Analgesic Efficacy and Tolerability of Intravenous Morphine Versus Combined Intravenous Morphine and Oxycodone in a 2-Center, Randomized, Double-Blind, Pilot Trial of Patients With Moderate to Severe Pain After Total Hip Replacement

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ABSTRACT

Background: Results from studies with a combination of oral morphine and oxycodone in postsurgical patients demonstrate significant analgesia and a tolerability profile comparable to other pain medications at morphine-equivalent doses. However, an intravenous (IV) combination has not previously been studied.

Objective: This study evaluated the efficacy and tolerability of IV morphine versus a combination of IV morphine and IV oxycodone in a 1:1 ratio.

Methods: This was a 2-center, randomized, double-blind, active-controlled pilot trial of 40 patients who had undergone total hip replacement. After surgery, when pain levels reached ≥4 (on the 11-point Numerical Pain Rating Scale), patients were randomized to 1 of 2 treatment groups. In part 1 of the study, patients were dosed every 5 minutes for the first 65 minutes (up to 13 doses) with study drug, provided that vital signs criteria were met. After an initial loading dose of either morphine 1.5 mg coadministered with oxycodone 1.5 mg or morphine 3 mg alone, patients received IV morphine 1.5 mg or IV morphine 0.75 mg/IV oxycodone 0.75 mg every 5 minutes. If patients achieved a pain score of 2 or experienced intolerable adverse events to drug when stable, they were permitted to enter part 2. In part 2, patients received **blinded** study medication (IV morphine plus IV oxycodone [0.5 mg/0.5 mg] or 1 mg IV morphine alone) via patient-controlled analgesia (PCA) for 47 hours.

Results: At baseline, treatment groups were comparable except for a higher proportion of females in the IV morphine group. Baseline pain intensity averaged 7 on the Numerical Pain Rating Scale of 0 to 10. One patient in the morphine group and 2 patients in the morphine/oxycodone group discontinued the study. The sum of the pain intensity differences from baseline to 65 minutes during the dose-titration phase was 1.8 for morphine alone versus 2.7 for morphine/oxycodone ($P = 0.12$); these values occurred at the same median number of doses (12) for each group. In part 2 (PCA dosing) of the study, similar levels of analgesia were achieved. During the study, 24% of the IV morphine/oxycodone group and 37% of the IV morphine group experienced nausea, and 10% of the IV morphine/oxycodone group and 16% of the IV morphine group had emesis. Two patients in the IV morphine/oxycodone group and 4 in the IV morphine alone group experienced oxygen desaturation.

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Conclusions: The combination of IV morphine and oxycodone provided pain relief with an acceptable tolerability profile in these patients experiencing moderate to severe postoperative pain. However, as an explorative pilot study, the power was not adequate to demonstrate statistical significance for differences between IV morphine/oxycodone and IV morphine alone. European Clinical Trials Data Base registration code: EudraCT-No. 2008-008527-14. (*Clin Ther.* 2012;34:1751–1760)

Key words: analgesia, intravenous, morphine, oxycodone, postoperative pain, tolerability.

INTRODUCTION

After surgery, many patients are unable to ingest oral medication and instead receive intravenous (IV) morphine.[1] Patient-controlled analgesia (PCA) with IV morphine is a more efficient method for optimizing the amount of pain control achieved without overdosing compared with administration of fixed doses of morphine every few hours.[2–5] Adjustable dosing using IV PCA accommodates the wide intersubject variation in the amount of morphine needed to control pain and the sensitivity of each patient to the adverse effects of morphine.[3,6] However, these adverse effects, including nausea, vomiting, mental sedation, and impaired breathing, can restrict the patient to low doses of morphine, resulting in inadequate pain control.[7]

A fixed-dose dual-opioid combination of morphine/oxycodone in a 3:2 ratio is available in oral capsule form.* Results from preclinical studies with combinations of opioids have shown synergistic analgesia without an increase in adverse events.[8,9] Recently, promising results from several double-blind controlled studies using this fixed-dose combination in postsurgical patients who were able to ingest oral medication demonstrated significant analgesia and a tolerability profile that was comparable to other pain medications at morphine-equivalent doses.[10,11] PCA dosing with a combination of IV morphine and oxycodone may represent a further optimization of pain control, not only postoperatively but also in emergency departments and in cancer pain management, by potentially providing improved pain relief and pharmacoeconomic benefits as a result of a significantly improved adverse event (AE) profile. The current double-blind, active-controlled pilot study was initiated to compare PCA dosing with a dual-opioid combination of IV morphine/oxycodone versus IV morphine alone in patients experiencing moderate to severe pain after total hip replacement surgery.

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PATIENTS AND METHODS

This was a double-blind, active-controlled, investigator-initiated study conducted in Germany at the University of Witten/Herdecke Medical Center Cologne and Cologne University Hospital, with patients enrolled between July 2009 and May 2010. Patients undergoing total hip replacement surgery who developed moderate to severe pain were eligible. The primary objectives of this study were to compare adverse effects with coadministration of IV morphine and oxycodone versus IV morphine alone at equal doses and to compare the analgesic efficacy of IV morphine/oxycodone versus IV morphine alone. The study was conducted in accordance with Good Clinical Practice and European Medicines Agency guidelines.[12,13] An appropriate institutional review board of Witten/Herdecke University (approval number, F-08/2009) reviewed and approved the study protocol, and patients provided written informed consent before entering a screening phase of the study. The study was approved and controlled by the German Federal Pharmacy Approval Agency.

Study Design

The study consisted of screening, pretreatment, baseline, treatment (2 parts), and follow-up periods. The screening period lasted from 1 to 30 days and allowed screening for inclusion in the study. The pretreatment period included the time from arrival at the surgical site, the surgical procedure, and the initial period in the postanesthesia unit. The period ended when the patient reported moderate to severe pain (score ≥4 on the 11-point [0 = no pain to 10 = most intense pain] Numerical Pain Rating Scale [NPRS]) and had an oxygen saturation level ≥95% measured by using pulse oximetry, a respiratory rate ≥12 breaths/minute, systolic blood pressure ≥100 mm Hg, diastolic blood pressure ≥60 mm Hg, a pulse at maximum 10% below preoperative baseline, or a pulse ≤100 beats/min. The baseline period was the time from onset of moderate or