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Original article

Efficacy and safety of oxycodone HCl/niacin tablets for the treatment of moderate-to-severe postoperative pain following bunionectomy surgery

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Abstract

Objective:
To evaluate the efficacy and safety of two dose strengths of oxycodone hydrochloride (HCl)/niacin tablets* for the treatment of moderate-to-severe postoperative pain following bunionectomy surgery.

Research design and methods:
Randomized, double-blind, placebo-controlled, US multicenter, repeat-dose study (Clinicaltrials.gov: NCT00654069). A total of 606 patients aged ≥18 years with moderate-to-severe pain post-bunionectomy were screened, and 405 patients were randomized to receive placebo, 2 × 5/30 mg oxycodone HCl/niacin tablets, or 2 × 7.5/30 mg oxycodone HCl/niacin tablets administered every 6 hours for 48 hours. Ketorolac tromethamine was available as rescue medication.

Main outcome measures:
Primary efficacy endpoint was the sum of pain-intensity difference scores during the 48 hours ($SPID_{48}$) following the initial dose of study drug. Secondary efficacy endpoints included a responder analysis and use of rescue medication. Safety evaluations included adverse events (AEs), vital signs, and clinical laboratory assessments.

Results:
Both doses of oxycodone HCl/niacin tablets demonstrated superior reductions in pain intensity compared with placebo as evidenced by the $SPID_{48}$ ($p < 0.0001$ for both oxycodone HCl/niacin 2 × 5/30 mg and 2 × 7.5/30 mg). AEs were consistent with the known effects of oxycodone HCl and niacin. Most AEs were mild or moderate in intensity, and no serious AEs occurred. There were no discontinuations due to AEs in the placebo group; 2/135 (1.5%) discontinued due to AEs in the 2 × 5/30 mg group and 4/134 (3.0%) in the 2 × 7.5/30 mg group. A limitation of this study was that there was no active comparator arm.

Conclusions:
Oxycodone HCl/niacin tablets (5/30 mg and 7.5/30 mg) provide effective analgesia and are generally well tolerated in patients with moderate-to-severe pain following bunionectomy surgery.

Introduction

Opioids are highly effective analgesics that play an integral role in the management of a variety of pain syndromes, both acute and chronic[1,2].

*Acurox® with Niacin Tablets. King Pharmaceuticals®, Inc., Bristol, TN, USA.

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Short-acting opioids, including immediate-release oxycodone hydrochloride (HCl), have a well-established role in relieving post-surgical pain[3]. Although achieving 'no pain' may be an unrealistic treatment goal[4], when acute pain such as post-surgical pain is inadequately treated, patients may experience a delay in return to function. If acute pain is untreated it may become a chronic condition[3,5–7].

Concern regarding the potential for misuse or abuse of opioid analgesics may limit the willingness of clinicians to prescribe opioid analgesics, which would contribute to the undertreatment of pain[8]. This concern is not entirely unfounded: in 2009 an estimated 5.3 million persons aged ≥12 years in the United States reported nonmedical use of prescription pain relievers in the past month[9]. Although physicians can address the risks for misuse or abuse with patients[2,8], evidence suggests that many medications do not remain in the hands of the original patient; an estimated 55% of nonmedical prescription pain relievers were obtained from a friend or relative at no cost[9].

The need exists for opioid analgesics that provide comparable efficacy to traditional agents, but with properties that make them less desirable for misuse or abuse. A formulation has been developed that combines oxycodone HCl, a subtherapeutic dose of niacin (30 mg), and three inactive, but functional, excipients that discourage crushing and snorting, as well as make the tablets difficult to dissolve in solvents for injection. When taken in excess, these oxycodone HCl/niacin* tablets are associated with dose-dependent, unpleasant, but temporary niacin-induced effects (e.g., flushing and pruritus). Niacin is an essential vitamin (B_3) found in many foods[10]. Immediate-release niacin is used at dosages up to 6000 mg/day to treat dyslipidemias[11]. The amount of niacin associated with appropriate use of oxycodone HCl/niacin tablets – 60 mg every 6 hours – is generally well tolerated[12,13]; thus, patients should not be adversely affected by the niacin in oxycodone HCl/niacin tablets when the agent is administered at the recommended doses.

A prior study had demonstrated that experienced opioid abusers prefer an equivalent oral dose of oxycodone tablets over oxycodone HCl/niacin tablets[14]. This study was designed to investigate whether the oxycodone HCl/niacin tablet is efficacious and has an acceptable safety profile for the patient.

Here we report on the efficacy and safety of oxycodone HCl/niacin tablets for the treatment of moderate-to-severe pain following bunionectomy surgery, an acutely painful procedure that results in prolonged postoperative pain[15]. Bunionectomy surgery is commonly performed to correct distal first metatarsophalangeal joint deformities and is associated with severe pain that can last up to 10 days. The acute postoperative pain model has been used widely to assess the efficacy of analgesic agents[15–17].

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Patients and methods

Ethical practices

The protocol and informed consent form were approved by a central institutional review board prior to patient enrollment. All patients gave written informed consent before participating in the study. This study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol and statistical analysis plan were agreed to in advance with the US Food and Drug Administration via a Special Protocol Assessment.

Inclusion and exclusion criteria

Patients included in this study were aged ≥18 years, scheduled to undergo bunionectomy surgery, and required to be alert and capable of taking an oral opioid analgesic. Patients had to be generally in good health based on medical history; physical examination; laboratory results for clinical chemistry, hematology, and urinalysis; vital signs; and 12-lead electrocardiogram. Patients also had to have the ability to comprehend the requirements of the study, be able to communicate effectively, and voluntarily give informed consent. Non-postmenopausal and non-sterile women were required to use an acceptable method of birth control, and pregnant or lactating women were not included in the study. Prior to randomization, patients rated their pain on a 4-point scale ranging from 0 to 3 and were required to have a rating of 2 (moderate pain) or 3 (severe pain) to be eligible for treatment.

Exclusion criteria included a history of drug abuse (legal or illegal substances) or malignancy in the past 5 years. Patients could not have pulmonary, cardiovascular, neurologic, endocrine, hepatic, gastrointestinal, or kidney disease. Patients could not be taking opioid or nonopioid analgesics at doses that would interfere with study evaluations, nonopioid analgesics for acute pain (other than the pain associated with the need for bunionectomy surgery), systemic corticosteroids within 7 days of surgery, antipsychotic agents, central nervous system depressants, or antidepressants (unless on a stable dose for >1 month). Additional exclusion criteria included mental or emotional unsuitability; current evidence of alcohol abuse of >4 U/day (1 U = ½ pint of beer, 1 glass of wine, or 1 ounce of spirits); documented hypersensitivity to opioid analgesics, niacin, or other nonsteroidal anti-inflammatory drugs; and an inability to take ketorolac tromethamine (the designated rescue medication). Patients were also excluded if dosed with any other investigational drug within 30 days prior to the screening visit.

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Study design

This was a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial (Sponsor study number AP-ADF-105; Clinicaltrials.gov: NCT00654069) of the efficacy and safety of repeated doses of two strengths of oxycodone HCl/niacin tablets vs. placebo for the treatment of moderate-to-severe postoperative pain following bunionectomy surgery. It was conducted at six sites in the United States between September 26, 2007, and March 7, 2008 (*SCIREX Research Centers* – Austin, Texas; Houston, Texas; and Salt Lake City, Utah; *Crossroads Research Inc.* – Owings Mills, Maryland; *Vertex Clinical Research, Inc.* – Bakersfield, California; *Clinical Management Services, Inc.* – Glendale, California). All study medication tablets (active and placebo) were identical in appearance.

The primary objective of this study was to evaluate the analgesic efficacy of oxycodone HCl/niacin (2 × 5/30 mg and 2 × 7.5/30 mg) tablets vs. placebo for the treatment of moderate-to-severe post-bunionectomy pain over 48 hours of repeat dosing every 6 hours. The secondary objective was to characterize the safety and tolerability of oxycodone HCl/niacin tablets by comparing the effects of two dose levels vs. placebo on the incidence of treatment-emergent adverse events (TEAEs), and treatment-emergent changes in physical and neurological examinations, clinical laboratory values, and vital signs.

Efficacy evaluations

Efficacy assessments were based on pain intensity (PI) and pain relief (PR) scores. PI was assessed via a 100 mm visual analog scale (VAS), denoting 0 (no pain) to 100 (worst pain imaginable). PI scores were recorded at baseline (immediately predose), and at 0.5, 1, 2, 3, 4, 5, 6, 12, 18, 24, 30, 36, 42, and 48 hours after the initial dose of study medication. PI scores were also recorded each time a patient requested rescue medication. Additionally, patients rated that day's average PI at bedtime on study days 1 and 2, and at the end of the 48-hour treatment period.

PR scores were recorded by patients at 0.5, 1, 2, 3, 4, 5, and 6 hours after the initial dose of study medication, and at any time when a patient requested rescue medication. Patients rated their pain relief using a 5-point scale: 0 (none); 1 (a little); 2 (some); 3 (a lot); or 4 (complete).

The primary efficacy endpoint for this study was the sum of pain intensity difference scores from 0–48 hours ($SPID_{48}$), a time-weighted measure of pain intensity difference (PID) scores over the 48-hour treatment period.

Secondary endpoints included: (1) a responder analysis with responders defined as patients who met both these criteria: achieved 50% or higher maximum total PR over the 6-hour interval following treatment ($TOTPAR_6 \geq 12$), and used rescue medication ≤3 times within 6 hours of dosing between 6 PM on day 1 and 6 PM on day 3; (2) mean of patient average daily pain intensity (MPADPI) scores (average of PI scores obtained in the evening on day 1 and day 2, and at the end of the treatment period on day 3); (3) PID scores at 0.5, 1, 2, 3, 4, 5, 6, 12, 18, 24, 30, 36, 42, and 48 hours after the initial dose of study medication; (4) sum of PID scores from 0–6 hours ($SPID_6$); (5) PR scores at 30 minutes and 1, 2, 3, 4, 5, and 6 hours after the initial dose of study drug; (6) total PR from 0–6 hours ($TOTPAR_6$); (7) time to first perceptible pain relief (TPR); (8) time to meaningful pain relief (TMR); (9) pain relief plus pain intensity difference (PRID) scores were calculated using measurements at 30 minutes and 1, 2, 3, 4, 5, and 6 hours after the initial dose of study medication; (10) sum of pain relief and pain intensity difference scores from 0–6 hours ($SPRID_6$); (11) time to first use of rescue medication (TTR); (12) total rescue medication use (TRU) during each 6-hour interval and overall; (13) patients requiring rescue medication during each 6-hour dosing interval and overall (RESC_N); and (14) withdrawal due to lack of efficacy (WD_N). As the clinical significance for many of the secondary outcomes chosen for this study had not previously been identified, a *post hoc* analysis of the responder rate, based on the published criterion of ≥33% maxTOTPAR (in this case, over the 6-hour treatment interval, $TOTPAR_6$, but also including the criterion that responders use rescue medication ≤3 times within 6 hours of dosing within the 48 hours) was added as a measure of clinically important response[18].

Safety evaluation

Safety was assessed by adverse event (AE) reports, laboratory results, vital signs, and physical examinations. All AEs were collected from the time of dosage administration until completion of the follow-up visit and were followed until resolved or stabilized, or were no longer judged clinically significant. Serious AEs were collected from the time informed consent was obtained through the completion of the follow-up visit.

The study design is illustrated in Figure 1. Screened patients underwent bunionectomy surgery, after which patients who continued to meet eligibility requirements were admitted to the clinical research unit (CRU). Patients who reported moderate-to-severe pain within 6 hours after surgery entered the treatment phase and were randomized to one of three treatment arms: placebo, 2 × 5/30 mg oxycodone HCl/niacin tablets, or 2 × 7.5/30 mg oxycodone HCl/niacin tablets. Upon the patients' reporting of moderate-to-severe pain, they received the first dose of study medication followed by dosing every 6 hours for 48 hours (eight doses of study medication in total). Ketorolac tromethamine was available as a rescue medication upon patient request.

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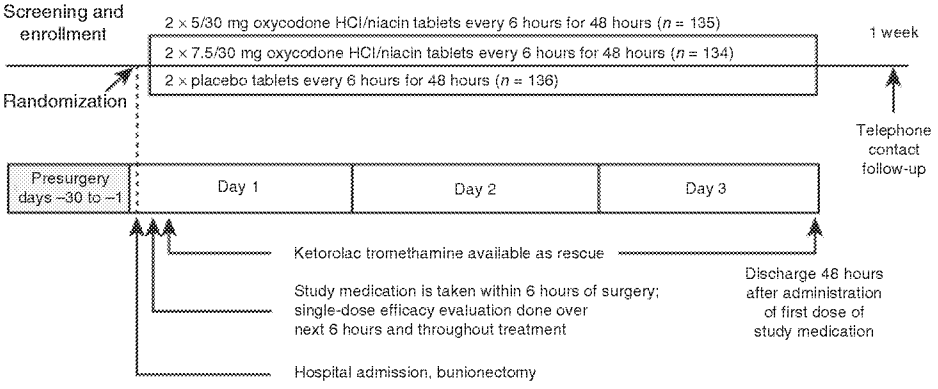

Figure 1. Study design and schedule of assessments.

Patients were discharged from the CRU and entered the follow-up phase 48 hours after the initial dose of study medication, pending satisfactory completion of all evaluations and if judged safe for discharge by the managing physician. Patients were provided with a prescription for an analgesic to treat any continuing postoperative pain on an as-needed basis. Follow-up was conducted by telephone approximately 1 week after discharge from the CRU.

The medical monitor, sponsor, and investigators and their staff remained blinded to each patient's treatment during the study. If an investigator broke the blind, they were required to notify the medical monitor immediately, and the date and reason were recorded in the appropriate section of the case report form.

Statistical methods

Sample-size calculation was based on an assumption of PID scores of 5 mm (at 6 hours) to 25 mm (at 48 hours) for placebo (mean $SPID_{48} = 90$ mm), and 30 mm for active drug (stable for 48 hours; mean $SPID_{48} = 272$ mm), and a common $SPID_{48}$ standard deviation of 460 mm. A t test with 90% power to detect a difference of 182 mm using a two-sided test at the 5% significance level required 135 patients per treatment arm. Randomization and assignment of patients to one of three double-blind treatment groups were accomplished using a site-specific computer-generated randomization schedule.

All statistical analyses were performed using appropriate procedures in SAS software version 8 or higher, with significance of effects determined by two-sided tests with a p value of ≤ 0.05, unless specified otherwise. All efficacy analyses were performed on the intent-to-treat (ITT) study population (i.e., all randomized patients who received ≥ 1 dose of study medication). The per-protocol (PP) population comprised all ITT patients who remained in the study for ≥ 48 hours of treatment, and did not incur a major protocol violation; the PP population was used to evaluate the sensitivity of analysis of the primary efficacy outcome. The safety population was identical to the ITT population, but was analyzed as treated (ITT population was analyzed as randomized).

The primary efficacy endpoint for this study was the $SPID_{48}$ using PI scores for the first 6-hour interval, time weighted, and the PI scores from 12, 18, 24, 30, 36, 42, and 48 hours after the initial dose of study medication. Baseline observation carried forward values were used if patients withdrew for reasons other than lack of efficacy. For patients who withdrew for lack of efficacy, last observation carried forward (LOCF) was used for PI and PR scores, imputing the PI and PR scores at the time of rescue for those patients requesting rescue, or the most recent scheduled PI and PR scores for those patients not requesting rescue. For patients who remained in the study, pain scores were recorded at the time of rescue medication using the LOCF method to the end of that 6-hour treatment interval. Pain scoring began again with the next scheduled dose. Any missing PI or PR score was derived by calculating the mean of the preceding score and the subsequent score.

Treatment differences ($SPID_{48}$) were determined by analysis of covariance (ANCOVA), adjusting for investigative sites and baseline PI scores. Pairwise comparisons of treatments used contrast statements in the ANCOVA model. Comparisons of each dose level with placebo were performed in a nested manner, with the significance of the comparison of the higher dose to placebo determining the need for testing the lower dose to placebo. This nested method eliminated the need to make adjustments for multiple comparisons. The two oxycodone HCl/niacin doses were not compared with each other.

Comparisons of treatment differences for MPADPI, $SPID_6$, and $SPRID_6$ were performed by ANCOVA, adjusting for investigative sites and baseline PI scores. Pairwise comparisons of treatments were performed using contrast statements in the ANCOVA model. Comparisons of treatment differences for time to first use of rescue medication were performed using a Kaplan-Meier time-to-event method. For PR, $TOTPAR_6$, PID, PRID, and TRU, tests for treatment differences were performed using contrasts

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Table 1. Demographic and other baseline characteristics: safety population.

		Placebo ($n=136$)	Oxycodone HCl/niacin 2 × 5/30 mg ($n=135$)	Oxycodone HCl/niacin 2 × 7.5/30 mg ($n=134$)	Total ($n=405$)
Age (years)	Mean (SD)	42.0 (13.0)	41.8 (14.0)	41.6 (13.6)	41.8 (13.5)
	Median	43.0	42.0	41.0	42.0
	Minimum, maximum	18, 71	18, 76	18, 77	18, 77
Gender, *n* (%)	Male	22 (16.2%)	10 (7.4%)	14 (10.4%)	46 (11.4%)
	Female	114 (83.8%)	125 (92.6%)	120 (89.6%)	359 (88.6%)
Race[a], *n* (%)	Asian	1 (0.7%)	2 (1.5%)	1 (0.7%)	4 (1.0%)
	Black	24 (17.6%)	31 (23.0%)	23 (17.2%)	78 (19.3%)
	White	109 (80.1%)	99 (73.3%)	99 (73.9%)	307 (75.8%)
	Other[a]	2 (1.5%)	3 (2.2%)	11 (8.2%)	16 (3.9%)
Ethnicity, *n* (%)	Hispanic/Latino	22 (16.2%)	20 (14.8%)	27 (20.1%)	69 (17.0%)
	Not Hispanic/Latino	114 (83.8%)	115 (85.2%)	107 (79.9%)	336 (83.0%)
Body Mass Index, kg/m^2	Mean	27.5	28.3	27.4	27.7
	Median	26.8	28.0	25.8	27.0
	Minimum, maximum	20.3, 30.2	22.7, 43.1	24.8, 34.4	20.8, 41.8
Baseline Pain Intensity (100 mm VAS)	Mean (SD)	64.2 (19.86)	63.2 (18.23)	64.0 (17.81)	63.8 (18.62)
	Median	67.5	62.0	64.0	65.0
	Minimum, maximum	17, 100	13, 100	24, 100	13, 100

[a]Patients with multiple race selections are included in the 'Other' category.
SD: standard deviation.

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from ANCOVA with similar model parameters as the primary endpoint. For TPR and TMR, treatment differences were analyzed using a Kaplan-Meier time-to-event method. For patients requiring rescue medication and those who withdrew due to lack of efficacy, tests for treatment differences were performed using a logistic regression analysis adjusting for investigative site and baseline PI. Pairwise comparisons of treatments were performed using contrast statements in the model in the same manner as specified for the primary endpoint. No inferential statistical analyses of safety data were planned.

Results

A total of 606 patients were screened for inclusion in the study; 405 ITT patients were randomized. No relevant between-group differences were observed for any demographic or other baseline characteristics (Table 1). The population was predominantly white and female. The mean PI score (SD) at baseline across all treatment groups was 63.8 (18.62) on the 100 mm VAS (range, 13–100 mm). Although patients in all treatment groups had a baseline rating of moderate-to-severe pain (2 or 3 on a 4-point scale used for eligibility), a few patients had baseline VAS scores <30 mm (7 [5.1%], 3 [2.2%], and 2 [1.5%] in the placebo, 2 × 5/30 mg oxycodone HCl/niacin, and 2 × 7.5/30 mg oxycodone HCl/niacin groups, respectively).

The mean (SD) interval between the end of surgery and the first dose of study medication, across all treatment groups, was 2.93 (1.33) hours (range, 0.5–6 hours). Of the 405 patients, 385 (95.1%) completed all eight doses; 384 (94.8%) completed the 48-hour double-blind period; and 21 (5.2%) discontinued from the study (Figure 2).

No meaningful differences were observed among treatment groups in the number of patients completing all eight doses (≈95% of each study group). Reasons for discontinuation are presented in Figure 2.

Clinical response

The primary efficacy endpoint was the $SPID_{48}$. Both doses of oxycodone HCl/niacin were statistically superior compared with placebo (2 × 5/30 mg: $p=0.0001$ for ITT; 2 × 7.5/30 mg: $p<0.0001$ for ITT; Figure 3).

A total of 46 patients were excluded from the PP population analysis because they did not complete the 48-hour treatment period and/or had protocol deviations: 17 from the placebo group, 11 from the 2 × 5/30 mg group, and 18 from the 2 × 7.5/30 mg group. The analysis results based on the PP population are supportive of those based on the ITT population. Both doses of oxycodone HCl/niacin demonstrated superiority compared with placebo (2 × 5/30 mg: $p=0.0011$ for PP; 2 × 7.5/30 mg: $p<0.0001$ for PP).

Both doses of oxycodone HCl/niacin also demonstrated statistically significant superiority compared with placebo as measured by the prespecified secondary endpoint of responder analysis (Table 2; greater than three-fold higher response rate in active groups vs. placebo). Responder rates were relatively low for all groups: placebo, 2.9% (4/136); 2 × 5/30 mg, 9.6% (13/135); and 2 × 7.5/30 mg, 10.4% (14/134). This was likely related to the strict definition for responders (≥50% $maxTOTPAR_6$ and use of rescue medication ≤3 times within 6 hours of

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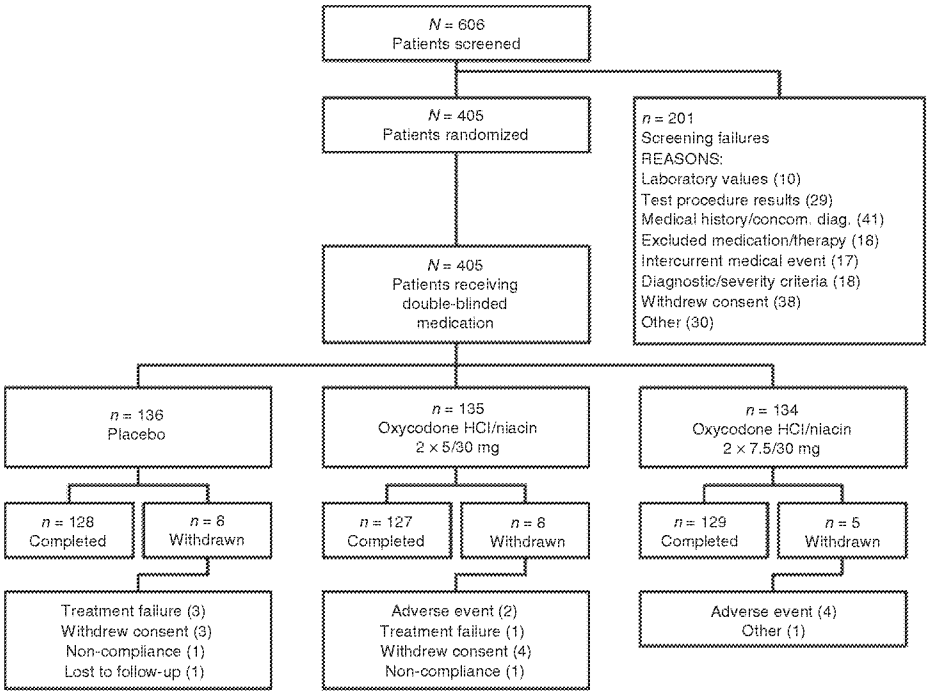

Figure 2. Disposition of patients.

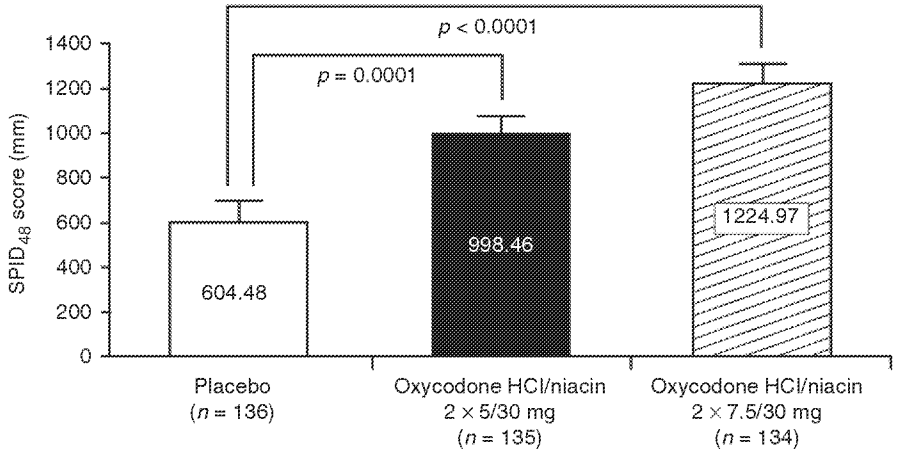

Figure 3. Sum of pain intensity difference scores ± standard error from 0 to 48 hours ($SPID_{48}$): ITT population.

dosing over the 48-hour course of the study). Using the published criterion with a lower threshold of ≥33% maxTOTPAR[18], with the same rescue medication limitation, and during the 6-hour treatment interval, the responder rate increased for all three treatment groups (Table 2; placebo, 10.3% [14/136]; 2 × 5/30 mg, 19.3% [26/135]; and 2 × 7.5/30 mg, 26.9% [36/134]), with substantially increased differentiation between each of the active groups and the placebo group. Furthermore, this result exhibits a clear dose response that was not evident when using the stricter responder definition. Importantly, the response rate of 19.3% of the lower-dose group compared with 10.3% of the placebo group demonstrated a statistically significant difference.

In secondary efficacy analyses (Table 2), both doses of oxycodone HCl/niacin demonstrated superiority compared with placebo for nearly all secondary endpoints. MPADPI, $SPID_6$, and $SPRID_6$ measurements demonstrated the statistically significant superiority of both doses of oxycodone HCl/niacin tablets compared with placebo. The MPADPI was 44.45 for the placebo group, 39.04 for the 2 × 5/30 mg group, and 36.06 for the 2 × 7.5/30 mg group. The primary comparison between the 2 × 7.5/30 mg group and the placebo group was highly significant

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Table 2. Secondary efficacy analyses: ITT population.

Secondary Efficacy Parameter	Placebo ($n=136$)	Oxycodone HCl/niacin		Primary comparison	
		2 × 5/30 mg ($n=135$)	2 × 7.5/30 mg ($n=134$)	Oxycodone HCl/niacin 2 × 5/30 mg vs. placebo	Oxycodone HCl/niacin 2 × 7.5/30 mg vs. placebo
Responder analysis (≥50% max $TOTPAR_6$ and ≤3 uses of rescue medication within 6 hours of dosing within 48 hours), *n* (%)	4 (2.9)	13 (9.6)	14 (10.4)	$p=0.0212$[a]	$p=0.0105$[a]
Post hoc Responder analysis (≥33% max $TOTPAR_6$ and ≤3 uses of rescue medication within 6 hours of dosing within 48 hours), *n* (%)	14 (10.3)	26 (19.3)	36 (26.9)	$p=0.0374$[a]	$p=0.0003$[a]
MPADPI, mean (SE)	44.45 (1.54)	39.04 (1.56)	36.06 (1.47)	$p=0.0124$[b]	$p<0.0001$[b]
PID (30 min), mean (SE)	3.1 (1.41)	5.4 (1.82)	10.7 (1.77)	$p=0.2509$[b]	$p=0.0009$[b]
PRID (30 min), mean (SE)	0.85 (0.20)	1.28 (0.245)	2.13 (0.256)	$p=0.1623$[b]	$p<0.0001$[b]
PR (30 min), mean (SE)	0.5 (0.07)	0.7 (0.08)	1.1 (0.09)	$p=0.0921$[b]	$p<0.0001$[b]
$SPID_6$, mean (SE)	−60.47 (9.53)	−11.36 (11.98)	5.56 (9.56)	$p<0.0001$[b]	$p<0.0001$[b]
$SPRID_6$, mean (SE)	−4.03 (1.14)	2.78 (1.49)	5.61 (1.24)	$p<0.0001$[b]	$p<0.0001$[b]
TTR, median (hours)	1.4	2.4	2.9	$p<0.0001$[c]	$p<0.0001$[c]
$TOTPAR_6$, mean (SE)	2.02 (0.30)	3.92 (0.41)	5.05 (0.42)	$p=0.0005$[b]	$p<0.0001$[b]
TPR, median (hours)	5.8	0.8	0.5	$p=0.0008$[c]	$p<0.0001$[c]
TMR, median (hours)	NA[d]	12.6	1.2	$p=0.0901$[c]	$p<0.0001$[c]
TRU_{48}, mean exposures (SE)	3.6 (0.16)	2.3 (0.16)	2.0 (0.15)	$p<0.0001$[b]	$p<0.0001$[b]
$RESC\_N_{48}$, *n* (%)	132 (97.1)	119 (88.1)	111 (82.8)	$p=0.0038$[a]	$p<0.0001$[a]

[a]*p* values are from a logistic regression model with treatment group and site as fixed effects, and baseline pain intensity as the covariate.
[b]*p* values are from an analysis of covariance model with treatment group and site as fixed effects and baseline pain intensity as the covariate.
[c]*p* values are from log-rank tests using only data from the two treatments in the pairwise comparison.
[d]Median could not be calculated because 50% of the placebo group did not achieve meaningful pain relief.
ITT: intent to treat; MPADPI: mean patient average daily pain intensity (higher score = more pain); NA: not available; PID: pain intensity difference; PR: pain relief; PRID: pain relief plus pain intensity difference scores; $RESC\_N_{48}$: number of patients requiring rescue medication over 48 hours; $SPID_6$: sum of pain intensity difference over 6 hours (*Note*: if pain relief is inadequate, pain tends to increase from baseline; if rescue medication was used [likely], then last observation carried forward [LOCF] imputation results in negative score); $SPRID_6$: sum of pain relief and pain intensity differences; TMR: time to meaningful pain relief; $TOTPAR_6$: total pain relief (increasing score indicates improved pain relief) over 6 hours; TPR: time to first perceptible pain relief; TRU: total use of rescue medication; TTR: time to first use of rescue medication; SE: standard error.

($p<0.0001$), as was the comparison between the 2 × 5/30 mg group and placebo ($p=0.0124$). The mean $SPID_6$ was −60.47 for the placebo group, −11.36 for the 2 × 5/30 mg group, and 5.56 for the 2 × 7.5/30 mg group. The primary comparison between the 2 × 7.5/30 mg group and the placebo group was highly significant, as was the comparison between the 2 × 5/30 mg and placebo groups (both $p<0.0001$). The mean $SPRID_6$ was −4.03 for the placebo group, 2.78 for the 2 × 5/30 mg group, and 5.61 for the 2 × 7.5/30 mg group. The primary comparison between the 2 × 7.5/30 mg group and the placebo group was highly significant, as was the comparison between the 2 × 5/30 mg and placebo groups (both $p<0.0001$).

The mean PID score in the 2 × 7.5/30 mg group was significantly superior compared with placebo at all time points ($p<0.05$); the 2 × 5/30 mg group also demonstrated statistically significant superiority compared with placebo at all time points except 30 minutes ($p=0.25$) and 48 hours ($p=0.79$) post-dose. The mean PRID score in the 2 × 7.5/30 mg group demonstrated statistically significant superiority compared with placebo at all time points ($p\leq0.001$). The PRID scores for the 2 × 5/30 mg group demonstrated statistically significant superiority compared with placebo at all time points, except 30 minutes post-dose.

For the secondary endpoints TMR and PR, only the 2 × 7.5/30 mg oxycodone HCl/niacin dose was significantly superior compared with placebo. The median TMR was 12.6 hours for the 2 × 5/30 mg group and 1.2 hours for the 2 × 7.5/30 mg group. The TMR scores for the 2 × 7.5/30 mg group demonstrated statistically significant superiority compared with placebo. The median for the placebo group could not be calculated since 50% of the placebo patients did not achieve meaningful PR. The overall *p* value comparing the three survival curves (Kaplan-Meier time-to-event method) was significant ($p<0.0001$). The primary comparison between the 2 × 7.5/30 mg group and the placebo group was significant ($p<0.0001$). The comparison between the 2 × 5/30 mg group and the placebo group was not statistically significant ($p=0.0901$).

The mean PR scores for the 2 × 5/30 mg group were similar compared with placebo. The mean PR score for the 2 × 5/30 mg group was 0.7 at 30 minutes post-dose, peaked at 1.1 at 1 hour post-dose, and subsequently

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decreased to 0.4 at 6 hours post-dose. The 2 × 7.5/30 mg group demonstrated statistically significant superiority compared with placebo at all time points (all $p<0.01$); the mean PR score for the 2 × 7.5/30 mg group was 1.1 at 30 minutes post-dose, peaked at 1.5 at 1 hour post-dose, then gradually decreased to 0.5 at 6 hours post-dose.

Four patients withdrew due to lack of efficacy – 3/136 (2.2%) in the placebo group and 1/135 (0.7%) in the 2 × 5/30 mg group. The comparisons between the active treatment groups and the placebo group were not statistically significant (2 × 5/30 mg vs. placebo: $p=0.9520$ and 2 × 7.5/30 mg vs. placebo: $p=0.9429$). The relatively low percentage of patient withdrawals due to treatment failure – which one would expect to be high in the placebo group – was likely the result of the availability of rescue medication. Use of rescue medication differed between placebo and active treatment groups, with placebo-treated patients requiring significantly more rescue medication during the entire 48-hour treatment period (mean, 3.6 times vs. 2.3 for 2 × 5/30 mg and 2 for 2 × 7.5/30 mg: $p<0.0001$ for both doses) and using it earlier during the study period (median, 1.4 hours), compared with the 2 × 5/30 mg (2.4 hours) and the 2 × 7.5/30 mg (2.9 hours) groups ($p<0.0001$ for both doses). Rescue medication was used by the majority of the patients (97.1% in the placebo group, 88.1% in the 2 × 5/30 mg group, and 82.8% in the 2 × 7.5/30 mg group).

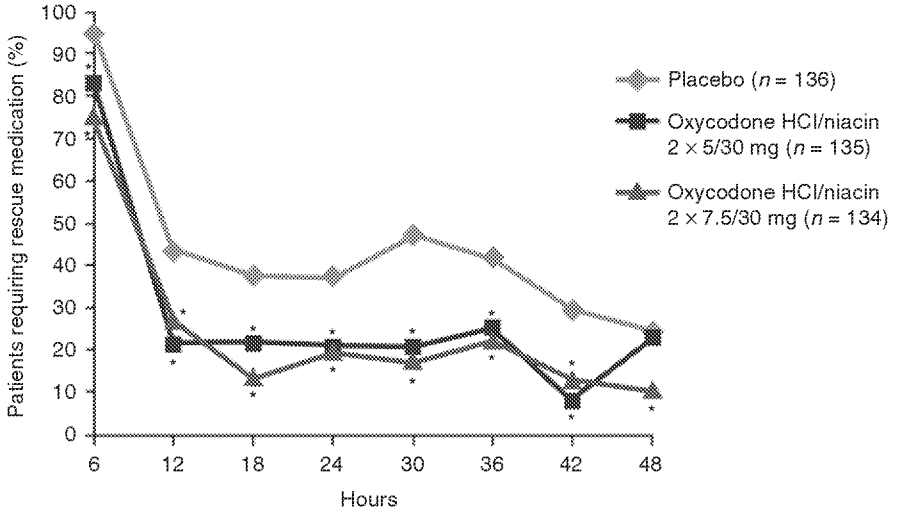
Observing each 6-hour dosing interval (Figure 4), the 2 × 7.5/30 mg dose demonstrated significant superiority compared with placebo at all time points and overall (all $p<0.01$), as did the 2 × 5/30 mg dose, except for the 42- to 48-hour time point ($p=0.7765$).

Safety

Of the 405 patients in the safety population, 273 (67.4%) experienced ≥1 TEAEs during the study. Most of the AEs were considered mild or moderate in intensity; no serious TEAEs or deaths occurred. The number of patients reporting severe AEs was 2/136 (1.5%) in the placebo group, 21/135 (15.6%) in the 2 × 5/30 mg group, and 24/134 (17.9%) in the 2 × 7.5/30 mg group, and included nausea, vomiting, dizziness, headache, syncope, erythema, urticaria, swelling, and postoperative wound infection.

The proportion of patients with any AE was largest in the higher-dose group: 117/134 (87.3%) with oxycodone HCl/niacin 2 × 7.5/30 mg vs. 104/135 (77.0%) with oxycodone HCl/niacin 2 × 5/30 mg and 52/136 (38.2%) with placebo. Among patients receiving active treatment, the most common TEAEs included nausea, vomiting, dizziness, flushing, and pruritus (Table 3). The AEs observed in this study are considered to be common for the administration of niacin and/or opioid analgesics.

The overall incidence of AEs was similar between males and females with the two active treatments. However, females in the oxycodone HCl/niacin groups had higher rates of nausea, vomiting, and dizziness than did males. Similarly, among placebo-treated patients, females had slightly higher rates of nausea, vomiting, diarrhea, dizziness, and headache than did males. Overall, a higher percentage of females in the placebo group had AEs compared with males (41% vs. 23%, respectively). Six patients experienced TEAEs that led to study discontinuation, including 2/135 (1.5%) in the 2 × 5/30 mg group and 4/134 (3.0%) in the 2 × 7.5/30 mg group. In the 2 × 7.5/30 mg group, the patients discontinued because of the following



Each time point represents the previous 6-hour interval.
* $p<0.01$ compared with placebo; p values are from a logistic regression model with treatment group and site as fixed effects, and baseline pain intensity as the covariate.

Figure 4. Patients requiring rescue medication (%) over time: ITT population.

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Table 3. Most frequently occurring treatment-emergent adverse events (≥3% of patients in any treatment group): safety population.

Preferred Term	Placebo ($n=136$) n (%)	Oxycodone HCl/niacin 2 × 5/30 mg ($n=135$) n (%)	Oxycodone HCl/niacin 2 × 7.5/30 mg ($n=134$) n (%)
Number of patients with any AE	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)
Constipation	1 (0.7)	4 (3.0)	6 (4.5)
Feeling hot	1 (0.7)	6 (4.4)	5 (3.7)
Dry mouth	0	1 (0.7)	4 (3.0)
Paresthesia	0	4 (3.0)	3 (2.2)
Hyperhidrosis	0	4 (3.0)	1 (0.7)
Diarrhea	5 (3.7)	1 (0.7)	0

AE: adverse event.

TEAEs: one patient due to bradycardia and hypotension, one patient due to bradycardia, one patient due to hypotension, and one patient due to vomiting. In the 2 × 5/30 mg group, one patient discontinued due to arthralgia and one due to urticaria. The two most common events, bradycardia and hypotension, are also known postoperative side effects of surgical anesthesia.

Baseline values for vital sign parameters were similar across groups, and the mean and median changes from baseline systolic and diastolic blood pressure generally indicated little change in the placebo group. The oxycodone HCl/niacin groups had slightly lower baseline systolic and diastolic blood pressure compared with placebo: systolic blood pressure decreased an average of 3.0 mmHg and 4.5 mmHg in the 2 × 5/30 mg group and the 2 × 7.5/30 mg group, respectively, compared with only 0.2 mmHg for placebo. Diastolic blood pressure decreased an average of 1.9 mmHg and 2.8 mmHg, respectively, relative to a 1.4-mmHg increase for placebo. No trends were apparent in group mean changes for heart rate, respiration rate, or laboratory values over time.

Discussion

This pivotal trial demonstrated the efficacy and safety of two dose strengths of oxycodone HCl/niacin (2 × 5/30 mg and 2 × 7.5/30 mg) for the management of moderate-to-severe pain. These doses of oxycodone HCl have been used in previous studies for the management of moderate-to-severe pain[15,19]. Bunionectomy is generally associated with significant postoperative pain that commonly lasts for a minimum of 10 days[17]. Hence, bunionectomy surgery is a good, validated model to evaluate the efficacy of analgesics[20]. In this trial, both doses of oxycodone HCl/niacin tablets demonstrated statistically significant superiority compared with placebo, as measured by the primary pain intensity endpoint ($SPID_{48}$), and by multiple secondary endpoints.

Oxycodone HCl/niacin tablets were associated mostly with mild and occasionally moderate AEs. The most frequently reported AEs were nausea, vomiting, dizziness, flushing, and pruritus, all of which are common side effects from exposure to opioids and/or niacin[21–23]. Nausea, vomiting, and dizziness are also known side effects of the rescue medication (ketorolac tromethamine)[24], which was used at some point in the study by the majority of patients. A previous trial using oxycodone HCl immediate release 10 mg for the management of post-bunionectomy pain reported comparable or slightly higher incidences of nausea, vomiting, dizziness, and pruritus[23] than those reported in this study for oxycodone HCl/niacin tablets 2 × 5/30 mg. This previous trial also reported a high rate of rescue medication use, including ketorolac[23]. In the present study, the incidences of flushing and pruritus, likely related to the niacin, were higher in the treatment groups than with placebo (<20% in each of the treatment groups and within 9%–15% of the rate with placebo). No patient discontinued the study due to these AEs.

Numerically, there were slightly lower systolic and diastolic blood pressures noted in the oxycodone HCl/niacin groups compared with placebo, and two patients discontinued due to hypotension in the higher dose group. Hypotension, rare in this study, is a known side effect of oxycodone[22].

Withdrawal due to TEAEs occurred in six (2.2%) of the 269 patients receiving either dose of oxycodone HCl/niacin, and none of the placebo-treated patients. No serious AEs or deaths were reported in any of the treatment groups.

Post-surgical patients generally experience pain that requires multiple doses of analgesic[25]. Accordingly, this study used multiple doses of oxycodone HCl/niacin during a 48-hour period. To encourage participation throughout the entire treatment period, patients were allowed to use rescue medication for pain as needed. A high rate of rescue medication use has been reported for bunionectomy pain in a multiple-dose study of oxycodone HCl immediate release 10 mg (80.6%) compared with tapentadol immediate release (76.5% with 100 mg and 80.6% with 50 mg)[23]. Similarly, rescue medication was used by a majority of patients over the course of the present study.

Based on the prespecified definition, the responder rates in all three treatment groups were relatively low. This modest outcome was likely related to the strict

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definition for responders used (≥50% maxTOTPAR$_6$ and ≤3 doses of rescue medication) compared with the more typical criterion using a lower threshold of ≥33% maxTOTPAR[18]. In a further analysis using ≥33% maxTOTPAR$_6$, as well as the strict criterion of ≤3 doses of rescue medication within 6 hours of dosing in a 48-hour period, the responder rates increased, with substantially increased differentiation between each of the active groups and the placebo group.

The study was designed to address the question of efficacy and safety of oxycodone HCl/niacin tablets vs. placebo, as would be necessary for product approval. As such, both doses of oxycodone HCl/niacin tablets demonstrated statistically significant superiority compared with placebo, as measured by the primary pain intensity endpoint (SPID$_{48}$), and by multiple secondary endpoints. The study did not include an active comparator (oxycodone) arm. Therefore, while the inclusion of niacin and other functional inactive ingredients does not affect the analgesic efficacy of oxycodone HCl in the product, future studies comparing relative efficacy and safety of the oxycodone HCl/niacin formulation with dose-equivalent oxycodone should be considered.

The oxycodone HCl/niacin formulation has been developed to provide limits and impediments to intentional oral overconsumption, intranasal snorting of crushed tablets, and intravenous injection of dissolved tablets. Studies have shown the oxycodone HCl/niacin formulation to reduce drug liking in comparison with oxycodone alone in recreational drug users[14,26].

Previous studies have shown that niacin is well tolerated by healthy volunteers at doses up to 60 mg[13] and that 75% of healthy volunteers rated oxycodone HCl 5 mg plus niacin 30 mg or 60 mg as easy to tolerate or as having no ill effect[12]. However, while the flushing and pruritus effects of the niacin are tolerable to the normal healthy volunteer group, they would have to be specifically evaluated in the post-bunionectomy group. In the present study, the incidence of flushing was only 15% and 10% greater than for placebo for oxycodone HCl/niacin tablets (2 × 5/30 mg and 2 × 7.5/30 mg, respectively). All of these reactions were mild to moderate, and no patient withdrew secondary to these side effects. Therefore, it would seem that the inclusion of niacin placed limited additional burden on the patients. Additional studies have been performed and are underway to evaluate alternate formulations.

Conclusion

Oxycodone HCl/niacin tablets (2 × 5/30 mg and 2 × 7.5/30 mg) provide effective analgesia and are generally well tolerated in patients with moderate-to-severe pain following bunionectomy surgery.

Transparency

Declaration of funding

This study was supported by Acura Pharmaceutical Technologies, Inc., and King Pharmaceuticals®, Inc. Authors of this manuscript served as investigators or consultants for the research or are employed by the sponsor. The authors did not receive compensation for the preparation of this manuscript. They accept sole responsibility for the accuracy of the manuscript, and also had final responsibility for the decision to submit for publication.

Declaration of financial/other relationships

S.E.D., M.G. and F.J.C. have disclosed that they are employees of Premier Research Group Limited, a company sponsored by Acura Pharmaceuticals to conduct this study. R.J.S. has disclosed that he is an employee and stock shareholder of Acura Pharmaceuticals. S.S. has disclosed that she is an employee of Lotus Clinical Research, Inc. and was a paid Clinical Trial Investigator, sponsored by Acura Pharmaceuticals.

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