Clinical Trial Results Summary
Study EN3203-004

Study Number: EN3203-004

Title of Study: Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose Ranging Comparison of the Analgesic Efficacy and Safety of Numorphan® IR (Oxymorphone HCl Immediate Release), Percolone, and Placebo in Patients With Postsurgical Pain Following Orthopedic Total Hip and Knee Replacement

Investigators: 29 Investigators

Study Center(s): 29 study centers located in the United States

Publication (reference): None

Study Period:
Date of First Enrollment: February 27, 2001
Date of Last Enrollment: March 9, 2002

Phase of Development: III

Objectives: The primary objective was to compare the analgesic efficacy of three dose levels of oxymorphone IR (10 mg, 20 mg, and 30 mg) to placebo in patients with acute moderate to severe postoperative pain following orthopedic surgery. Secondary objectives were: 1) to compare the analgesic efficacy and evaluate the dose response of three dose levels of oxymorphone IR [10 mg, 20 mg, and 30 mg]; and 2) to compare the safety of three dose levels of oxymorphone IR [10 mg, 20 mg, and 30 mg] to placebo and oxycodone IR 10 mg following total hip or total knee replacement surgery, or revision surgery provided the patient had an osteotomy.

Methodology: Multicenter, randomized, double-blind, placebo and active controls, 2-phase study of oxymorphone IR and oxycodone IR in patients with pain following total hip or total knee replacement surgery, or revision surgery provided the patient had an osteotomy.

The patients were placed on opioid analgesia postoperatively. Within 48 hours following surgery, all analgesic medication was stopped. If the patient developed moderate to severe pain on a categorical scale (no pain, mild pain, moderate pain, or severe pain), had an Initial Pain Intensity Score of at least 45 mm on a 100 mm visual analog scale (VAS) and met all other study entry criteria, he/she was randomized to one of 5 dose groups (oxymorphone IR 10 mg, oxymorphone IR 20 mg, oxymorphone IR 30 mg, oxycodone 10 mg, or placebo). Following dosing in the Single-Dose Phase, pain intensity and pain relief were recorded at the following times: 15, 30, 45, and 60 minutes, 1.5 hours, 2 hours, and hourly thereafter through Hour 8. Patients who tolerated the initial dose and requested re-medication ≥3 hours after the initial dose, or completed the 8 hours of assessments continued into the Multiple-Dose Phase. Patients who requested re-medication prior to 3 hours after the initial dose in the Single-Dose Phase received a rescue medication of the Investigator's choice and exited from the study after being evaluated. Patients receiving placebo during the Single-Dose Phase were rerandomized to receive one of the four active treatments during the Multiple-Dose Phase.

During the Multiple-Dose Phase, patients continued to be dosed for pain with study medication every 4-6 hours as needed, but not more than every 3 hours, for 48 hours after the beginning of the Single-Dose Phase. Patients who requested re-medication prior to 3 hours were terminated from the study. During the Multiple-Dose Phase, patients were to recall at bedtime their worst intensity of pain during the day and were to recall each morning, when they awoke, their worst intensity of pain during the nighttime. An Exit Evaluation for safety occurred upon early termination or completion of the Multiple-Dose Phase.

Number of Patients (planned and analyzed):

Number of Patients	Oxymorphone IR 10 mg	Oxymorphone IR 20 mg	Oxymorphone IR 30 mg	Oxycodone 10 mg	Placebo	Total
Planned	60	60	60	60	60	300
Randomized	59	59	65	60	57	300
Safety analyses	59	59	65	60	57	300
Efficacy evaluable	51	51	57	55	44	258

Diagnosis and Main Criteria for Inclusion: Patients were to be over the age of 18 and have an orthopedic condition requiring surgery involving osteotomy, were to have completed surgery within the past 48 hours and received pre-specified short-acting post-operative analgesia, were to have an initial pain intensity score of ≥45 mm on a 100 mm VAS and a categorical pain rating of moderate/severe, with no history of seizures, chronic opioid use/abuse, and no consumption of long-acting IV, IM, or oral analgesia for 12 hours (24 hours for COX2 drugs) prior to receiving study medication.

Test Product, Dose and Mode of Administration; Batch Number: Oxymorphone IR 10 mg, 20 mg, and 30 mg: over-encapsulated immediate-release oxymorphone 10 mg (1, 2 or 3 tablets) administered orally as a single dose in the Single-Dose Phase and up to 48 hours after the single dose in the Multiple-Dose Phase; lot number: 39906335

Duration of Treatment: Pp to 48 hours after commencing the Single-Dose Phase

Reference Therapy, Dose and Mode of Administration; Batch Number: Oxycodone 10 mg: over-encapsulated immediate-release oxycodone 5 mg (2 tablets) administered orally as a single dose in the Single-Dose Phase and up to 48 hours after the single dose in the Multiple-Dose Phase; lot number: PD287A; Placebo: placebo administered orally as a single dose in the Single-Dose Phase; lot number: 05215.03

Criteria for Evaluation:

Efficacy: Primary efficacy analysis was based on the Single-Dose Phase. The primary measure of efficacy was total pain relief (TOTPAR) over the entire 8-hour Single-Dose Phase. Secondary endpoints during the Single-Dose Phase were: pain intensity differences using the VAS and categorical pain intensity scale; time-to-onset of analgesia; duration of analgesia; time to re-medication, patient's global assessment of study medication; and the proportion and time patients first experienced 50% pain relief. During the Multiple-Dose Phase, the secondary endpoints were: worst pain during the day and night, and the patient's and physician's global assessment of study medication.

Safety: Adverse events, physical examination, clinical laboratory tests, vital signs.

Statistical Methods: Analysis of Variance (ANOVA), Kaplan-Meier Survival method; stratified log-rank test; Fisher's exact test; parallel line assay regression analysis.

SUMMARY:

EFFICACY RESULTS:

Oxymorphone IR 10, 20, and 30 mg were superior to placebo in this study as assessed by the primary efficacy endpoint, TOTPAR 0-8 hours.

Oxymorphone IR 10, 20, and 30 mg were superior to placebo for the majority of the secondary efficacy endpoints. There was no statistically significant difference between oxycodone 10 mg and placebo for any efficacy endpoint. There was a statistically significant dose-response relationship between oxymorphone dose level and efficacy assessments, including the primary efficacy endpoint. The dose-response relationship validates the assay sensitivity of the analgesic model. An analgesic plateau was reached with the 20 mg dose of oxymorphone IR, thus the efficacy of oxymorphone IR 30 mg was either similar to or slightly better than that seen with oxymorphone IR 20 mg. The mean worst pain scores were similar among the active treatment groups on Day 1 of the Multiple-Dose Phase and improved slightly on Days 2 and 3. The longest median dose interval of 9 hours 39 minutes was observed in the oxymorphone IR 30 mg group; the median dose intervals for oxymorphone IR 10 mg, oxymorphone IR 20 mg, and oxycodone 10 mg were 7 hours, 7 hours 11 minutes, and 7 hours 44 minutes, respectively. The majority of patients were satisfied with their treatment at the end of the study.

SAFETY RESULTS:

In both the Single- and Multiple-Dose Phases of the study, the most frequently occurring AEs in the oxymorphone treatment groups were those events typically associated with opioid analgesic medication (ie, nausea, vomiting, somnolence and pruritus). The most frequently occurring AEs in the placebo group also included some of these events (ie, nausea and somnolence), albeit at notably lower incidence rates. With the exception of pyrexia (in both phases of the study) and anemia (in the Multiple-Dose Phase), the majority of these events were considered by the Investigator to be treatment related. The incidence rates for these events were generally dose related, with incidence rates increasing as the dose of oxymorphone increased. The majority of AEs were mild or moderate in intensity. Although the overall incidence rates of AEs were higher in the Multiple-Dose Phase, the frequency of opioid-related AEs was similar in both phases; the higher incidence rates may be due to the longer treatment period in the Multiple-Dose Phase. The incidence of AEs was lower in the oxycodone group (27%) compared to the oxymorphone IR groups (39-50%) in the Single-Dose Phase; however, in the Multiple-Dose Phase, the incidence of AEs was higher in the oxycodone groups (82%) compared to the oxymorphone IR groups (61-71%).

There were no deaths in the study. Only 2 non-fatal serious AEs were reported during the Single-Dose Phase of the study; the rate of occurrence of non-fatal SAEs was ≤10% in each treatment group in the Multiple-Dose Phase of the study. In the Single-Dose Phase, incidence rates of withdrawal from the study due to AEs increased as the dose of oxymorphone increased (from 3.4% in the oxymorphone IR 10 mg group to 12.3% in the oxymorphone IR 30 mg group). In the Multiple-Dose Phase, the rate of withdrawal due to AEs was higher in the oxymorphone IR 20 mg group (20.8%) than in the oxymorphone IR 10 mg and 30 mg groups (7.9% and 5.1%, respectively); the rate of withdrawal in the oxycodone IR 10 mg group was 10.3%. The AEs most commonly associated with withdrawal from the study were those events typically associated with opioid treatment (ie, nausea, vomiting, dizziness, headache).

None of the mean changes in any of the serum chemistry, hematology, or urinalysis tests were considered to be clinically meaningful when reviewed in light of this acute postoperative setting. No clinical laboratory results were reported as serious AEs and none caused discontinuation from the study. All were considered mild or moderate in intensity and the majority was considered unrelated to study medication. No clinically significant mean changes from baseline in vital signs were seen in any of the treatment groups, and no clinically significant changes in physical examinations were seen.
Date of Report: 14-Oct-2002