Oxycodone HCl/Niacin in Relieving Moderate-to-Severe Postoperative Pain Following Bunionectomy Surgery: Timing of Analgesic Response

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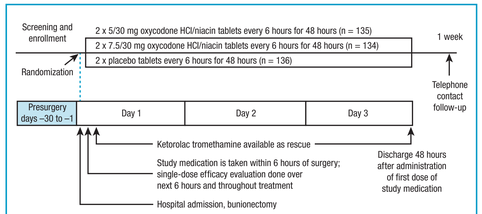
INTRODUCTION

- Opioids are highly effective analgesics that play an integral role in the management of both acute and chronic pain.[1,2]
- Short-acting opioids, including immediate-release (IR) oxycodone HCl, have a well-established role in relieving postsurgical pain.[3,4]
- Concern regarding the potential misuse or abuse of opioid analgesics may limit their use by clinicians, and thus contribute to the undertreatment of pain.[5]
- In 2009, an estimated 5.3 million persons aged ≥12 years in the United States reported non-medical use of prescription pain relievers in the past month.[4,6]
- Opioids, including IR oxycodone HCl, are commonly abused via oral routes—mainly by swallowing and chewing—but can also be abused intranasally or intravenously.[7]
- There is a need for opioid analgesics that provide efficacy comparable to traditional agents, but with properties that make them less desirable for abuse.
- An oxycodone HCl/niacin oral tablet formulation has been developed that, in addition to oxycodone HCl, contains 30 mg of niacin intended to discourage excess oral consumption.
- Here we report on the efficacy and safety of oxycodone HCl/niacin tablets and the timing of analgesia for the treatment of moderate-to-severe pain following bunionectomy surgery.

METHODS

- This was a phase 3, randomized, double-blind, placebo-controlled, multicenter repeat-dose study (Figure 1).
- The study population consisted of 405 patients (359 women and 46 men) aged ≥18 years who were in good health, required bunionectomy surgery, and met the class I-III patient criteria of the American Society of Anesthesiologists.
- The protocol and informed consent form were approved by a central institutional review board prior to patient enrollment. All patients gave written informed consent.
- Screened patients underwent primary unilateral first-metatarsal bunionectomy surgery without collateral procedures.

Figure 1. Study Design and Schedule of Assessments



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- Patients meeting selection criteria entered the treatment phase and were randomized to 1 of 3 treatment arms: 2 x 5/30 mg oxycodone HCl/niacin tablets (n = 135), 2 x 7.5/30 mg oxycodone HCl/niacin tablets (n = 134), or placebo (n = 136).
- Dosing occurred every 6 hours for 48 hours following the surgery, during which no prescription or nonprescription analgesics, sedatives, or muscle relaxants were permitted.
- Ketorolac tromethamine was available to all patients as rescue medication, upon request.

Analgesic Analysis

- Efficacy assessments were based on:
  - Pain intensity (PI) score: recorded by patient using a 100-mm visual analog scale (VAS; denoting 0 [no pain] to 100 [worst pain imaginable]).
  - Pain relief (PR) score: recorded by patient using a 5-point categorical scale (0 = none, 1 = a little, 2 = some, 3 = a lot, and 4 = complete).
- Primary efficacy endpoint was the sum of PI difference scores ($SPID_{48}$), a time-weighted measure of PI difference (PID) scores over the 48-hour treatment period.
- Secondary endpoints included:
  - Time-weighted sum of PR and PI difference scores from 0 to 6 hours ($SPRID_6$).
  - Time to first perceptible pain relief (TPR).
  - Time to meaningful pain relief (TMR).
  - Time to first use of rescue medication (TTR).
- Efficacy analyses were performed on the intent-to-treat population and included all randomized patients who received ≥1 dose of medication.
- TPR and TMR were assessed using the 2-stopwatch method; timing and use of rescue medication were recorded by site personnel.

Statistical Analysis

- Treatment differences in $SPID_{48}$ were determined by analysis of covariance (ANCOVA), adjusting for investigative sites and baseline PI scores.
- Comparisons of both doses of oxycodone HCl/niacin tablets with placebo were made in a nested manner, in which significance of the comparison of the higher dose with placebo determined the need for comparing the lower dose with placebo.
- Treatment differences for TPR, TMR, and TTR were assessed using Kaplan-Meier time-to-event methodology and the log-rank test.
  - For TPR and TMR, patients were censored upon administration of ketorolac.

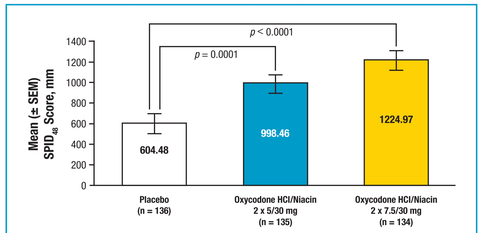
Safety Evaluation

- Safety was assessed from the recording of adverse events (AEs), vital signs, clinical laboratory tests, and physical examinations.

RESULTS

- The majority of the patient population (N = 405) was white (76%) and female (89%); mean age was 41.8 years (range, 18-77).
  - There were no demographic differences between treatment groups.
- For the primary efficacy endpoint, mean $SPID_{48}$ score (Figure 2), both oxycodone HCl/niacin doses were statistically superior vs placebo (2 x 5/30 mg, $p = 0.0001$; 2 x 7.5/30 mg, $p < 0.0001$).
- Secondary efficacy analyses:
  - Mean $SPRID_6$ score (Figure 3) was –4.03 for placebo, 2.78 for the 2 x 5/30 mg dose, and 5.61 for the 2 x 7.5/30 mg dose (both doses $p < 0.0001$ compared with placebo).
  - Mean PR scores over time (Figure 4) were significantly greater for the 2 x 5/30 mg dose vs placebo at 1, 2, 3, 4, and 5 hours post-dose ($p < 0.05$). Mean PR scores for the 2 x 7.5/30 mg dose were significantly superior vs placebo at all time points (all $p < 0.01$).
  - Median TPR was 0.8 and 0.5 hours for oxycodone HCl/niacin 2 x 5/30 mg and 2 x 7.5/30 mg, respectively, compared with 5.8 hours for placebo. The survival curves were significantly different from placebo ($p = 0.0008$ and $p < 0.0001$, respectively).
  - Median TMR was 12.6 hours for oxycodone HCl/niacin 2 x 5/30 mg and 1.2 hours for 2 x 7.5/30 mg. The median for the placebo group could not be calculated since 50% of placebo patients did not achieve meaningful PR. The TMR survival curve for 2 x 7.5/30 mg was statistically significantly superior vs placebo ($p < 0.0001$; Figure 5).

Figure 2. Effect of Oxycodone HCl/Niacin Tablets on Pain Intensity as Measured by $SPID_{48}$ on 100-mm VAS[a]



[a]Intent-to-treat population (N = 405).
The sum of pain intensity difference scores ($SPID_{48}$) used time-weighted pain intensity (PI) scores for the first 6-hour interval and the PI scores from 12,18, 24, 30, 36, 42, and 48 hours after the initial dose of study medication.
Treatment differences in the $SPID_{48}$ were determined by ANCOVA, adjusting for investigative sites and baseline PI scores.
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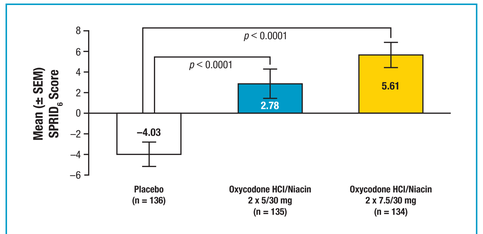
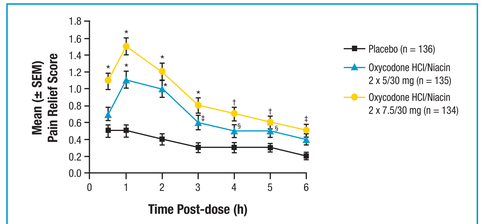
Figure 3. Effect of Oxycodone HCl/Niacin Tablets on the Time-Weighted $SPRID_6$[a]



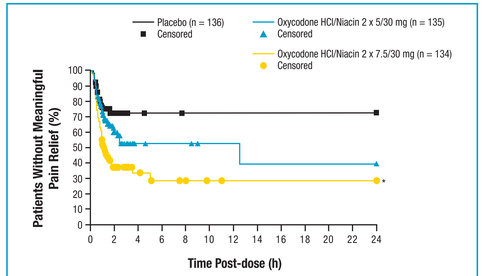
[a]Intent-to-treat population (N = 405).
p values are from an ANCOVA model with treatment group and site as fixed effects and baseline pain intensity as the covariate.
$SPRID_6$ = time-weighted sum of pain relief and pain intensity difference scores from 0 to 6 hours.

Figure 4. Pain Relief Scores Over Time[a]



[a]Intent-to-treat population (N = 405).
Comparisons vs placebo: *$p < 0.0001$; †$p < 0.001$; ‡$p < 0.01$; §$p < 0.05$.

Figure 5. Time to Meaningful Pain Relief Over Time[a]



[a]Intent-to-treat population (N = 405).
*$p < 0.0001$ vs placebo.

- Median TTR occurred at 1.4 hours in the placebo group vs 2.4 and 2.9 hours for oxycodone HCl/niacin 2 x 5/30 mg and 2 x 7.5/30 mg, respectively (both survival curves $p < 0.0001$ compared with placebo).
- Rescue medication was used by the majority of patients, although the use was significantly higher in the placebo group (97.1%) vs in the oxycodone HCl/niacin 2 x 5/30 mg group (88.1%, $p = 0.0038$) and in the 2 x 7.5/30 mg group (82.8%, $p < 0.0001$).

Safety/Tolerability

- Of 405 patients, 273 (67.4%) experienced ≥1 treatment-emergent AE (TEAE) during the study.
- 2.2% of patients receiving active drug (6/269) withdrew due to TEAEs.
- The most frequently occurring TEAEs (≥5% of patients in any treatment group) are listed in Table 1.
- Most AEs were mild or moderate; there were no serious AEs or deaths.
- The most prevalent AEs were nausea, vomiting, dizziness, flushing, and pruritus, which are common AEs with opioid medication and/or niacin use.
- No trends were apparent in group mean changes for heart rate, respiration rate, or laboratory values over time.

Table 1. Most Frequently Occurring TEAEs (≥5% of Patients in Any Treatment Group)[a]

Preferred Term, n (%)	Placebo (n = 136)	Oxycodone HCl/Niacin 2 x 5/30 mg (n = 135)	Oxycodone HCl/Niacin 2 x 7.5/30 mg (n = 134)
Patients with any TEAE	52 (38.2)	104 (77.0)	117 (87.3)
Nausea	14 (10.3)	68 (50.4)	83 (61.9)
Vomiting	5 (3.7)	46 (34.1)	67 (50.0)
Dizziness	6 (4.4)	22 (16.3)	32 (23.9)
Flushing	2 (1.5)	22 (16.3)	15 (11.2)
Pruritus	1 (0.7)	17 (12.6)	13 (9.7)
Headache	3 (2.2)	13 (9.6)	11 (8.2)
Pruritus generalized	1 (0.7)	8 (5.9)	10 (7.5)
Somnolence	2 (1.5)	8 (5.9)	6 (4.5)

[a]Safety population.
TEAE = treatment-emergent adverse event.
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CONCLUSIONS

- **Oxycodone HCl/niacin tablets (2 x 5/30 mg and 2 x 7.5/30 mg) provided effective analgesia and were generally well tolerated in adult patients with moderate-to-severe pain following bunionectomy surgery, when administered every 6 hours for 48 hours following the procedure.**
- **Both doses of oxycodone HCl/niacin tablets demonstrated statistically significant superiority compared with placebo, as measured by the primary pain intensity endpoint ($SPID_{48}$).**
- **For secondary efficacy endpoints ($SPRID_6$, TPR, and TTR), statistically significant superiority vs placebo was shown for both doses.**
- **Oxycodone HCl/niacin 2 x 5/30 mg and 2 x 7.5/30 mg both produced statistically significant pain relief by 1 hour post-dose.**
- **Statistically significant superiority for TMR was shown only for the higher dose.**
- **Oxycodone HCl/niacin tablets were well tolerated and produced mostly mild and occasionally moderate AEs.**

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