Comparison of the Efficacy and Safety of Dual-Opioid Treatment With Morphine Plus Oxycodone Versus Oxycodone/Acetaminophen for Moderate to Severe Acute Pain After Total Knee Arthroplasty

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ABSTRACT

Background: In acute pain models, coadministration of low doses of morphine and oxycodone markedly enhanced analgesia relative to either opioid given alone. Enhanced analgesia with coadministration of morphine and oxycodone has also been reported in acute and chronic moderate to severe pain conditions during double-blind studies.

Objective: The goal of this study was to compare the efficacy and tolerability of a flexible dose regimen of the morphine/oxycodone combination versus oxycodone/acetaminophen and fixed low-dose morphine/oxycodone.

Methods: This was a 5-center, randomized, open-label study of hospitalized patients (n = 44) with acute moderate to severe postoperative pain after total knee arthroplasty. Inpatients were randomized to a flexible dose regimen of morphine/oxycodone (3 mg/2 mg to 24 mg/16 mg), fixed low-dose morphine/oxycodone regimen (3 mg/2 mg), or oxycodone/acetaminophen (5 mg/325 mg). Treatment was initiated following surgery after intravenous (IV) morphine patient-controlled analgesia. An algorithm was evaluated for converting the patient-controlled analgesia morphine dose to an initial oral dose of morphine/oxycodone. The primary efficacy variable was the time-weighted sum of pain intensity difference from 0 to 48 hours.

Results: The median values for the sum of the pain intensity difference from 0 to 48 hours for the morphine/oxycodone flexible dose and oxycodone/acetaminophen were similar and approximately twice that of fixed morphine/oxycodone 3 mg/2 mg (148.0, 139.5, and 71.3, respectively). Moderate to severe gastrointestinal adverse events occurred in 50% of patients in the oxycodone/acetaminophen group compared with 15% of the equianalgesic morphine/oxycodone group. On several items of the Brief Pain Inventory (general activity, walking ability, and sleep), the morphine/oxycodone flexible dose produced greater benefit than oxycodone/acetaminophen.

Conclusions: Flexible dose morphine/oxycodone was superior to low-dose morphine/oxycodone and comparable to oxycodone/acetaminophen. Flexible dose morphine/oxycodone-treated patients had a lower rate of moderate to severe nausea or vomiting than equianalgesic oxycodone/acetaminophen-treated patients. Thus, morphine/oxycodone offers an attractive alternative to oxycodone/acetaminophen for the management of moderate to severe postoperative pain. ClinicalTrials.gov: identifier: NCT00818493. (*Clin Ther*. 2013;35:498–511) © 2013 Published by Elsevier HS Journals, Inc.

Key words: dual opioid, gastrointestinal adverse effects, morphine, morphine/oxycodone, nausea, oxycodone, oxycodone/acetaminophen, postoperative pain, total knee arthroplasty, vomiting.

INTRODUCTION

Better postoperative analgesia may facilitate earlier recovery, hasten rehabilitation after major knee surgery,[1] and reduce the presence of chronic postoperative pain.[2] Pain has been shown to produce negative clinical outcomes and is a common cause of delayed discharge after ambulatory surgery.[3] Opioids are considered to be the standard of care to relieve moderate to severe acute postoperative pain. However, their utility

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is often limited by intolerable adverse effects,[4] including nausea, vomiting, and constipation.[5,6]

Multimodal and opioid-sparing regimens, based on a deeper understanding of the different classes of opioid receptors and the synergies between them, have evolved in an effort to maintain the analgesic efficacy of opioids while reducing their adverse effects.[4,7–10] In an effort to decrease the adverse effects of opioids, NSAIDs, acetaminophen, the selective cyclooxygenase-2 inhibitors (COX-2), and other analgesic adjuvants (eg, ketamine, gabapentin) have been shown to reduce postoperative opioid consumption while maintaining pain control.[3,11] However, each of these opioid combinations has significant problems in the postoperative acute pain setting. NSAIDs are well known to increase the risk of bleeding or renal complications after surgery, COX-2 inhibitors increase the risk of major cardiac adverse events, and acetaminophen increases the risk of hepatic injury such that the US Food and Drug Administration (FDA) has recently announced it is limiting the amount of acetaminophen in opioid combination products to 325 mg per dose.[12–16] Ketamine and gabapentin are not FDA approved for the management of acute pain after surgery or in other acute pain conditions. Thus, there remains a significant medical need for effective postoperative pain control with decreased adverse effects.

Currently, there are no opioid–opioid combination products approved for use in the United States or elsewhere. The concept of combining opioids arose from studies in acute pain models in rodents in which markedly enhanced analgesia with coadministration of low doses of morphine and oxycodone were observed relative to either opioid given alone.[17] Evidence for enhanced analgesia with coadministration of morphine and oxycodone, as reflected in reduced opioid doses to achieve analgesic effects in patients, were reported with a variety of acute and chronic moderate to severe pain conditions in double-blind studies conducted in Australia, Switzerland, Brazil, and the United States.[17–22]

The current postsurgical pain study evaluated an immediate-release capsule formulation of the combination of oxycodone and morphine* in a fixed 3:2 ratio for its analgesic and adverse-effect properties compared with that of a widely used opioid/acetaminophen† combination product. In addition, a fixed low-dose morphine/oxycodone regimen was included to explore the dose-response properties of morphine/oxycodone. Finally, this study also evaluated the adequacy of an algorithm for conversion of intravenous (IV) patient-controlled (PCA) morphine to the initial dose of a flexible regimen of morphine/oxycodone.

METHODS

Study Design

This was an open-label, 5-center (all located in the United States), 3-arm, multiple-dose, Phase II trial of morphine/oxycodone for the management of acute moderate to severe postoperative pain after primary unilateral total knee arthroplasty (n = 40) or unilateral hip arthroplasty (n = 4) (**Figure 1**). The study included a 30-day pretreatment screening period; the day of surgery, which included PCA morphine given immediately postsurgery for up to 24 hours; randomization in a 1:1:1 ratio to a 48-hour treatment regimen of morphine/oxycodone flexible dose, morphine/oxycodone fixed low dose (3 mg/2 mg), or a flexible dose of 1 to 2 tablets of oxycodone/acetaminophen (5 mg/325 mg) starting on the day after surgery; and a 48- to 72-hour follow-up period. Patients were randomized to treatment at the end of the IV PCA dosing period once pain became moderate to severe (pretreatment baseline) if they met all eligibility criteria, including those for pain intensity.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guideline and any applicable regulatory requirements. An appropriate institutional review board for each site approved the study protocol. All patients or a legal representative provided written informed consent before participating in any study activities or procedures.

Patient Selection

Men and nonpregnant women ≥18 years of age who were in general good health were eligible if they met the American Society of Anesthesiologists' Class I to III classification and were scheduled for primary unilateral total knee arthroplasty. During the trial, the protocol was amended to allow patients receiving unilateral hip arthroplasty to enroll provided that the patients met the same enrollment criteria as patients re-

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†Trademark: Percocet® (Endo Pharmaceuticals Inc, Malvern, Pennsylvania).