Relative Oral Bioavailability of an Abuse-Deterrent, Extended-Release Formulation of Morphine Versus Extended-Release Morphine: A 2-Period, Single-Dose, Randomized Crossover Study in Healthy Subjects

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ABSTRACT

Purpose: Morphine ARER is a novel oral, abuse-deterrent, extended-release (ER) formulation of morphine sulfate with physical and chemical properties that deter misuse and abuse by nonoral routes of administration. Here we evaluate the relative bioavailability of morphine ARER and extended-release morphine.

Methods: This single-dose, 2-treatment, 2-period, 2-sequence, randomized crossover study in healthy adult subjects compared the relative bioavailability of morphine ARER 100 mg to that of ER morphine 100 mg in the fasted condition. At 12 and 1.5 hours before dosing and 12 hours after dosing, all subjects received a 50-mg oral naltrexone tablet to minimize opioid-related side effects. Pharmacokinetic parameters including the AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of morphine and its metabolite morphine-6-glucuronide (M6G) were determined at various times up to 48 hours postdose. The bioequivalence of morphine ARER and ER morphine was determined using an ANOVA of the least-squares mean values of morphine and M6G bioavailability.

Findings: Forty-nine subjects completed the study. Both morphine ARER and ER morphine exhibited peak plasma morphine and M6G concentrations of ~30 ng/mL and ~200 ng/mL, respectively, at 3 hours postdose. The 90% CIs of the ln-transformed values of morphine AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were within the 80% to 125% range for bioequivalence. M6G values also indicated bioequivalence of morphine ARER and ER morphine. The most common adverse events were nausea and somnolence.

Implications: These data show that, in these subjects, morphine ARER was bioequivalent to ER morphine, a treatment for pain with well-established efficacy and safety profiles. (*Clin Ther*. 2018;■:1–9)

Key words: abuse-deterrent formulation, bioequivalence, morphine, opioids, pharmacokinetics.

INTRODUCTION

Misuse and abuse of prescription opioids has become a major public health concern. In 2016, nonmedical use of prescription pain relievers was reported in ~11.5 million individuals aged 12 years or older in the United States.[1] Deaths resulting from overdose of prescription opioids have been increasing steadily, and surpassed deaths from motor vehicle accidents in 2009.[2] According to the Centers for Disease Control and Prevention, in 2015 alone, >15,000 deaths involved prescription opioid overdose.[3]

Prescription opioid abusers use several methods to achieve enhanced psychoactive effects of the drug. Ingesting a larger-than-prescribed dose of intact tablets/capsules orally is the most common method of abuse; however, abusers may manipulate tablets physically (crush or chew) or chemically to extract the active ingredient from extended-release (ER) formulations.[4] Physical and chemical manipulation often bypasses the ER characteristics of tablets and increases the

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bioavailability of the drug. After physical manipulation and/or chemical extraction, abusers also use alternative routes of administration (eg, intranasal ["snorting"], IV injection) that allow for quicker delivery of the drug to the brain for a potent and rapid feeling of euphoria or a "high."[5,6] Opioid formulations that are more easily prepared for these routes of administration are more attractive to abusers who use nonoral routes of abuse.[6]

The development of abuse-deterrent formulations (ADFs) of opioids is one of several approaches to combatting prescription opioid misuse and abuse, and is considered a public health priority by the US Food and Drug Administration (FDA).[7] Morphine ARER,* a novel FDA-approved ADF of ER morphine sulfate tablets, is formulated with technology that has both physical and chemical properties that contribute to abuse deterrence.† In addition, the active ingredient is contained within a polymer matrix of inactive ingredients. The active ingredient is difficult to visibly distinguish or physically separate from the polymer matrix (data on file, Inspirion Delivery Sciences, LLC). Morphine ARER resists physical tampering by cutting, crushing, or breaking; forms a nonsyringeable viscous material when subjected to a liquid environment; and maintains its ER characteristics despite physical manipulation and intranasal administration.[8–10] A previously published study in nondependent recreational opioid abusers demonstrated a significant reduction in "drug liking" with crushed intranasal morphine ARER compared with crushed intranasal ER morphine ($P < 0.0001$).[11] Here, the pharmacokinetic (PK) profiles of morphine ARER and ER morphine were assessed for bioequivalence.

SUBJECTS AND METHODS

Subjects

This study enrolled healthy adult male and female subjects aged 18 to 45 years and was conducted at Novum Pharmaceutical Research Services (Las Vegas, Nevada). Subjects were excluded if they were opioid naïve; had history of allergy or sensitivity to naltrexone, morphine, or other opioids; or used pharmacologic agents that induced or inhibited drug-metabolizing enzymes. Female subjects were also excluded if they were pregnant, breastfeeding, or likely to become pregnant. Any subject who experienced emesis within 8 hours of dosing with morphine was removed from the study; subjects who experienced, with naltrexone pretreatment, adverse events (AEs) that in the investigator's opinion were indicative of possible previous recent opioid use/abuse were removed from the study before dosing with morphine sulfate. All study participants provided written informed consent as approved by Novum's independent institutional review board.

Study Design and Treatment

This single-dose, 2-treatment, 2-period, 2-sequence, randomized crossover study evaluated the relative oral bioavailability of morphine ARER 100 mg and ER morphine 100 mg‡ under fasted conditions.

The study included a 28-day screening period and 2 treatment periods, each lasting 2 days. Study subjects received a single dose of morphine ARER or ER morphine according to the 2-treatment, 2-sequence randomization schedule. At 12 and 1.5 hours (±30 minutes) before dosing with either morphine ARER or ER morphine and at 12 hours (±30 minutes) after dosing, all subjects were given a 50-mg oral naltrexone tablet with 240 mL of water to minimize opioid-related side effects. After naltrexone pretreatment, a single oral dose of either morphine ARER 100 mg or ER morphine 100 mg was administered following an overnight fast of at least 10 hours. Tablets were administered orally with 240 mL of room-temperature tap water. A thorough mouth check was performed after each dose, to ensure that the tablet was swallowed whole without chewing or biting. Subjects continued to fast for 4 hours postdose, at which time a standardized meal was served. Subjects remained at the clinical facility from 13 hours before dosing until after the 36-hour blood-collection postdose and returned to the facility for the 48-hour postdose blood collection. Each treatment period was separated by an interval of 7 days.

The study was conducted in accord with the International Conference on Harmonisation's guideline for Good Clinical Practice, the Declaration of Helsinki, and all applicable federal and local

* Trademark: MorphaBond ER (Daiichi Sankyo, Inc, Basking Ridge, New Jersey).

† Trademark: SentryBond™ (Inspirion Delivery Sciences LLC, Morristown, New Jersey).

‡ Trademark: MS Contin (Purdue Pharma LP, Stamford, Connecticut).