol. Accuracy, precision, and short-term sample stability were established for each assay. The intrarun and interrun %CVs were 1.7% to 10.7% and 4.9% to 9.3%, respectively, for the morphine assay; 1.4% to 26.9% and 4.8% to 13.6% for the naltrexone assay; 5.0% to 14.8% and 1.0% to 27.7% for the higher-concentration 6-β-naltrexol assay; and 0.7% to 7.7% and 1.9% to 5.3% for the lower-concentration 6-β-naltrexol assay.

Noncompartmental pharmacokinetic analysis was conducted using WinNonlin Enterprise Edition version 4.0 (Pharsight Corporation, Mountain View, California). The pharmacokinetic measures included the determination of plasma morphine, naltrexone, and 6-β-naltrexol concentrations at each time point, as well as C_{max} and T_{max}, by direct observation of the mean concentration–time data from individual subjects and estimation of AUC_{0-t}, using the linear trapezoidal rule and extrapolated to infinity ($AUC_{0-\infty}$) by calculating $AUC_{0-t} + C_{last}/\lambda_z$, where λ_z was the apparent first-order terminal elimination rate constant estimated using linear least squares regression.

Quality control was run every 8 hours in the laboratory when the analyzers were in use. Specimen volumes and collection devices, as well as processing, transport, and storage requirements, were specified by the laboratory's standard operating procedures.

Tolerability Assessment

Subjects were to report to the investigator or a designated member of the research staff whenever they believed an AE occurred at any time during the study, from consent until resolution. AEs were collected on a one-on-one basis throughout the duration of the study. Subjects were reminded to refrain from discussing AEs with one another, and those experiencing AEs such as vomiting were isolated from the other subjects until no further episodes occurred and the subject was feeling better. AEs were deemed resolved by the investigator.

Blood pressure, heart rate, respiratory rate, and temperature were measured at screening and before the administration of study drug. Blood pressure, heart rate, and respiratory rate were measured at ~2, 4, 8, 12, 24, 36, 72, and 168 hours after administration. Blood pressure was measured after 3 minutes of rest using the right arm and an automated sphygmomanometer. One-minute respiration rate was measured manually. Hematology (hemoglobin, hematocrit, total and differential leukocyte count, red blood cell count, and platelet count), serum chemistry (albumin, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, sodium, potassium, chloride, lactate dehydrogenase, uric acid, and glucose), and urinalysis (pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase, and urobilinogen) were conducted by CEDRA at screening and discharge using an automated dipstick method.

Oxygen saturation via pulse oximetry was measured and assessed before the administration of each study drug and at ~2, 4, 8, 12, and 24 hours after administration.

The investigator (F.A.B.) monitored tolerability and provided appropriate medical care to all of the study participants.

Statistical Analysis

The pharmacokinetic parameters (C_{max} and AUC) were compared between treatments using an ANOVA model, with sequence, subject within sequence, treatment, and period as variables and using the natural logarithms (ln) of the data. The 90% CIs were constructed for the test/reference ratios of both parameters using the ln-transformed data and the two 1-sided *t* tests procedure. The analysis applied FDA criteria for bioequivalence, which require that the 90% CIs for ratios of the geometric means (ln[C_{max}] and ln[AUC]) fall within an interval of 80% to 125%.[29–31] Correction for body weight was not indicated in the FDA guidance[29]; the correction was not performed. Per FDA guidance, an additional statistical analysis excluded data from subjects who experienced emesis during the proposed dosing interval (up to 12 hours after administration).

RESULTS

Study Population

Of the 24 subjects enrolled in the study, 23 completed it. One subject was withdrawn before the second dosing period because of a positive urine drug screen result. Data from this subject were excluded from the pharmacokinetic analysis. Most of the subjects were white (19/24 [79%]), male (15/24 [63%]), and had never smoked (19/24 [79%]); the mean (SD) age was 39.3 (11.2) years and the mean weight was 77.6 (13.5) kg (range, 55.0–102.5 kg).

Plasma Naltrexone Concentrations

Plasma concentrations of naltrexone were not significantly different between MS-sNT crushed pellets and naltrexone solution at any time point (**Figure 1**). The first quantifiable plasma naltrexone concentrations occurred at 0.5 hour after administration, and peak concentrations were attained at 1 hour after the administration of MS-sNT crushed pellets and naltrexone solution. The maximum mean (SD) naltrexone concentrations were 599 (408) and 629 (439) pg/mL with the MS-sNT crushed pellets and naltrexone solution, respectively.

Plasma naltrexone concentrations for times beyond those shown in **Figure 1** were below the lower limit of quantitation (LLOQ). After the administration of the whole, intact MS-sNT capsule, plasma naltrexone was below the LLOQ (4 pg/mL) in all subjects, with the exception of one subject who had a single value of 5.50 pg/mL at 72 hours after administration. No further analysis could be conducted on plasma naltrexone concentrations from MS-sNT whole capsules.

A summary of pharmacokinetic assessments for MS-sNT crushed pellets and naltrexone solution is provided in **Table I**. The 90% CIs for the treatment (MS-sNT crushed pellets and naltrexone solution) ratios of the ln-transformed naltrexone C_{max} (mean ratio, 98.5% [90% CI, 83.8%–115.9%]) and $AUC_{0-\infty}$ (93.1% [90% CI, 84.4%–102.7%]) were within the regulatory range for assuming bioequivalence. The exclusion of data from subjects who had emesis during the 12-hour dosing interval did not affect plasma naltrexone pharmacokinetic statistical comparisons of MS-sNT crushed pellets and naltrexone solution.

Plasma 6-β-Naltrexol Concentrations

Plasma concentrations of 6-β-naltrexol appeared similar after oral administration of MS-sNT crushed pellets and naltrexone solution (**Figure 2**). The first quantifiable plasma 6-β-naltrexol concentrations occurred at 0.5 hour after administration, and peak concentrations were attained at 1 hour after the administration of MS-sNT crushed pellets and 1.5 hours after the administration of oral naltrexone solution. The maximum mean (SD) 6-β-naltrexol concentrations were 3120 (994) and 3570 (1360) pg/mL with MS-sNT crushed pellets and naltrexone solution, respectively. Plasma 6-β-naltrexol concentrations were quantifiable (>0.250 pg/mL) during ≥1 time point through 168 hours after administration in most of the subjects (MS-sNT crushed, 23/23 [100%]; MS-sNT whole, 14/23 [60.9%]; naltrexone solution, 23/23 [100%]).

Plasma 6-β-naltrexol pharmacokinetic assessments are provided in **Table II**. The 90% CIs of the ratios for 6-β-naltrexol C_{max} and $AUC_{0-\infty}$ (94.7% [90% CI, 86.3%–104.0%] and 92.2% [90% CI, 85.5%–99.5%], respectively) fell within the regulatory range for assuming bioequivalence of MS-sNT crushed pellets and naltrexone solution. The exclusion of data from subjects who had emesis during the proposed dosing interval did not affect comparisons of plasma 6-β-naltrexol after the administration of MS-sNT crushed pellets and naltrexone solution.

Following the administration of the whole, intact MS-sNT capsule, 14 subjects had quantifiable concentrations of 6-β-naltrexol (≥0.25 pg/mL) at some or all

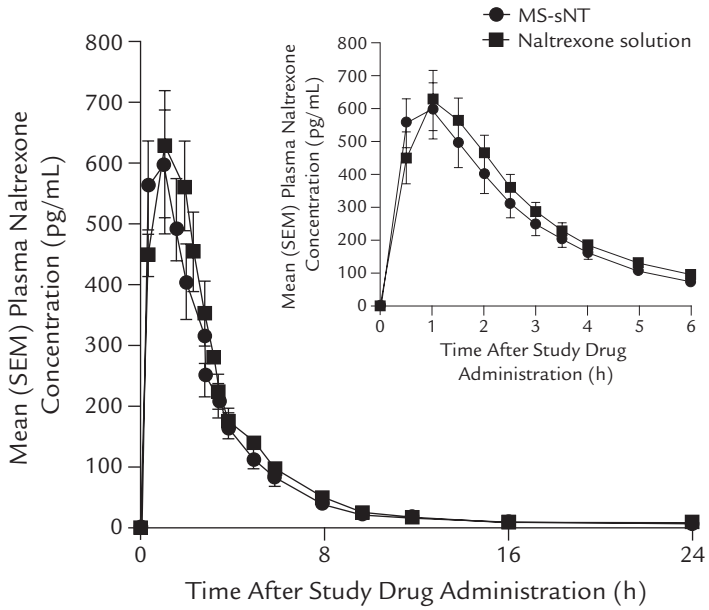

Figure 1. Plasma concentration–time curve of naltrexone (lower limit of quantitation, 4 pg/mL) after oral administration of crushed pellets from morphine sulfate/sequestered naltrexone hydrochloride (HCl) (MS-sNT) extended-release fixed-dose combination (60 mg morphine/2.4 mg naltrexone) capsules (test) and naltrexone HCl 2.4-mg solution (reference) in healthy volunteers. Concentrations of naltrexone were not detectable with MS-sNT whole, intact capsules. Inset: First 6 hours after administration.

time points, making up ~34% of the total number of samples for the 6-β-naltrexol analysis. The highest individual 6-β-naltrexol concentration with MS-sNT whole capsules was 49.5 pg/mL at 60 hours after administration, and the highest mean 6-β-naltrexol concentration was 4.53 pg/mL at 72 hours after administration. As a comparison, the mean C_{max} of 6-β-naltrexol with MS-sNT crushed pellets (3530 pg/mL) was 71-fold greater than the highest individual 6-β-naltrexol concentration observed (49.5 pg/mL) after administration of the intact capsule. The mean C_{max} from the oral solution was 75-fold greater.

Plasma Morphine Concentrations

The plasma morphine concentration–time profiles distinctly differed between MS-sNT crushed pellets and whole capsules (**Figure 3**). At 2 hours after administration (the first postdose blood sample for plasma morphine determinations), the mean plasma morphine concentration with MS-sNT crushed pellets was ~15-fold greater than that with MS-sNT whole capsules (26.1 vs 1.75 ng/mL). In most subjects, plasma morphine remained quantifiable (>0.200 ng/mL) through 72 hours after administration of whole capsules. Nine subjects (39%) had quantifiable plasma morphine concentrations at 72 hours after administration of the crushed pellets.

Because minimal samples were collected for morphine pharmacokinetic analysis within the first 6 hours after administration, a precise morphine T_{max} with MS-sNT crushed pellets could not be determined in this study. C_{max} was reached by 2.00 hours with the crushed pellets, while T_{max} with the MS-sNT whole capsule was 7.03 hours (range, 6.00–12.00 hours) (**Table III**). The observed mean C_{max} with MS-sNT crushed pellets was 24.5 ng/mL, while mean C_{max} with the MS-sNT whole capsule was 7.7 ng/mL, with ln-transformed ratios for C_{max} outside of the regulatory range to assume bioequivalence (80%–125%; ratio, 314%; 90% CI, 289–342). Total systemic exposure based on AUC_{0-t} was not significantly different (mean crushed/whole ratio, 93.4%; 90% CI, 87.5–99.6). The systemic exposure based on $AUC_{0-\infty}$ was significantly lower with MS-sNT crushed pellets relative to MS-sNT whole capsules (mean ratio, 87.6%; 90% CI, 78.0–98.3). When subjects who had

Table I. Naltrexone pharmacokinetics of crushed pellets from morphine sulfate/sequestered naltrexone hydrochloride (HCl) (MS-sNT) extended-release fixed-dose combination (60 mg morphine/2.4 mg naltrexone) capsules (test) and naltrexone HCl 2.4-mg solution (reference) after oral administration in healthy volunteers.*

Assessment	MS-sNT Crushed Pellets	Naltrexone
Nontransformed data		
All subjects	(n = 23)	(n = 23)
C_{max}, mean (%CV), pg/mL	579 (62.8)	584 (62.3)
AUC_{0-t}, mean (%CV), h · pg/mL	1811 (61.2)	1954 (57.6)
$AUC_{0-\infty}$, mean (%CV), h · pg/mL	1870 (61.3)	2000 (56.9)
T_{max}, median (range), h	1.00 (0.50–2.00)	1.00 (0.50–2.00)
Excluding subjects who experienced emesis during the proposed labeled dosing interval (12 h)	(n = 18)	(n = 22)
C_{max}, mean (%CV), pg/mL	543 (69.2)	560 (61.6)
AUC_{0-t}, mean (%CV), h · pg/mL	1775 (64.3)	1913 (59.3)
$AUC_{0-\infty}$, mean (%CV), h · pg/mL	1843 (64.4)	1959 (58.6)
T_{max}, median (range), h	1.00 (0.50–2.00)	1.00 (0.50–2.00)
Ln-transformed data		
All subjects	(n = 23)	(n = 23)
C_{max}		
Geometric mean†	571	580
Test/reference ratio (90% CI), %	98.5 (83.8–115.9)	
AUC_{0-t}		
Geometric mean†	1798	1949
Test/reference ratio (90% CI), %	92.3 (83.3–102.1)	
$AUC_{0-\infty}$		
Geometric mean†	1857	1994
Test/reference ratio (90% CI), %	93.1 (84.4–102.7)	
Excluding subjects who experienced emesis during the proposed dosing interval	(n = 18)	(n = 22)
C_{max}		
Geometric mean†	524	535
Test/reference ratio (90% CI), %	98.0 (82.6–116.3)	
AUC_{0-t}		
Geometric mean†	1734	1855
Test/reference ratio (90% CI), %	93.5 (85.4–102.4)	
$AUC_{0-\infty}$		
Geometric mean†	1802	1903
Test/reference ratio (90% CI), %	94.7 (86.9–103.1)	

ln = natural logarithm.
*Values for MS-sNT whole capsules were below the lower limit of quantitation.
† Geometric means were based on the least squares means of ln-transformed values.

emesis during the proposed 12-hour dosing interval were excluded, plasma morphine pharmacokinetic properties were not significantly different from those obtained when all subjects were included.

Safety Profile

Over the course of the study, a total of 89 treatment-emergent AEs were reported by 15 of 24 subjects (63%) (**Table IV**). Of these, 87 were considered by the inves-

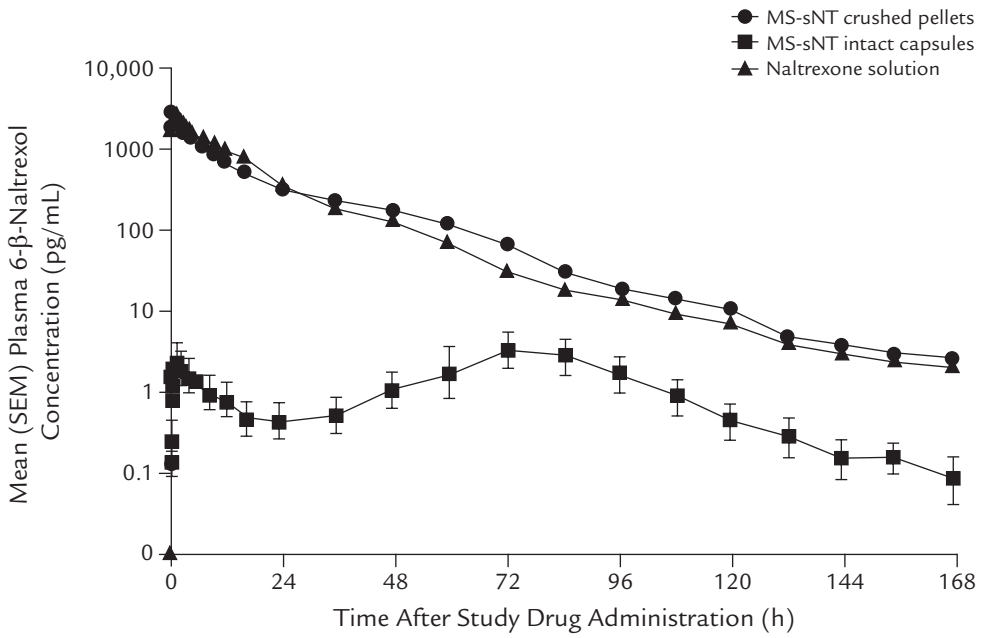

Figure 2. Plasma concentration–time curves of 6-β-naltrexol (lower level of quantitation, 0.25 pg/mL) after oral administration of crushed pellets or whole, intact capsules of morphine sulfate/sequestered naltrexone hydrochloride (HCl) (MS-sNT) extended-release fixed-dose combination (60 mg morphine/2.4 mg naltrexone) capsules (test) and naltrexone HCl 2.4-mg solution (reference) in healthy volunteers.

tigator as mild and 2 were considered moderate (vomiting and nausea after treatment with intact MS-sNT). Forty-six of the AEs (52%) were considered by the investigator to be definitely related to the study treatment; 10 (11%), probably related; 9 (10%), possibly related; and 24 (27%), unrelated. The most common AEs were nausea (8/23 [35%], 10/24 [42%], 3/23 [13%] subjects in the crushed, whole, and naltrexone groups, respectively) and emesis (6 [26%], 7 [29%], and 2 [9%]). Subjects who were excluded from the pharmacokinetic analysis because of vomiting were included in the tolerability analysis. None of the subjects were withdrawn from study participation due to AEs, and there were no serious AEs reported in any of the treatment groups.

In the opinion of the investigator, no clinically significant abnormalities in clinical laboratory assessments were observed when results from baseline (screening) were compared to those from study discharge. No clinically significant observations were identified on physical examination including vital sign measurements (eg, pulse oximetry and respiratory rate). Although naloxone was available for use in the event of decreased oxygen saturation, none of the subjects required this rescue medication during the study.

DISCUSSION

The findings from this study suggest that the naltrexone sequestered within the core of each pellet in MS-sNT capsules is fully released if the pellets are crushed and administered orally. The plasma naltrexone C_{max} and AUC (bioavailability) after the administration of MS-sNT crushed pellets were not significantly different from those of the equivalent dose of naltrexone solution, with the mean plasma concentration–time profiles suggesting similar disposition. With MS-sNT crushed pellets and naltrexone treatments, a T_{max} of 1 hour was found with naltrexone and its primary active metabolite, 6-β-naltrexol. As with plasma naltrexone, 6-β-naltrexol had a similar disposition in plasma with both treatments, with similar pharmacokinetic profiles with MS-sNT crushed pellets and the naltrexone solution. MS-sNT crushed pellets and the naltrexone solution were not significantly different

Table II. Pharmacokinetics of 6-β-naltrexol after oral administration of crushed pellets (test) or whole, intact capsules of morphine sulfate/sequestered naltrexone hydrochloride (HCl) (MS-sNT) extended-release fixed-dose combination (60 mg morphine/2.4 mg naltrexone) capsules and naltrexone HCl 2.4-mg solution (reference) in healthy volunteers.

Parameter	MS-sNT Crushed Pellets	MS-sNT Intact Capsules	Naltrexone Solution
Nontransformed data			
All subjects	(n = 23)	(n = 11)	(n = 23)
C_{max}, mean (%CV), pg/mL	3530 (35.4)	8.9 (95.9)	3710 (34.4)
AUC_{0-t}, mean (%CV), h · pg/mL	38,130 (30.5)	304 (119)	41,330 (29.6)
$AUC_{0-\infty}$, mean (%CV), h · pg/mL	38,210 (30.5)	368 (110)*	41,440 (29.7)
T_{max}, median (range), h	1.00 (0.50–2.00)	60.0 (1.50–84.0)	1.00 (0.50–2.53)
Excluding subjects who experienced emesis during the proposed labeled dosing interval (12 h)	(n = 18)	(n = 9)	(n = 22)
C_{max}, mean (%CV), pg/mL	3280 (37.5)	13.2 (80.4)	3610 (31.7)
AUC_{0-t}, mean (%CV), h · pg/mL	35,700 (25.5)	374 (109)	41,000 (30.4)
$AUC_{0-\infty}$, mean (%CV), h · pg/mL	35,760 (25.5)	388 (107)	41,100 (30.4)
T_{max}, median (range), h	1.00 (0.50–2.00)	60.0 (1.50–84.0)	1.25 (0.50–2.53)
Ln-transformed systemic exposure: MS-sNT crushed pellets vs naltrexone HCl solution			
All subjects	(n = 23)	(n = 11)	(n = 23)
C_{max}			
Geometric mean†	3501	–	3696
Test/reference ratio (90% CI), %		94.7 (86.3–104.0)	
AUC_{0-t}			
Geometric mean†	38,133	–	41,339
Test/reference ratio (90% CI), %		92.2 (85.5–99.5)	
$AUC_{0-\infty}$			
Geometric mean†	38,211	–	41,451
Test/reference ratio (90% CI), %		92.2 (85.5–99.5)	
Excluding subjects who experienced emesis during the proposed dosing interval	(n = 18)	(n = 9)	(n = 22)
C_{max}			
Geometric mean†	3192	–	3335
Test/reference ratio (90% CI), %		95.7 (85.1–107.6)	
AUC_{0-t}			
Geometric mean†	35,434	–	37,567
Test/reference ratio (90% CI), %		94.3 (86.7–102.6)	
$AUC_{0-\infty}$			
Geometric mean†	35,503	–	37,651
Test/reference ratio (90% CI), %		94.3 (86.7–102.6)	

ln = natural logarithm.
*n = 10.
† Geometric mean for crushed pellets from MS-sNT capsules (test) and naltrexone HCl solution (reference) based on least squares means of ln-transformed values.

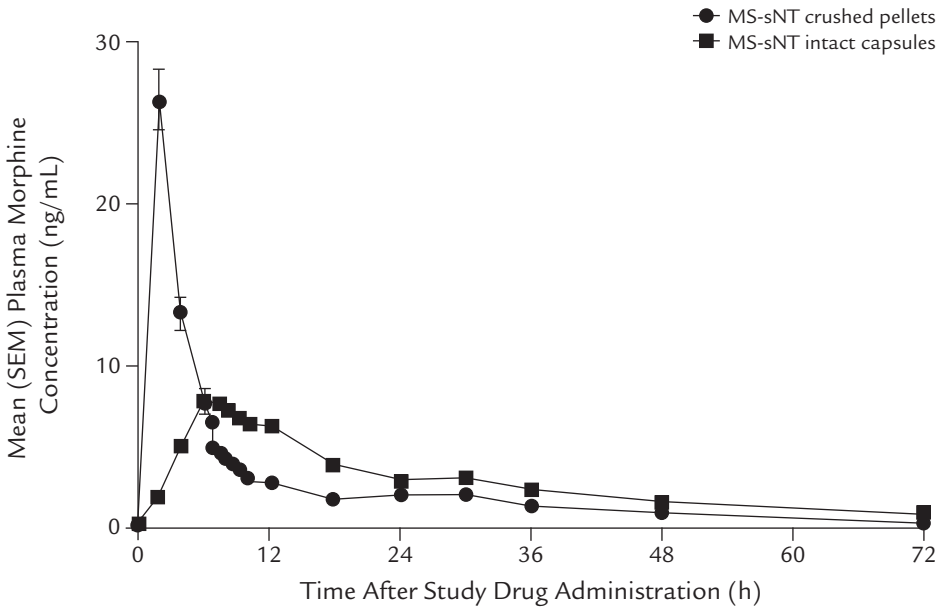

Figure 3. Plasma concentration–time curve of morphine (lower limit of quantitation, 0.2 ng/mL) after oral administration of crushed pellets or whole, intact capsules of morphine sulfate/sequestered naltrexone hydrochloride (MS-sNT) extended-release fixed-dose combination (60 mg morphine/2.4 mg naltrexone) capsules in healthy volunteers.

Table III. Pharmacokinetics of morphine after oral administration of crushed pellets or whole, intact capsules of morphine sulfate/sequestered naltrexone hydrochloride (MS-sNT) extended-release fixed-dose combination (60 mg morphine/2.4 mg naltrexone) capsules.

Parameter	MS-sNT Crushed Pellets	MS-sNT Intact Capsules
All subjects	(n = 23)	(n = 23)
C_{max}, mean (%CV), ng/mL	24.5 (35.0)	7.7 (42.4)
AUC_{0-t}, mean (%CV), h · ng/mL	163 (33.1)	174 (31.4)
$AUC_{0-\infty}$, mean (%CV), h · ng/mL	177 (29.3)	202 (37.5)
T_{max}, median (range), h	2.00 (2.00–2.10)	7.03 (6.00–12.00)
Excluding subjects who experienced emesis during the proposed labeled dosing interval	(n = 18)	(n = 19)
C_{max}, mean (%CV), ng/mL	22.8 (35.1)	7.4 (44.3)
AUC_{0-t}, mean (%CV), h · ng/mL	156 (31.6)	168 (33.3)
$AUC_{0-\infty}$, mean (%CV), h · ng/mL	171 (28.1)	184 (31.2)
T_{max}, median (range), h	2.00 (2.00–2.03)	7.03 (6.00–12.00)

Table IV. Treatment-emergent adverse events (AEs) after oral administration of crushed pellets or whole, intact capsules of morphine sulfate/sequestered naltrexone hydrochloride (HCl) (MS-sNT) extended-release fixed-dose combination (60 mg morphine/2.4 mg naltrexone) capsules (test) and naltrexone HCl 2.4-mg solution (reference) in healthy volunteers. Values are number (%) of subjects.

Parameter	MS-sNT Crushed Pellets (n = 23)	MS-sNT Intact Capsules (n = 24)	Naltrexone Solution (n = 23)
Subjects with ≥1 AE	10 (43)	11 (46)	7 (30)
Drug-related AEs	10 (43)	10 (42)	2 (9)
Adverse event			
Nausea	8 (35)	10 (42)	3 (13)
Emesis	6 (26)	7 (29)	2 (9)
Dizziness	6 (26)	5 (21)	2 (9)
Headache	3 (13)	4 (17)	3 (13)
Paresthesia	2 (9)	0	0
Vasovagal syncope	2 (9)	0	0
Asthenia	1 (4)	2 (8)	0
Somnolence	1 (4)	0	1 (4)
Disorientation	1 (4)	0	0
Drug hypersensitivity	1 (4)	0	0
Dysgeusia	1 (4)	0	0
Euphoric mood	1 (4)	0	0
Eustachian tube obstruction	1 (4)	0	0
Pharyngolaryngeal pain	1 (4)	0	0
Skin irritation	1 (4)	0	0
Cough	0	1 (4)	1 (4)
Abdominal pain	0	1 (4)	0
Anorexia	0	1 (4)	0
Dyspnea	0	1 (4)	0
Pruritus	0	1 (4)	0
Tremor	0	1 (4)	0
Oral herpes	0	0	1 (4)
Rhinitis	0	0	1 (4)
Upper respiratory tract infection	0	0	1 (4)

with respect to plasma naltrexone and 6-β-naltrexol concentrations in this study population.

The occurrence of emesis apparently did not affect the bioavailability determinations. This finding may have been due to the absorption of naltrexone, with T_{max} at ~1 hour after the administration of MS-sNT crushed pellets or naltrexone solution. Because narcotic antagonism of naltrexone has been reported to be related to plasma naltrexone concentrations,[16,24] the data suggest that opioid antagonism might be achieved even in subjects who experience emesis after the administration of tampered (crushed) MS-sNT.

MS-sNT whole capsules were administered in a separate arm of the study to observe the extended-release characteristics of morphine relative to the crushed product and to further assess naltrexone sequestration. Because of limitations on blood volume collection and the focus on naltrexone pharmacokinetics, a minimal number of samples were collected for morphine pharmacokinetic analyses. A precise T_{max} for morphine from the MS-sNT crushed pellets could not be determined. The T_{max} of morphine absorption after the administration of MS-sNT crushed pellets was ~5 hours faster compared with that of the intact capsule (≤2 vs 7 hours),

and it was similar to that of a short-acting morphine solution (1.2 hours) reported in a pharmacokinetics study of comparable design.[32] Peak exposure to morphine after the administration of MS-sNT crushed pellets was ~3-fold greater than that with the intact capsule (24.5 vs 7.73 ng/mL). The relative bioavailability of plasma morphine was statistically similar between crushed and whole MS-sNT.

When MS-sNT was administered whole, as intended, plasma naltrexone concentrations were below the LLOQ (4.00 pg/mL). Thirty-four percent of samples analyzed had quantifiable concentrations of 6-β-naltrexol that ranged from 0.250 pg/mL (LLOQ) to 49.5 pg/mL. However, these concentrations were a fraction of those observed with MS-sNT crushed pellets and naltrexone solution (mean C_{max} with MS-sNT crushed pellets was 71-fold greater and that for naltrexone was 75-fold greater than the highest individual value for the intact capsule). The presence of 6-β-naltrexol suggests that a trace amount of naltrexone (below the LLOQ [4.00 pg/mL]) may be released from the intact product.

In healthy adults and subjects dependent on heroin or methadone, naltrexone has been reported to be rapidly absorbed, metabolized in the liver to 6-β-naltrexol, the primary active metabolite, and predominantly excreted in the urine.[15–18,20,33,34] Due to the high first-pass effect, oral bioavailability of naltrexone ranges from 5% to 60%.[16,20,21,26] The opioid antagonistic properties of 6-β-naltrexol are considerably less (1/50th to 1/12th) than those of naltrexone.[16,25] Although opioid antagonism is predominantly due to naltrexone, it has been suggested that 6-β-naltrexol contributes to the extent and duration of the antagonism.[16,24]

The trace amount of naltrexone detected does not appear to affect the efficacy of MS-sNT. A randomized, double-blind, active-controlled study in patients with chronic moderate to severe osteoarthritis pain (N = 113) reported that the maintenance of pain control associated with MS-sNT was not significantly different from that of marketed extended-release morphine sulfate capsules that do not contain naltrexone.[35] In that study, plasma naltrexone concentrations in most of the patients were below the LLOQ (4.00 pg/mL); most of the patients had ≥1 quantifiable 6-β-naltrexol concentration (range, 0.3–520 pg/mL). These values are consistent with those with MS-sNT whole capsules in the present study. Patients' pain scores were not negatively affected, and clinical opioid withdrawal syndrome was not reported. Because small amounts of plasma naltrexone (up to 25.5 pg/mL) were measured in <22% of patients at any individual time point in this and the previous study, the prevalence of opioid withdrawal in patients receiving long-term treatment with MS-sNT for chronic moderate to severe pain has been investigated in later clinical trials and will be published elsewhere.[36,37]

Dose-finding studies using commercially available solutions of immediate-release naltrexone HCl and morphine sulfate had been conducted to determine the appropriate ratio of naltrexone to morphine required to mitigate the euphoric effects of morphine in opioid-experienced, nondependent opioid drug users.[38] Concurrent administration of naltrexone and morphine at a ratio of 1:25 (naltrexone/morphine 4.8/120 mg) resulted in a reduction in morphine-induced euphoria of >30%, assessed using a visual analog scale of drug liking, in >50% of the subjects completing the study. This degree of reduction by naltrexone in morphine drug liking was considered sufficient to reduce morphine abuse potential. This ratio was confirmed as effective in providing analgesia in patients with chronic moderate to severe pain when the product was administered as directed[35] and to mitigate subjective positive effects of morphine when the product was crushed and consumed orally.[32]

This study had several limitations. It was an open-label study in 24 healthy volunteers. It is not known whether a pharmacokinetic analysis conducted in a larger sample or in patients receiving long-term opioid treatment would yield similar results. Another limitation was the inclusion and exclusion criteria used in this study, which may not be typical of that in individuals who are likely to misuse or abuse opioids. The product was crushed with a mortar and pestle and administered orally; people intent on misuse/abuse of MS-sNT may devise other methods of crushing or tampering with MS-sNT or use routes of administration other than the oral route used in this study. Possible effects of intravenous injection of crushed pellets of MS-sNT will be published elsewhere.[39]

Other methods of crushing MS-sNT and the effects of snorting the crushed product were not assessed. A clinical simulation of the potential effects of intravenous administration of crushed MS-sNT has been conducted (data on file, King Pharmaceuticals study no. ALO-01-07-106).[39]

However, many activities in which opioid abusers and addicts are likely to engage to attain euphoria from prescription pain medications are unsafe and cannot be safely studied. Data from long-term clinical studies and

analysis of misuse and abuse of MS-sNT in practice are needed to determine whether the inclusion of sequestered naltrexone in the MS-sNT formulation will be a deterrent to prescription opioid abuse.

CONCLUSIONS

The findings from this study in healthy volunteers suggest that naltrexone sequestered within the core of each pellet was released on tampering by crushing the contents of an MS-sNT capsule. With respect to the bioavailability of naltrexone and its primary active metabolite, 6-β-naltrexol, crushed pellets of MS-sNT yielded plasma concentrations comparable to those with an equal dose of orally administered naltrexone HCl solution. When MS-sNT capsules were administered whole, concentrations of naltrexone and 6-β-naltrexol were not clinically meaningful. Although the overall systemic morphine exposure was not significantly different between MS-sNT crushed pellets and whole capsules, the extended-release characteristics of MS-sNT administered whole were apparent from a longer T_{max} and a lower C_{max} compared with those with MS-sNT crushed pellets. The AEs found with MS-sNT 60 mg, crushed or intact, were typical of opioid products. The results suggest that naltrexone released after the ingestion of crushed pellets of MS-sNT capsules is bioavailable to antagonize the pharmacologic effects of morphine and potentially render this extended-release morphine formulation less attractive for tampering. More long-term clinical and postsurveillance data are needed in populations of opioid abusers to establish whether MS-sNT will be less desirable for misuse and abuse.

ACKNOWLEDGMENTS

Alpharma Pharmaceuticals LLC, the manufacturer of MS-sNT, is a wholly owned subsidiary of King Pharmaceuticals, Inc. Funding for this research and for writing and editorial support was provided by King Pharmaceuticals. Publication was sponsored by King Pharmaceuticals. Writing support and editorial support were provided by Quintiles and were conducted in close consultation with the authors.

The authors are grateful to Paul F. Cavanaugh, Jr, PhD; Don Manning, MD, PhD; Chao Wang, PhD; and Doreen Sekora, MPH, of King Pharmaceuticals, for their review of the manuscript.

Mr. Johnson was an employee of King Pharmaceuticals, held stock and/or stock options in the company, and was involved in the study design and analysis. Dr. Stauffer also was an employee of King Pharmaceuticals, and was involved in the study design and analysis. Dr. Bieberdorf (deceased) was a study investigator and provided input and revisions to the manuscript drafts. Dr. Stark is, and Dr. Bieberdorf was, an employee of CEDRA, a contract research facility. Alpharma Pharmaceuticals was responsible for the study design, protocol concept, and clinical monitoring. All of the authors were responsible for the manuscript drafts and revisions. Mr. Johnson and Drs. Stark and Stauffer provided final approval of the manuscript. CEDRA provided the clinical study site; prepared the protocol; obtained institutional review board approval; and was responsible for clinical conduct of the study, biostatistics, bioanalysis, pharmacokinetic analyses, preparation of the clinical study report, and document review. StatWorks Inc. was responsible for clinical data management.

The authors have indicated that they have no other conflicts of interest regarding the content of this article.

REFERENCES

1. Rhodin A. The rise of opiophobia: Is history a barrier to prescribing? *J Pain Palliat Care Pharmacother.* 2006;20:31–32.
2. Woolf CJ, Hashmi M. Use and abuse of opioid analgesics: Potential methods to prevent and deter non-medical consumption of prescription opioids. *Curr Opin Investig Drugs*. 2004;5:61–66.
3. Simon L, Lipman SL, Jacox A, et al. *Guidelines for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis*. 2nd ed. Glenview, Ill: American Pain Society; 2002.
4. Gruener D, Lande SD, eds. *Pain Control in the Primary Care Setting*. Vol 1. Glenview, Ill: American Pain Society; 2006.
5. Lipman AG, Jackson KC II. Opioid pharmacotherapy. In: Warfield CA, Bajwa ZH, eds. *Principles and Practice of Pain Medicine*. 2nd ed. New York, NY: McGraw-Hill; 2004; 583–600.
6. Sloan P, Babul N. Extended-release opioids for the management of chronic non-malignant pain. *Expert Opin Drug Deliv*. 2006;3:489–497.
7. Gourlay GK. Sustained relief of chronic pain. Pharmacokinetics of sustained release morphine. *Clin Pharmacokinet*. 1998;35:173–190.
8. Wright C IV, Kramer ED, Zalman MA, et al. Risk identification, risk assessment, and risk management of abusable drug formulations. *Drug Alcohol Depend*. 2006;83 (Suppl 1):S68–S76.
9. Højsted J, Sjøgren P. Addiction to opioids in chronic pain patients: A literature review. *Eur J Pain*. 2007;11:490–518.

10. Kuehn BM. Opioid prescriptions soar: Increase in legitimate use as well as abuse. *JAMA*. 2007;297:249–251.
11. Katz NP, Adams EH, Chilcoat H, et al. Challenges in the development of prescription opioid abuse-deterrent formulations. *Clin J Pain*. 2007;23:648–660.
12. Bhamb B, Brown D, Hariharan J, et al. Survey of select practice behaviors by primary care physicians on the use of opioids for chronic pain. *Curr Med Res Opin*. 2006;22:1859–1865.
13. Gagnon AM, Kahan M, Srivastava A. Opioid use and abuse: Is there a problem? *Clin J Pain*. 2007;23:661–662.
14. Paulozzi LJ. Trends in unintentional drug overdose deaths. US Dept of Health and Human Services; Testimony before Senate Judiciary Subcommittee on Crime and Drugs. 2008. http://www.hhs.gov/asl/testify/2008/03/t20080312b.html. Accessed February 8, 2010.
15. Wall ME, Brine DR, Perez-Reyes M. The metabolism of naltrexone in man. In: Willette RE, Barnett G, eds. *Naltrexone Research Monograph No. 28*. Bethesda, Md: National Institute on Drug Abuse; 1980:105–131.
16. Gonzalez JP, Brogden RN. Naltrexone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. *Drugs*. 1988;35:192–213.
17. National Institute for Health and Clinical Excellence (NICE). Naltrexone for the management of opioid dependence. London, UK; 2007. http://www.nice.org.uk/. Accessed February 10, 2007.
18. Crabtree BL. Review of naltrexone, a long-acting opiate antagonist. *Clin Pharm*. 1984;3:273–280.
19. Resnick RB, Volvavka J, Freedman AM, Thomas M. Studies of EN-1639A (naltrexone): A new narcotic antagonist. *Am J Psychiatry*. 1974;131:646–650.
20. Revia (naltrexone) [package insert]. Montvale, NJ: Barr Pharmaceuticals, Inc; 2007.
21. Meyer MC, Straughn AB, Lo MW, et al. Bioequivalence, dose-proportionality, and pharmacokinetics of naltrexone after oral administration. *J Clin Psychiatry*. 1984;45:15–19.
22. Bashaw ED, Kaiko RF, Grandy RP, et al. Relative bioavailability of controlled-release oral morphine sulfate during naltrexone blockade. *Int J Clin Pharmacol Ther*. 1995;33:524–529.
23. Kaiko RF, Grandy RP, Reder RF, et al. A bioequivalence study of oral controlled-release morphine using naltrexone blockade. *J Clin Pharmacol*. 1995;35:499–504.
24. Gold MS, Dackis CA, Pottash AL, et al. Naltrexone, opiate addiction, and endorphins. *Med Res Rev*. 1982;2:211–246.
25. Verebey K. The clinical pharmacology of naltrexone: Pharmacology and pharmacodynamics. Naltrexone pharmacochemistry and sustained release preparations. In: Willette RE, Barnett G, eds. *Naltrexone Research Monograph No. 28*. Bethesda, Md: National Institute on Drug Abuse; 1980:147–158.
26. Verebey K, Volavka J, Mulé SJ, Resnick RB. Naltrexone: Disposition, metabolism, and effects after acute and chronic dosing. *Clin Pharmacol Ther*. 1976;20:315–328.
27. EMBEDA (morphine sulfate and naltrexone hydrochloride) [package insert]. Bristol, Tenn: King Pharmaceuticals, Inc; June 2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022321s000lbl.pdf.
28. FDA Approves EMBEDA for Management of Moderate to Severe Chronic Pain. http://www.medicalnewstoday.com/articles/160756.php. Accessed April 27, 2010.
29. US Dept of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Guidance for industry: Bioavailability and bioequivalence studies for orally administered drug products—general considerations. 2003. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf. Accessed March 15, 2010.
30. US Dept of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Guidance for industry: Statistical approaches to establishing bioequivalence. 2001. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070244.pdf. Accessed March 15, 2010.
31. Gibaldi M, Perrier D. Noncompartmental analysis based on statistical moment theory. In: *Pharmacokinetics.* 2nd ed. New York, NY: M. Dekker; 1982.
32. Stauffer J, Setnik B, Sokolowska M, et al. Subjective effects and safety of whole and tampered morphine sulfate and naltrexone hydrochloride (ALO-01) extended-release capsules versus morphine solution and placebo in experienced non-dependent opioid users: A randomized, double-blind, placebo-controlled, crossover study. *Clin Drug Investig*. 2009;29:777–790.
33. Mason BJ, Goodman AM, Dixon RM, et al. A pharmacokinetic and pharmacodynamic drug interaction study of acamprosate and naltrexone. *Neuropsychopharmacology*. 2002;27:596–606.
34. Perez-Reyes M, Wall ME. A comparative study of the oral, intravenous, and subcutaneous administration of 3H-naltrexone to normal male volunteers. In: Willette RE, Barnett G, eds. *Naltrexone Research Monograph No. 28*. Bethesda, Md: National Institute on Drug Abuse; 1980:93–101.
35. Katz N, Sun S, Johnson F, Stauffer J. ALO-01 (morphine sulfate and naltrexone hydrochloride) extended-

release capsules in the treatment of chronic pain of osteoarthritis of the hip or knee: Pharmacokinetics, efficacy, and safety. *J Pain*. 2010;11: 303–311.
36. Jones JB, Fox L, Katz N, et al. Efficacy and tolerability of ALO-01 (morphine sulfate extended-release with sequestered naltrexone hydrochloride) capsules in patients with chronic moderate-to-severe pain from osteoarthritis of the hip or knee. *Arch Phys Med Rehab*. 2008; 89(11):e97. Poster 238.
37. Webster L, Brewer RP, Sekora D, et al. Long-term safety of ALO-01 (morphine sulfate extended-release with sequestered naltrexone hydrochloride) capsules in patients with chronic, moderate to severe, nonmalignant pain. *Reg Anesth Pain Med*. 2008;32:5. Abstract 5.
38. Alpharma Pharmaceuticals LLC. ALO-01 (morphine sulfate extended-release with sequestered naltrexone hydrochloride capsules) for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time: NDA open session briefing package. http://www.fda.gov/ohrms/dockets/AC/08/briefing/2008-4395b2-02-ALPHARMA.pdf. Accessed February 8, 2010.
39. Webster L, Jones JB, Johnson F, et al. Relative drug-liking/euphoria effects of intravenous morphine alone and in combination with naltrexone in recreational opioid users. International Association for the Study of Pain (IASP) 12th World Congress on Pain; August 17–22, 2008; Glasgow, United Kingdom. Abstract 2993.

Address correspondence to: Franklin K. Johnson, MS, ClinPharm PK Consulting LLC, 625 Talamini Road, Bridgewater, NJ 08807. E-mail: franklinkjohnson@yahoo.com