Clinical Trial Results Summary
Study EN3202-005

Study Number: EN3203-005

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo and Active Controls, Single-Dose Study of Oxymorphone IR and Oxycodone IR in Patients With Pain Following Orthopedic Surgery.

Investigators: Nine investigators

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

Publication (reference): None

Study Period:
Date of First Enrollment: July 18, 2001
Date of Last Enrollment: December 20, 2001

Phase of Development: III

Objectives:
Primary: To compare the analgesic efficacy of 10 mg and 20 mg oxymorphone IR to placebo in patients with acute moderate to severe pain following orthopedic surgery.

Secondary: To compare the relative analgesic efficacy of oxymorphone IR 10 mg and oxymorphone IR 20 mg with oxycodone IR 15 mg and oxycodone IR 30 mg. To compare the safety and tolerability of oxymorphone IR 10 mg and oxymorphone IR 20 mg with oxycodone IR 15 mg and oxycodone IR 30 mg.

Methodology: Multicenter, randomized, double-blind, placebo and active controls, single-dose study of oxymorphone IR and oxycodone IR in patients with pain following orthopedic surgery involving osteotomy. The study was conducted with inpatients who had undergone orthopedic surgery involving osteotomy. The patients were placed on standard opioid analgesia postoperatively. Within 72 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 50 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, oxycodone IR 15 mg, oxycodone IR 30 mg, or placebo); stratification was based on their initial categorical pain severity. Following dosing, pain intensity and pain relief were recorded at the following times: 15, 30, 45, and 60 minutes, and hourly thereafter through Hour 8. All efficacy assessments were recorded by the patients in a diary. Patients who requested remedication prior to completing the study received a rescue medication of the investigator's choice and were discontinued from the study.

Number of Patients (Planned and Analyzed):

Number of Patients	Oxymorphone IR 10 mg	Oxymorphone IR 20 mg	Oxycodone IR 15 mg	Oxycodone IR 30 mg	Placebo	Total
Planned	60	60	60	60	60	300
Randomized	63	67	65	63	66	324
Safety analyses	63	67	65	63	66	324
Efficacy evaluable	56	65	62	60	59	302

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 72 hours and received pre-specified short-acting post-operative analgesia, were to have an initial pain intensity score of ≥ 50 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 and 20 mg: over-encapsulated immediate-release oxymorphone 10 mg (1 tablet or 2 tablets) administered orally as a single dose; lot number: 310029

Duration of Treatment: single dose

Reference Therapy, Dose and Mode of Administration; Batch Number:
oxycodone IR 15 mg and 30 mg: over-encapsulated immediate-release oxycodone 5 mg (3 tablets or 6 tablets) administered orally as a single dose; lot number: RH533A; Placebo: placebo administered orally as a single dose; lot number: 2106

Criteria for Evaluation:
Efficacy: Primary: 8-hour Total Pain Relief scores (TOTPAR8) (categorical). Secondary: TOTPAR8 (VAS); 8-hour Sum of Pain Intensity Differences (categorical and VAS); 4- and 6-hour TOTPAR (categorical and VAS); 4- and 6-hour Sum of Pain Intensity Differences (categorical and VAS); 4-, 6-, and 8-hour Sum of Combined Pain Relief and Pain Intensity Differences (categorical and VAS); time to first perceptible pain relief; time to onset of meaningful pain relief; time to remedication; hourly pain relief scores, hourly pain intensity difference scores; hourly combined pain relief and pain intensity difference scores; and global evaluation.

Safety: Adverse events, 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 20 mg was superior to placebo in this study as assessed by the primary efficacy endpoint, TOTPAR (categorical) 0-8 hours. Oxymorphone IR 20 mg was superior to placebo for all of the secondary efficacy endpoints, except for time to first perceptible pain relief, where none of the four active treatments could be distinguished from placebo. Oxymorphone IR 10 mg was superior to placebo for time to remedication and time to meaningful pain relief, indicating comparable duration of pain relief to oxymorphone IR 20 mg and oxycodone IR 15 mg and 30 mg. For all other endpoints, the numerical values for oxymorphone IR 10 mg were superior to placebo, although not statistically different. These results suggest that oxymorphone IR 10 mg in this single-dose acute pain model is probably the minimally effective dose. There were no statistically significant differences between oxymorphone IR 20 mg and oxycodone IR groups for all of the efficacy endpoint measurements, including the primary endpoint. Both doses of oxycodone IR (15 mg and 30 mg) were superior to placebo for all variables, and there was no difference between the 2 doses. Due to this lack of dose response in the oxycodone groups, analgesic equivalency modeling could not be applied and, therefore, no conclusion can be drawn regarding the relative analgesic potency of oxycodone and oxymorphone.

SAFETY RESULTS: The short duration of this trial in an acute post-operative setting requires cautious interpretation of the incidence rates of adverse events.

As expected, in all treatment groups, the most frequently occurring adverse events by body system were nervous system disorders, gastrointestinal disorders, and general disorders/administration site conditions. In the oxymorphone IR 10-mg group, the most frequently occurring adverse events were pyrexia (11/63 patients, or 17.5%) and somnolence (9/63 patients, or 14.3%). In the oxymorphone IR 20-mg group, the most frequently occurring adverse events were somnolence (14/67 patients, or 20.9%), dizziness (12/67 patients, or 17.9%), and nausea (10/67 patients, or 14.9%). In the oxycodone IR 15-mg group, the most frequently occurring adverse events were nausea (11/65 patients, or 16.9%), pyrexia (10/65 patients, or 15.4%), and somnolence (9/65 patients, or 13.9%). In the oxycodone IR 30-mg group, the most frequently occurring adverse events were nausea (15/63 patients, or 23.8%) and somnolence (14/63 patients, or 22.2%). In the placebo group, the most frequently occurring adverse event was pyrexia (8/66 patients, or 12.2%).

No patient died during this study. Fourteen (14) of the 324 patients (4.3%) had at least one serious adverse event. Of these 14 patients, only 1 patient (oxymorphone IR 20 mg) had events (coma, tremors, upper extremity flexing) that were considered by the investigator to be probably related to study medication. However, these events were most likely confounded by the patient's age, impaired renal function, and concomitant medications. Adverse events resulted in the discontinuation of 12 of 324 patients (3.7%). The majority of events (7/12, or 58.3%) were considered to have an unlikely relationship to study medication, and only one event was considered serious. No clinically meaningful mean changes in blood pressure, heart rate, or temperature were seen.

Date of Report: 23-Aug-2002