Study Number: EN3225-002
Title of Study: A Single-center, Randomized, Double-blind, Placebo-controlled, Single-dose Study of the Safety and Efficacy of Low-dose Percocet® Compared to OxyContin® in Patients With Acute Pain Following Third Molar Extraction
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Publications (reference): Gammaitoni et al. Randomized, double-blind, placebo-controlled comparison of the analgesic efficacy of oxycodone 10 mg/acetaminophen 325 mg versus controlled-release oxycodone 20 mg in postsurgical pain. *J Clin Pharm.* 2003;43:296-304.
Studied period (years): 22 May 2002 to 6 June 2002 — **Phase of development**: Phase 4
Objectives: The primary objective was to determine if the analgesic efficacy of Percocet® is superior to OxyContin® in patients with acute pain following oral surgery. The secondary objectives were to determine if Percocet® dosed at 50% of the opiate content of OxyContin® provides pain relief similar to that of OxyContin® in patients with acute pain following oral surgery and to determine the safety of Percocet® treatment in patients with acute pain following oral surgery.
Methodology: This single-center study was conducted using a randomized, double-blind, placebo-controlled, parallel group design in which a single dose of study medication was administered to patients with moderate or severe pain following oral surgery. After surgery was completed, patients experiencing persistent (not transient) moderate or severe pain were randomly assigned to 1 of 3 treatments (Percocet® 10 mg/325 mg, OxyContin® 20 mg, or placebo) using a 2:2:1 ratio. Patients remained at the study site for the first 6 hours following study drug administration. Each patient was given two stopwatches. At the time of dosing, both watches were started. Patients were asked to stop the first stopwatch when pain relief was first perceived and to stop the second watch when meaningful pain relief was felt. Pain intensity and pain relief were recorded at baseline, 15 minutes, 30 minutes, 45 minutes, 60 minutes, and hourly thereafter through Hour 6. Patients were encouraged to wait at least until Hour 1 after administration of study medication before using rescue medication. Efficacy assessments were completed after 6 hours of evaluation or following the need for rescue medication. Patients were allowed to discontinue from the study at any time. Volunteered and observed adverse events (AEs) were assessed and recorded for up to 24 hours following administration of study medication.
Number of Subjects (Planned and Analyzed): A total of 150 patients were planned for the study; 30 allocated to receive placebo, 60 allocated to receive Percocet® 10 mg/325 mg and 60 allocated to receive OxyContin® 20 mg. One hundred-fifty patients were randomized and received study drug; 30 treated with placebo, 61 treated with OxyContin® 20 mg and 59 treated with Percocet® 10 mg/325 mg. One hundred forty-one patients completed the Hour 1 evaluation; 5 patients treated with OxyContin® and 4 patients treated with Percocet® were discontinued because of vomiting prior to the Hour 1 evaluation and were not evaluable for efficacy. All subjects randomized were included in the safety analysis.
Diagnosis and Main Criteria for Inclusion: Patients 16 to 60 years of age who were in generally good health, had at least two mandibular molars extracted that were either partially or fully bone impacted, had at least a moderate trauma rating (meaningful bone removal and not an easy extraction), and had an initial pain intensity score of at least 50 mm on a 100-mm Pain Intensity Visual Analogue Scale (PIVAS) and a categorical pain rating of moderate or severe on a scale of none, mild, moderate, or severe.
Test Product, Dose and Mode of Administration, Batch Number(s): Percocet® 10 mg/325 mg, single dose administered orally; lot number 10/325: 313911NV.

Duration of Treatment: Single dose with a 6-hour period of observation for efficacy and 24-hour period for safety assessment.

Reference Therapy, Dose and Mode of Administration, Batch Number(s): OxyContin® 20 mg, single dose administered orally; lot number 7L51.

Placebo capsule, single dose administered orally; lot number 05215.01.

Criteria for Evaluation:

Efficacy:

Protocol-Specified Endpoints

- 6-hour total pain relief score on a categorical scale (TOTPAR)
- 6-hour total pain relief score on a visual analogue scale (VAS) (VASTOTPAR)
- 6-hour sum of pain intensity difference scores (SPID, categorical scale; VASSPID, VAS)
- Hourly pain relief and pain intensity difference scores (categorical and VAS)
- Time to first perceptible pain relief, time to onset of meaningful pain relief, and time to remedication
- Patient-scored global evaluation

Non-Protocol Specified Endpoints

- 6-Hour Sum of Combined Pain Relief and Pain Intensity Differences, SPRID (categorical and VAS)
- Hourly Combined Pain Relief and Pain Intensity Scores, PRID (categorical and VAS)
- Proportion of patients with meaningful pain relief
- Peak pain intensity difference, PPID (categorical and VAS)
- Time (in hours) to peak pain intensity difference, TPPID (categorical and VAS)
- Peak pain relief, PPAR (categorical and VAS)
- Time (in hours) to peak pain relief, TPPAR (categorical and VAS)

Safety:

Incidence of AEs, including serious adverse events (SAEs).

Statistical Methods:

Demographic and Baseline Characteristics:

Demographic (age and race) and baseline pain intensities were summarized by descriptive statistics and frequency distributions, as appropriate, for the Intent-to-Treat (ITT) population.

Efficacy:

Efficacy analyses were performed on the ITT population (patients who received study medication and had a 1-hour efficacy evaluation without receiving rescue medication or vomiting before the evaluation). Total pain relief scores (TOTPAR), sum of pain intensity differences (SPID), and sum of pain relief and intensity differences (SPRID) (categorical and VAS) were calculated from each patient's pain relief evaluation as the area under that patient's pain relief curve. The area under the curve (AUC) was calculated by summing the areas of the trapezoids formed by adjacent (in time) pain relief evaluations. AUC scores were analyzed using a two-way analysis of variance model with treatment and baseline pain intensity as factors. Pairwise comparisons were conducted using contrast statements. Time-to-first perceptible pain relief, time-to-onset of meaningful pain relief, time-to-remedication, time-to-peak pain intensity difference, and time-to-peak pain relief were estimated using Kaplan-Meier product limit procedure. Pairwise comparisons between treatment groups were conducted using a Log-rank test.

Patient global assessment of pain relief was summarized and a pair-wise comparison between treatment groups was conducted using a Wilcoxon rank sum test stratified by baseline pain intensity (moderate or severe).

The proportion of patients with meaningful pain relief was analyzed using the Fisher's exact test.

Safety:

Safety analyses were performed on the safety population.

SUMMARY:

Efficacy Results:

This study provides a comparison of two active analgesic drugs indicated for moderate to severe pain in an acute pain model following third molar extraction. The two active analgesics have different formulation objectives. OxyContin® 20 mg is designed as a controlled-release tablet with a dosing interval of 12 hours, whereas Percocet® 10 mg/325 mg is an immediate-release formulation with a dosing interval of 6 hours.

The results indicate that analgesia, reflected as pain relief or reduction in pain intensity, increased gradually with OxyContin® 20 mg reaching a plateau between 3 and 5 hours following administration. Analgesic activity with Percocet® 10 mg/325 mg was more rapid, reaching a peak generally within 1 hour and then decreasing slowly through the end of the 6 hour evaluation period observation to a level similar to that provided by OxyContin® 20 mg. According to the analyses of analgesia summed over the 6-hour evaluation period, the level of analgesia provided by Percocet® 10 mg/325 mg was 29 (according to TOTPAR [VAS]) to 238% (according to SPID [categorical]) greater than that for OxyContin® 20 mg, although the mean differences between the two active treatment groups did not always achieve statistical significance. The important pharmacologic difference between these two formulations for patients in acute pain, however, is the early onset of analgesic activity of Percocet® 10 mg/325 mg compared to OxyContin® 20 mg. Analgesia produced by Percocet® 10 mg/325 mg was superior to OxyContin® 20 mg both clinically and statistically between 30 minutes and 2 hours following administration, an interval important to patients in acute pain.

These differences in analgesic activity are also reflected in a statistically and clinically significant shorter median time to the need for remedication for OxyContin® 20 mg (2 hours and 45 minutes) than for Percocet® 10 mg/325 mg (4 hours and 31 minutes). For patients with breakthrough pain from dental extraction following the administration of OxyContin® 20 mg the time of over 9 hours to the next indicated dose would be intolerable compared to a wait of only 1.5 hours for Percocet® 10 mg/325 mg.

The advantages in efficacy of Percocet® 10 mg/325 mg over OxyContin® 20 mg demonstrated in this study were achieved with half the dose of oxycodone as that contained in OxyContin® 20 mg.

Safety Results:

AEs were reported for 44.1% (N=26) of patients receiving Percocet® 10 mg/325 mg, 55.7% (N=34) receiving OxyContin® 20 mg, and 16.7% (N=5) receiving placebo. AEs of the gastrointestinal tract including nausea and vomiting are not uncommon following extraction of third molars. In this study, the extraction had to involve at least a moderate degree of trauma associated due to the necessity of removal of a meaningful amount of bone. Nausea and vomiting were the most frequently reported AEs; the incidence was lowest in the group treated with placebo (6.7% for both events), intermediate in the group treated with Percocet® 10 mg/325 mg (34 and 31% for nausea and vomiting, respectively), and highest in the group treated with OxyContin® 20 mg (38 and 44% for nausea and vomiting, respectively). Overall, the AEs in 92% or more of the patients were attributed to study medication, including placebo. Across all treatment groups, vomiting in 94% to 100% of patients was considered to be severe while the associated nausea in the majority of patients in all treatment groups was considered to be mild or moderate in severity. There were no deaths, non-fatal SAEs, or discontinuations resulting from AEs in either treatment group.