ORIGINAL ARTICLE

A Randomized Study to Demonstrate Noninferiority of Once-Daily OROS® Hydromorphone with Twice-Daily Sustained-Release Oxycodone for Moderate to Severe Chronic Noncancer Pain

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■ **Abstract:** This was a randomized, open-label, comparative, parallel group study designed to demonstrate the noninferiority of once-daily OROS® hydromorphone compared with twice-daily sustained-release (SR) oxycodone in subjects with chronic noncancer pain severe enough to require continuous opioid therapy. The core phase (24 weeks) consisted of titration and maintenance periods. This was followed by an optional extension phase (28 weeks), which collected data used to assess long-term safety and efficacy outcomes. Five hundred four subjects were randomized between the 2 treatment groups. The primary efficacy analysis showed that OROS hydromorphone was noninferior to SR oxycodone ($P = 0.011$) as measured by change in Brief Pain Inventory (BPI) pain severity subscore "pain right now." The treatment difference with respect to change in BPI pain severity subscore "pain right now" was 0.29 (95% confidence interval: –0.27 to 0.84). The equianalgesic doses were 16 mg OROS hydromorphone and 40 mg SR oxycodone (median values). Secondary outcomes included other BPI scale items, the Medical Outcomes Study (MOS) Sleep Indices, and quality of life measured by the Short Form 36 (SF-36) questionnaire. Both treatment groups showed improvements in the main secondary efficacy endpoints. No statistically significant differences were shown between the treatment groups, except for the scores for somnolence (MOS sleep subscale) and physical functioning (SF-36), which both had a statistically significant difference between treatments groups in favor of OROS hydromorphone. Both study medications had equivalent and acceptable safety profiles. The results of this open-label study showed that once-daily OROS hydromorphone is a safe and well-tolerated treatment for chronic pain and as efficacious as twice-daily SR oxycodone. ■

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INTRODUCTION

The management of chronic noncancer pain is a central problem in primary care. Evidence-based recommendations advocate the use of long-acting opioids for the treatment of chronic pain, to be administered with caution and with careful monitoring of the patient.[1] Oral morphine is often seen as the gold standard because of global availability and extensive clinical experience.[1,2] However, some patients do not receive adequate analgesia, or suffer intolerable morphine-related side effects. As response to a particular opioid varies among individuals, multiple treatment options are needed. Rotation to an alternative opioid has been shown to improve pain control as well as reduce opioid-related toxicity,[3] but the mechanisms are unclear.[4,5]

Hydromorphone is a potent μ-receptor agonist that has been used extensively for postoperative pain since the 1920s,[6–8] and its analgesic efficacy is well established. It is included in clinical practice guidelines and is recommended for the management of cancer pain.[2,6] OROS® hydromorphone (Jurnista™, Janssen-Cilag, Beerse, Belgium) combines hydromorphone with a delivery system that uses Push-Pull™ active osmotic technology developed by ALZA Corporation (Mountain View, CA, U.S.A.). This maintains consistent hydromorphone plasma concentrations over a 24-hour dosing interval.[9–11] Using this delivery system, hydromorphone is steadily released, allowing more constant pain control. The advantage of once-daily dosing is that treatment is more convenient for patients, which may result in higher treatment compliance. One of the major causes of suboptimal therapy outcomes is poor adherence to prescribed treatment regimens,[12] and poor compliance is common in patients with chronic disease requiring long-term maintenance treatment.[13]

Sustained-release (SR) oxycodone (Oxycontin®, Napp Pharmaceuticals, Cambridge, UK) is also a semisynthetic long-acting opioid analgesic with high oral bioavailability. It is twice as potent as morphine,[14–16] and its clinical efficacy and tolerability has been well documented. SR oxycodone has a biphasic delivery system. There is a rapid phase with a mean half-life of 37 minutes, accounting for 38% of the dose, and a slow phase with a half-life of 6.2 hours, which accounts for the residual 62%.[17]

The primary objective of the study was to demonstrate noninferiority of once-daily OROS hydromorphone compared with twice-daily SR oxycodone with regard to pain control as measured with the Brief Pain Inventory (BPI) scale and to determine the equianalgesic dosage of both treatments. A noninferiority concept was chosen for the study. This was because the primary outcome was "sufficient pain control, which should have been achieved with both treatments using an individual dose titration for each subject."

METHODS

This was an open-label, international multicenter, randomized, comparative, parallel group, flexible dose, noninferiority study. Written informed consent was obtained at the screening visit in accordance with the principles of the Declaration of Helsinki. All centers had institutional review board approval.

Blinding of trial medication was ruled out because blinding would have required a double-dummy approach, with a twice-daily study medication consisting of 1 active (hydromorphone) and 1 inactive (placebo), and 2 active (oxycodone) formulations. Although compliance was recorded, subjects were allowed to adapt their medication frequency to his/her individual needs by taking the medication once rather than twice daily. In this case, subjects allocated to the hydromorphone group would have been exposed to the risk of omitting active treatment while taking only the inactive (placebo) formulation.

The sample size was calculated at 151 subjects per treatment arm to determine noninferiority with a noninferiority margin of 1 in the numeric pain severity scale, assuming an estimated standard deviation (SD) of 2.4 at the 0.025 one-sided significance level with a power of 90%. Including an estimated rate of 40% subjects that could not be evaluated in the per protocol (PP) population, 252 subjects were planned to be included in each treatment group. Subjects from sites across Europe were assigned to 1 of the 2 treatment groups in a ratio of 1:1 based on central randomization to receive either OROS hydromorphone once daily or SR oxycodone twice daily (both taken orally). Allocation to the 2 groups was balanced according to "previous pain treatment" (opioid naïve subjects vs. subjects previously treated with opioids) and "underlying disease" (chronic low back pain, musculoskeletal pain, neuropathic pain, or other chronic pain conditions usually responsive to opioid therapy such as peripheral arterial occlusion disease, phantom limb pain or chronic pancreatitis).

Treatment started with starting doses of 8 mg OROS hydromorphone or 20 mg SR oxycodone (administered as 2 × 10 mg doses). Patients were either instructed to take the SR oxycodone in the morning and evening, with the doses 12 hours apart, or OROS hydromor-

phone once a day always at the same time of the day to achieve sufficient analgesia. The subject diary was completed before drug intake. These doses were individually titrated over a 4-week titration period until sufficient pain control was achieved. The maximum daily dose was 32 mg OROS hydromorphone or 80 mg SR oxycodone. Flexible dosing continued during the subsequent 20-week maintenance period. The titration and maintenance periods made up the core phase (24 weeks) of the study.

Subjects from selected sites could elect (with written informed consent) to continue in the study for an extension phase of a further 28 weeks. Data collected during the extension phase were used to assess long-term safety and efficacy outcomes by using descriptive statistics.

The study included opioid naïve subjects (who had not taken an opioid for at least 3 years), subjects treated with weak opioids such as codeine, dihydrocodeine, or tramadol, and subjects treated with a daily oral dose of up to 60 mg morphine or an equivalent dose of another oral strong opioid, and subjects using fentanyl transdermal therapeutic system (TTS) 25 mcg/h or buprenorphine TTS 35 mcg/h. Subjects had to discontinue their opioid therapy the day before first study drug intake. Subjects treated with transdermal opioids had to remove the last patch 24 hours before first study drug intake.

Subjects were excluded if they were expected to undergo any treatment (eg, neurological techniques, surgery) within the next 6 months that may abruptly alter the degree or nature of pain experienced, or if they had a history of diseases or a current illness or therapy that was contraindicated. Add-on medication of acetaminophen (maximum 2 g/day) and prophylactic treatments (antiemetics and laxatives) were allowed. Some medications were allowed as concomitant therapy, provided that administration had been started at least 2 weeks before study inclusion and was maintained at a stable or reduced dosage on a continuous basis throughout the entire study. These were nonopioid analgesics such as anti-inflammatory drugs (selective cyclooxygenase-2 inhibitors or nonselective nonsteroidal anti-inflammatory drugs, disease-modifying agents, corticosteroids, biphosphonates, or other medications targeted to treat the underlying disease, which may influence pain severity, neuroleptics, and antidepressants, if exclusively used as pain treatment. The following treatments were not allowed during the treatment period: any other opioid analgesics, neuroleptics (with the exception of haloperidol or droperidol up to 2 mg/day for up to 30 days during the course of the study to treat nausea or vomiting), hypnotics (with the exception of short-acting hynoptics taken for sleep inducrion for up to 30 days during the course of the study), sympathomimetic drugs, monoamine oxidase inhibitors, and tetrabenazines. All concomitant medications were recorded at baseline and throughout the study.

Outcomes

The primary efficacy evaluation was pain control with once-daily OROS hydromorphone compared with twice-daily SR oxycodone measured by "pain right now" on the BPI scale. This was measured during normal office hours. If noninferiority of pain control at endpoint of the core phase was demonstrated, the co-primary endpoint equianalgesic dose was to be determined descriptively.

Main secondary efficacy evaluations included in hierarchical order the following: change in "pain at its worst" measured on the BPI scale; change in sleep quality measured by Medical Outcomes Study (MOS) Index 1; change in subject diary evening mean pain score "pain right now"; change in subject diary morning mean pain score "pain right now"; proportion of subjects with dose escalation. Other secondary outcomes included other items on the BPI scale, other aspects of sleep quality, quality of life aspects measured by the Short Form 36 (SF-36) questionnaire, and resource utilization.

Safety was evaluated by measuring a number of variables over the study, including vital signs, adverse events (AEs), and their relationship to the study medication. AEs were reported by subjects at their treatment visits, and all subjects had a physical examination. Long-term safety data were collected from subjects in the extension phase.

Statistical Analysis

The noninferiority of OROS hydromorphone compared with SR oxycodone in terms of change in "pain right now" from baseline to the end of the core phase was done in a confirmatory sense. The following hypotheses were tested (Δ denotes change from baseline): H_0: ΔOROS hydromorphone—ΔSR oxycodone ≥ 1; and H_1: ΔOROS hydromorphone—ΔSR oxycodone < 1. Hypothesis testing was done by computing a two-sided 95% confidence interval (CI) of the treatment difference in actually observed endpoint results for the numeric pain severity scale and comparing this interval with the maximum allowed clinically relevant difference of 1. The CI of the treatment difference was based on the least square (LS) means and error terms based on analysis of

covariance (ANCOVA) with baseline as covariate, and country, previous pain treatment, underlying disease, and treatment as factors. In addition, the *P* value was obtained from ANCOVA for testing these hypotheses. It should be stressed that the *P* value here tests the null hypothesis that OROS hydromorphone is inferior to SR oxycodone by 1 point on the BPI scale. A significant *P* value demonstrates that OROS hydromorphone is not inferior. A noninferiority margin of 1 point was chosen as this is considered a clinically significant difference.

The intent-to-treat (ITT) population was defined as all randomized subjects who took the study medication at least once, excluding subjects who had no postbaseline efficacy data. The PP population was defined as all subjects included in the ITT population who were without major protocol violations. The primary analysis population was the PP population, and the same analysis was done for the ITT population. The PP population was used for the primary analysis because this is the more conservative population to use for a noninferiority study (see International Conference on Harmonisation E9 guidelines, Sections 3.3 and 5.2[18]). Endpoint calculations for the ITT population used last observation carried forward analysis, which means a result was generated for each subject in the trial. If noninferiority was established, the equianalgesic dosage of once-daily OROS hydromorphone and twice-daily SR oxycodone (the average daily dose at endpoint) was determined descriptively at the endpoint of the core phase.

The secondary endpoints were calculated using confirmatory two-sided testing to evaluate superiority of OROS hydromorphone compared with SR oxycodone. ANCOVA or Cochran–Mantel–Haenszel chi-square statistic was used as test statistic, as applicable. The statistical significance level used was 0.05 two sided and a closed hierarchical testing approach was used to control overall Type I error. This means that only if the test for the first main secondary endpoint was significant at the 0.05 level was the next secondary endpoint assessed and so on. Once a test failed to demonstrate significance at the 0.05 level, the hierarchical procedure was stopped.

All other statistical tests were exploratory in nature only, and therefore, no alpha error adjustment was conducted. All *P* values shown describe the difference between the treatments at the end of the core phase. These *P* values show the test of the null hypothesis that OROS hydromorphone and SR oxycodone are equivalent treatments. A significant value shows that there is a difference between the 2 treatments.

RESULTS

Five hundred four subjects were randomized to 2 treatment groups in a ratio of 1:1. There was no difference between the 2 treatment groups regarding the demographic and baseline characteristics of the patients (Table 1). Subjects were almost exclusively (99.6%) Caucasian and were recruited from 11 different European countries. The most common cause of underlying disease was chronic low back pain. Almost all subjects (502 subjects [99.6%]) reported taking concomitant medications throughout the study. The most commonly used concomitant medications were for additional pain treatment. Paracetamol was taken by 25% to 30% of the population during the core phase. Metoclopramide was taken by 29% of the subjects to treat nausea during the titration period and by 18% of the subjects during

Table 1. Demographic and Baseline Characteristics (Safety Population)

	OROS® Hydromorphone (*n* = 254)		Sustained-Release Oxycodone (*n* = 250)		Total (*n* = 504)	
Age (years)						
Mean (SD)	57.1	(13.1)	58.0	(12.8)	57.5	(12.9)
Sex (% female)	142	(55.9)	152	(60.8)	294	(58.3)
Underlying disease						
Chronic low back pain	147	(57.9)	141	(56.4)	288	(57.1)
Musculoskeletal pain such as osteoarthritis, rheumatoid arthritis	57	(22.4)	66	(26.4)	123	(24.4)
Neuropathic pain such as postherpetic neuralgia, diabetic polyneuropathia	26	(10.2)	23	(9.2)	49	(9.7)
Other chronic pain conditions usually responsive to opioid treatment	24	(9.4)	20	(8.0)	44	(8.7)
Previous opioid treatment						
Opioid naïve subjects	77	(30.3)	72	(28.8)	149	(29.6)
Subjects previously treated with opioids*	177	(69.7)	178	(71.2)	355	(70.4)

* This includes subjects treated with weak opioids and subjects treated with a daily oral dose of up to 60 mg morphine or an equivalent dose of another oral strong opioid and subjects using fentanyl transdermal therapeutic system (TTS) 25 mcg/h or buprenorphine TTS 35 mcg/h. Subjects had to discontinue their opioid therapy the day before first study drug intake. Subjects treated with transdermal opioids had to remove the last patch 24 hours before first study drug intake.
SD, standard deviation.

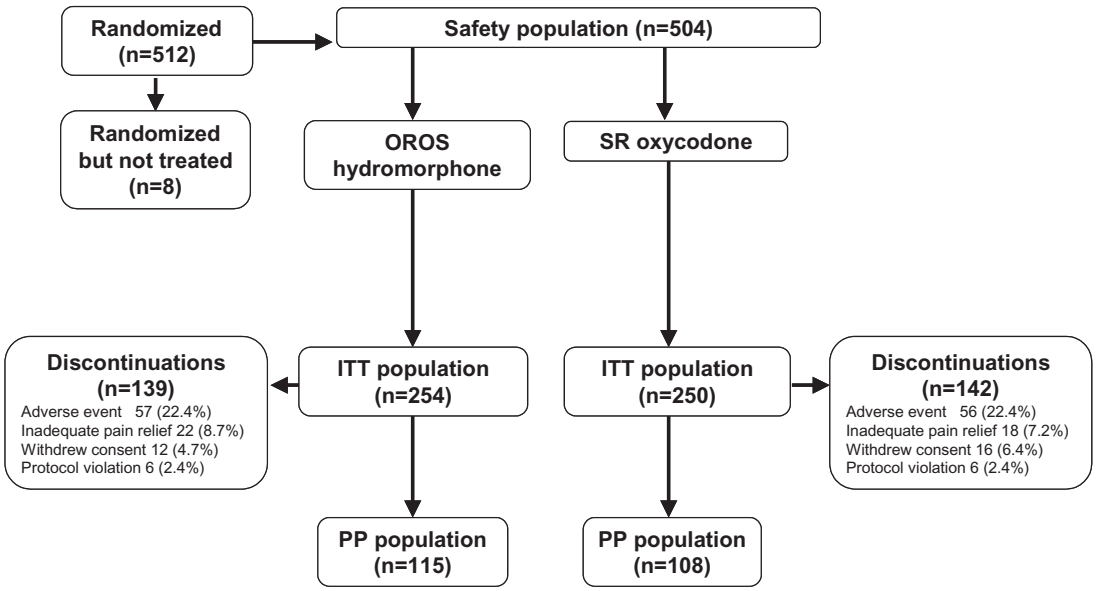

Figure 1. Flow diagram of subjects through the study. SR, sustained-release; ITT, intent-to-treat; PP, per protocol.

the maintenance period. The frequencies of concomitant medication use were similar for both treatment groups.

Subjects who did not enter the extension phase had a mean exposure of 110.8 days for OROS hydromorphone and 112.9 days for SR oxycodone. Subjects who entered the extension phase had a mean exposure of 371.0 days for OROS hydromorphone and 380.5 days for SR oxycodone. Two hundred seventy-seven subjects completed the core phase, and a comparable number of subjects withdrew from the study from both treatment arms. One hundred twelve subjects entered the extension phase, and 97 (87%) completed it. See Figure 1 for a flow diagram of subjects through the study. A relatively small proportion of patients entered the extension phase because of the nonparticipation of some countries in this part of the study.

Efficacy Analyses

All efficacy outcomes were determined from changes from baseline to the end of the core phase. The primary outcome was analyzed using the PP population. The first part of the primary objective was to demonstrate noninferiority of OROS hydromorphone compared with SR oxycodone with regard to pain control, with the primary endpoint being assessed by the change in pain on the BPI severity score for "pain right now" from baseline to the end of the core phase. A change of ≥1 was considered clinically relevant. There was a similar decrease in pain in both treatment groups (Figure 2).

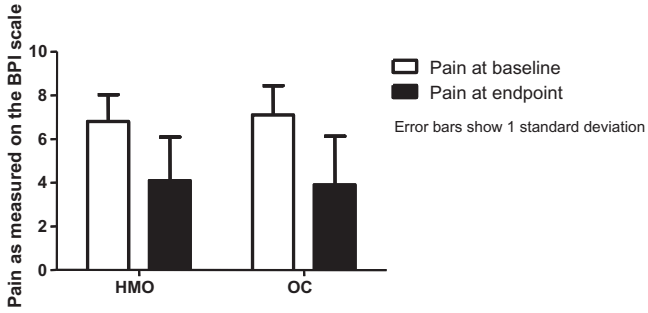

Figure 2. Primary efficacy analysis. BPI, Brief Pain Inventory; HMO, hydromorphone; OC, oxycodone.

The difference between the means was 0.29 in favor of SR oxycodone (CI −0.27 to 0.84). Since the upper bound of the CI was <1, noninferiority was concluded ($P = 0.011$). This P value tests the noninferiority null hypothesis and shows that the treatments are noninferior to each other, not that they are different. A similar analysis was performed on the ITT population, which showed similar results. The difference between the means was −0.12 in favor of OROS hydromorphone (CI −0.53 to 0.29), thus proving noninferiority ($P \leq 0.001$).

The second part of the primary objective was to determine the equianalgesic dosage of once-daily OROS hydromorphone and twice-daily SR oxycodone. The median doses were 16 mg OROS hydromorphone and 40 mg SR oxycodone (mean daily doses 18.4 mg OROS hydromorphone and 43.8 mg SR oxycodone), showing

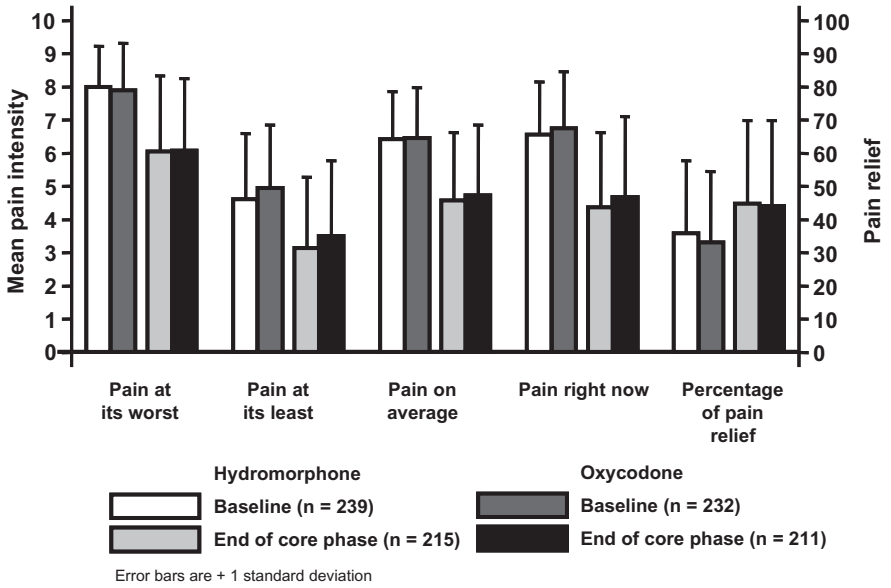

Figure 3. Other items on the Brief Pain Inventory scale.

a relative analgesic dose of 2:5. There was a slightly higher proportion of subjects in the SR oxycodone group that required dose escalation during the core phase (13.6% compared with 10.6% in the OROS hydromorphone group), but this was not statistically significant ($P = 0.249$).

All secondary outcomes were analyzed using the ITT population. The first secondary outcome was change in BPI pain severity subscore "pain at its worst." The difference between LS means was 0.08 (CI –0.32 to 0.470, P value of 0.706), showing no statistically significant difference between the 2 treatments. Consequently, the hierarchical two-sided testing procedure of the main secondary endpoints for a statistically significant difference between OROS hydromorphone and SR oxycodone was stopped here. All subsequent tests were only exploratory in nature, and thus, corresponding P values for other secondary endpoints only represent the comparison-wise alpha error probabilities.

There was an improvement in all other BPI items (Figure 3), showing that once-daily OROS hydromorphone was as efficacious as twice-daily SR oxycodone as an analgesic in terms of these variables. Changes in subject diary evening and morning mean pain scores for "pain right now" were similar between treatment groups. Evening pain was relieved from 6.5 (SD ± 1.67) to 4.3 (SD ± 2.12) in the OROS hydromorphone group compared with 6.6 (SD ± 1.80) to 4.6 (SD ± 2.26) in the SR oxycodone group. There was no statistically significant difference between the treatments ($P = 0.348$). Morning pain data showed similar results ($P = 0.616$).

Sleep interference was measured by the sleep subscale of the MOS Indices 1 and 2. This scale ranges from 1 to 100 with lower values indicating better sleep quality. For Index I, the difference between the means was –2.87 in favor of OROS hydromorphone with a CI of –5.94 to 0.19, but statistical significance was not shown. MOS Index 2 showed similar results.

Sleep quality was analyzed in more detail using the MOS subscales. There were no statistically significant differences between treatments for any outcome apart from somnolence (drowsiness). The change from baseline to the end of the core phase was –2.4 (SD ± 21.42) for OROS hydromorphone and 3.7 (SD ± 21.37) for SR oxycodone. This was a statistically significant difference between the groups in favor of OROS hydromorphone for somnolence, with a treatment difference of –4.16 (CI –7.67 to –0.65), $P = 0.020$ (Figure 4).

Quality of life was assessed using the SF-36 questionnaire. SF-36 scores range from 1 to 100 with higher scores indicating a better health-related quality of life. There was an increase in all scores for both treatments. One score, "physical functioning," showed a statistically significant treatment difference in favor of OROS hydromorphone, with a difference of 4.05 (CI 0.94 to 7.16), $P = 0.010$ (Figure 5). Other scores measured were "mental health index," "emotional role," and "social functioning," and there were no other statistically significant treatment differences.

Slightly more subjects in the OROS hydromorphone group rated their treatment as either "convenient" or "very convenient"; this was 78% (159/205) for OROS

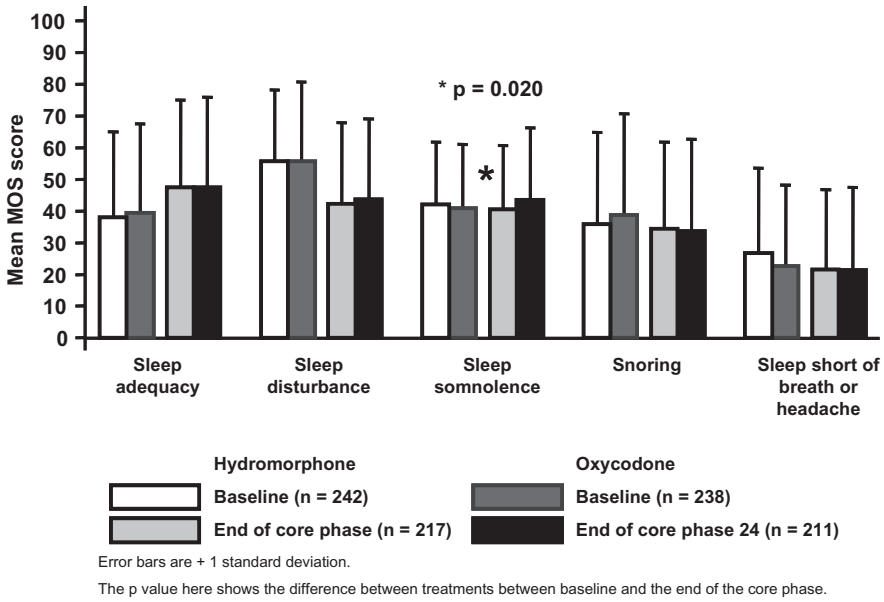

Figure 4. MOS sleep subscales intent-to-treat population, last observation carried forward. MOS, medical outcomes study.

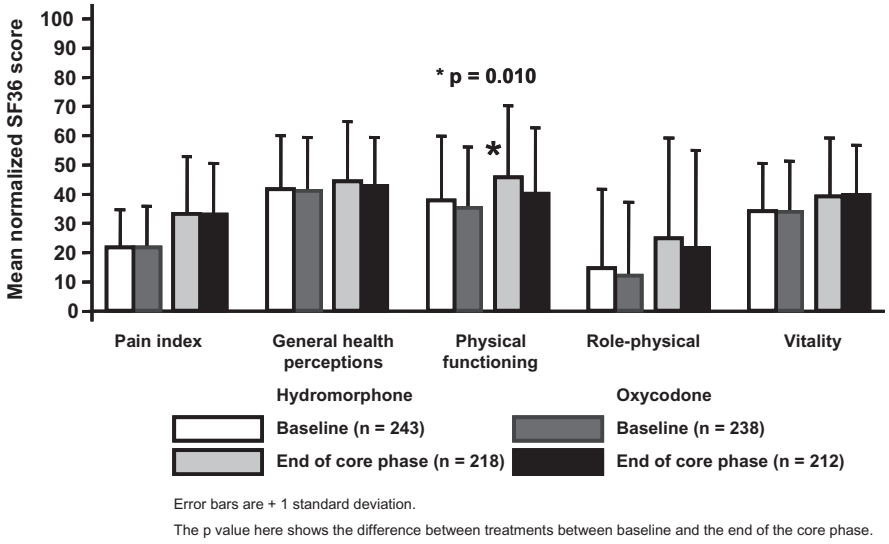

Figure 5. SF-36 Quality of life scores: physical aspects, intent-to-treat populations, last observation carried forward. SF-36; short form 36.

hydromorphone and 73% (143/195) for SR oxycodone at the end of the core phase.

Resource utilization was similar between groups, with a mean number of additional visits of 1.9 (±1.98) for the OROS hydromorphone groups and 1.6 (±1.97) for the SR oxycodone group.

Extension Phase

Subjects who entered the extension phase had a lower pain severity score and a higher pain relief score, and showed greater improvements in sleep quality and quality of life at the end of the core phase compared with subjects who did not enter the extension phase (Table 2). The 2 treatment groups were equally balanced in these variables. During the extension phase, the dose of OROS hydromorphone decreased by an average of 0.9 mg, while the dose of SR oxycodone increased by 1.5 mg. Changes in efficacy outcomes between the baseline and the end of the core phase, and between the baseline and the end of the extension phase were generally comparable between the 2 treatment groups for all outcome measures.

Safety

Most subjects (81% of the OROS hydromorphone group and 85% of the SR oxycodone group) experi-

Table 2. Differences between Subjects That Did and Did Not Enter the Extension Phase (Intent-to-Treat Population, Last Observation Carried Forward)

	Baseline	End of Core Phase	End of Extension Phase
Change in pain severity "pain right now" (BPI item 6)			
Patients who did not enter the extension phase, mean (SD)			
OROS hydromorphone	6.5 (1.63) (*n* = 187)	4.7 (2.42) (*n* = 174)	—
SR oxycodone	6.7 (1.76) (*n* = 185)	5.0 (2.47) (*n* = 173)	—
Patients who did enter the extension phase, mean (SD).			
OROS hydromorphone	6.8 (1.46) (*n* = 60)	3.8 (1.80) (*n* = 60)	3.9 (1.82) (*n* = 57)
SR oxycodone	6.9 (1.56) (*n* = 52)	3.5 (1.80) (*n* = 52)	4.1 (1.84) (*n* = 52)
Change in "pain relief" (BPI item 8). Pain relief is measured between 1 to 100, with 100 as complete pain relief			
Patients who did not enter the extension phase, mean (SD)			
OROS hydromorphone	35.7 (22.84) (*n* = 176)	40.3 (27.00) (*n* = 173)	—
SR oxycodone	32.6 (21.65) (*n* = 176)	40.1 (26.36) (*n* = 165)	—
Patients who did enter the extension phase, mean (SD).			
OROS hydromorphone	33.8 (18.84) (*n* = 56)	55.3 (20.04) (*n* = 60)	53.2 (22.00) (*n* = 56)
SR oxycodone	35.6 (19.39) (*n* = 50)	56.1 (21.55) (*n* = 51)	59.2 (20.28) (*n* = 52)
Change in sleep disturbance (MOS Index 1). This is measured 1 to 100, with 100 as worst sleep disturbance			
Patients who did not enter the extension phase, mean (SD)			
OROS hydromorphone	49.4 (18.31) (*n* = 186)	42.3 (19.98) (*n* = 177)	—
SR oxycodone	47.8 (21.09) (*n* = 188)	43.8 (20.50) (*n* = 175)	—
Patients who did enter the extension phase, mean (SD).			
OROS hydromorphone	33.8 (18.84) (*n* = 56)	34.1 (20.50) (*n* = 60)	37.6 (20.46) (*n* = 57)
SR oxycodone	35.6 (19.39) (*n* = 50)	37.7 (17.16) (*n* = 52)	40.4 (16.84) (*n* = 52)

BPI, Brief Pain Inventory; SD, standard deviation; SR, sustained-release; MOS, medical outcomes study.

Table 3. Summary of Adverse Events (AE) (Safety Population)

	OROS® Hydromorphone (*n* = 254)	SR Oxycodone (*n* = 250)	Total (*n* = 504)
Total AEs *n* (%) e*	206 (81.1) 947	212 (84.8) 877	418 (82.9) 1,824
Related to study medication	171 (67.3) 628	174 (69.6) 543	345 (68.5) 1,171
Resulting in withdrawal	67 (26.4) 152	63 (25.2) 133	130 (25.8) 285
AE outcome			
Recovered	194 (76.4) 733	196 (78.4) 671	390 (77.4) 1,404
Ongoing†	93 (36.6) 213	96 (38.4) 205	189 (37.5) 418
Unknown	1 (0.4) 1	1 (0.4) 1	2 (0.4) 2
Most common AEs by preferred term			
Gastrointestinal disorders			
Nausea	68 (26.8) 82	79 (31.6) 93	147 (29.2) 175
Constipation	73 (28.7) 93	65 (26.0) 76	138 (27.4) 169
Vomiting	32 (12.6) 38	36 (14.4) 43	68 (13.5) 81
Fatigue	36 (14.2) 38	31 (12.4) 33	67 (13.3) 71
Hyperhidrosis	29 (11.4) 35	22 (8.8) 22	51 (10.1) 57
Total SAEs	25 (9.8) 36	21 (8.4) 35	46 (9.1) 71
Related to study medication	4 (1.6) 8	6 (2.4) 8	10 (2.0) 16
Resulting in withdrawal	9 (3.5) 14	9 (3.6) 12	18 (3.6) 26
SAE outcome			
Recovered	20 (7.9) 28	21 (8.4) 26	41 (8.1) 54
Ongoing†	6 (2.4) 8	3 (1.2) 9	9 (1.8) 17

* Each column shows *n* (number of subjects), percentages (based on the number of subjects in the respective treatment group), and e (number of events).
† Ongoing at the end of the study (none of them had been classified as related to study medication).
SAE, serious adverse events; SR, sustained-release.

enced at least 1 AE (Table 3). The majority (90%) of the total number of AEs were classed as mild or moderate (1633/1824). The body systems most affected were the gastrointestinal system (nausea, constipation, vomiting, and diarrhea), the nervous system (headache, dizziness, and somnolence) and the skin (hyperhidrosis and pruritus). Fatigue was also common. The AEs were distributed equally across treatment groups, and at the end of the study, 77% of the total AEs were resolved.

There were 71 serious AEs (SAEs) reported in 46 (9%) subjects, which were similar in frequency and incidence between treatment groups. Subjects had recovered from the majority of SAEs (54/71) by the end of the study. Nine subjects from each treatment group

were withdrawn because of an SAE, and there were 9 subjects (6 subjects in the OROS hydromorphone group and 3 in the SR oxycodone group) who had an ongoing SAE at the end of the study. The most common system organ class for SAEs leading to withdrawal was nervous system disorders.

The majority of SAEs (55/71) were classed as unrelated to the study medication, and the incidences of SAEs, together with no fatal events, indicated no safety concerns. The most frequent SAEs that were related to study medication were vertigo and somnolence, both affecting 1 subject per treatment group (0.4% of safety population).

Ten subjects experienced 16 SAEs classed as related to the study medication, with 8 SAEs reported in each treatment group. Of these 10 subjects, 5 withdrew from the study. By the end of the study, all SAEs classed as related to the study medication were resolved.

SAEs relating to the gastrointestinal tract were the most common SAEs overall. These accounted for 13 events in 9 subjects (1.8%); 5 subjects (2%) in the OROS hydromorphone groups and 4 (1.6%) in the SR oxycodone group. Each of the 13 SAEs was different. Three were "very likely related" to the study medication in the SR oxycodone group (abdominal pain upper, inguinal hernia, and nausea) and 2 in the OROS hydromorphone group (constipation and gastrointestinal disorder). There was 1 SAE of rectocele in the SR oxycodone group that was classed as possibly related.

The extension phase did not show any difference between treatment groups for number of AEs, nor body system affected.

DISCUSSION

This study demonstrated that once-daily OROS hydromorphone was a noninferior treatment to twice-daily SR oxycodone for subjects with chronic moderate to severe noncancer pain in terms of the "pain right now" score on the BPI. Both treatments reduced pain by at least 2.8 points on the 11-point BPI scale, which is a clinically relevant change.[19]

Although the time of day was not recorded for the "pain right now" BPI scores for primary efficacy analysis, subjects had to complete a pain diary during the core phase and had to answer a subset of questions from the BPI both in the morning and the evening of the 4 days before the next scheduled visit. The evaluation of this pain diary revealed that both treatments seemed to work in a comparable manner, and there were no statistically significant differences between the 2 treatments for the pain measures recorded in the morning and evening. The data collected in this study are closely related to another study that also demonstrated the effectiveness of OROS hydromorphone in treating chronic osteoarthritis pain.[20] The results of this short-term, 6-week study showed that once-daily OROS hydromorphone was comparable with twice-daily SR oxycodone in terms of pain relief. Further evidence for the efficacy of OROS hydromorphone is provided from other studies in subjects with chronic osteoarthritis[21] and chronic lower back pain.[22] This study included an inhomogeneous population of subjects who were either opioid naïve or had taken opioids in the past and have varying diagnoses of chronic noncancer pain. The proportions were evenly spread between treatment groups.

Hanna and Thipphawong[23] evaluated the efficacy and safety of once-daily OROS hydromorphone relative to twice-daily SR morphine in patients with chronic cancer pain. The results of this short-term, double-blind comparative study demonstrated that once-daily OROS hydromorphone was at least as effective as twice-daily SR morphine in relieving chronic cancer pain. Taken together, these studies provide evidence that OROS hydromorphone is a safe and effective analgesic for subjects with severe pain due to cancer or noncancer disease. They have given similar results despite the pharmacokinetic difficulties in evaluating a once-daily formulation with a twice-daily one.

The study was successful in establishing an equianalgesic dosage. The equianalgesic dose was 16 mg OROS hydromorphone to 40 mg SR oxycodone group per day, a ratio of 2:5. This is in line with other published data on potency calculations in relation to morphine, which put OROS hydromorphone at 5 times more potent than morphine[9] and 2.5 times more potent than SR oxycodone, which has been shown to be 2 times more potent than morphine.[24] Other calculations of relative opioid potency vary, but our results agree with the previous dose-conversion study using OROS hydromorphone.[9]

Although it has not been proven sufficiently, the unique release formulation of OROS hydromorphone may aid sleep by maintaining plasma levels more consistently, thereby enabling long-lasting analgesia. Some studies have investigated OROS hydromorphone and SR oxycodone in patients with moderate to severe osteoarthritis pain and chronic low back pain, although it should be pointed out that the study in chronic low back pain was a single arm, noncomparative trial.[20,22] Both found improvements to sleep quality, and one found greater improvement with OROS hydromor-

phone.[20] Poor sleep quality is highly prevalent in chronic pain patients.[25] This may warrant further investigation, as improving sleep quality and quantity for subjects with painful disorders may concomitantly improve pain relief.[26]

Both treatments improved outcomes for quality of life and aspects of sleep quality, and showed comparable effects. There were 2 statistically significant treatment differences, physical functioning and somnolence, and these were both in favor of OROS hydromorphone. These data need to be interpreted with caution as these tests were done after the formal hierarchical testing had ended and are therefore exploratory in nature. However, the provisional data on the statistically significantly treatment difference between OROS hydromorphone and SR oxycodone for improving somnolence from baseline is interesting. OROS hydromorphone has been shown to be statistically significantly better than SR oxycodone at improving "waking short of breath" in a similar study[27] (a secondary publication on a study already reported in this paper[20]). The relationship between pain and sleep is complicated, with both having a negative influence on the other; pain can upset sleep, and poor sleep quality can exacerbate pain.[28] Future studies need to concentrate on the effects of SR opioids on sleep as a primary outcome to provide more concrete evidence in this field.

Changes in the secondary efficacy endpoints from baseline to the end of the core phase and the end of the extension phase were generally comparable. This indicates that the achieved efficacy was maintained during the entire time period studied for both treatments. This provides preliminary evidence that OROS hydromorphone has long-term efficacy for improvements in pain measured on the BPI scale. The safety data showed that OROS hydromorphone and SR oxycodone were equally well tolerated. The high number of AEs in this study was expected and consistent with other long-term opioid studies.[29,30] The most common AEs are side effects most commonly associated with opioid use such as nausea and constipation. The extension phase of the study demonstrated a long-term safety profile for OROS hydromorphone and showed it to be comparable with SR oxycodone. The proportion of subjects who discontinued the study during the maintenance phase is also comparable with other studies.[9,22]

Once-daily OROS hydromorphone is an effective treatment for chronic pain and compares favorably with current medications. Evidence shows that it is at least as effective as other treatments available. It may be efficacious in increasing patient compliance and adherence to treatment regimens owing to the advantage of once-daily dosing.[9] Over this year-long study it was safe and well-tolerated, and resource utilization was unaffected.

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REFERENCES

1. Evidence Based Recommendations for Medical Management of Chronic Non-Malignant Pain. Reference Guide for Clinicians (2000). Facilitated by the College of Physicians and Surgeons of Ontario. Available from URL: http://www.ihs.gov/NonMedicalPrograms/NC4/Documents/EBMchronicpainguidelines2000.pdf (last accessed September 19, 2008).

2. Hanks GW, Conno F, Cherny N, et al. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer.* 2001;84:587–593.

3. Cherny NJ, Chang V, Frager G, et al. Opioid pharmacotherapy in the management of cancer pain: a survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration. *Cancer.* 1995;76:1283–1293.

4. Ashby MA, Martin P, Jackson KA. Opioid substitution to reduce adverse effects in cancer pain management. *Med J Aust.* 1999;170:68–71.

5. MacDonald N, Der L, Allan S, Champion P. Opioid hyperexcitability: the application of alternate opioid therapy. *Pain.* 1993;53:353–355.

6. Quigley C, Wiffen P. A systematic review of hydromorphone in acute and chronic pain. *J Pain Symptom Manage.* 2003;25:169–178.

7. Chaplan SR, Duncan SR, Brodsky JB, Brose WG. Morphine and hydromorphone epidural analgesia. A prospective, randomized comparison. *Anesthesiology.* 1992;77:1090–1094.

8. Goodarzi M. Comparison of epidural morphine, hydromorphone and fentanyl for postoperative pain control in children undergoing orthopaedic surgery. *Paediatr Anaesth.* 1999;9:419–422.

9. Palangio M, Northfelt DW, Portenoy RK, et al. Dose conversion and titration with a novel, once-daily, OROS® osmotic technology, extended-release hydromorphone formulation in the treatment of chronic malignant or nonmalignant pain. *J Pain Symptom Manage.* 2002;23:355–368.

10. Angst MS, Drover DR, Lotsch J, et al. Pharmacodynamics of orally administered sustained-release hydromorphone in humans. *Anesthesiology.* 2001;94:63–73.

11. Drover DR, Angst MS, Valle M, et al. Input characteristics and bioavailability after administration of immediate and a new extended-release formulation of hydromorphone in healthy volunteers. *Anesthesiology.* 2002;97:827–836.

12. Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry.* 2002;63:892–909.

13. Blackwell B. From compliance to alliance. A quarter century of research. *Neth J Med.* 1996;48:140–149.

14. Riley J, Eisenberg E, Müller-Schwefe G, Drewes AM, Arendt-Nielsen L. Oxycodone: a review of its use in the management of pain. *Curr Med Res Opin.* 2008;24:175–192.

15. Kaplan R, Parris WC, Citron ML, et al. Comparison of controlled-release and immediate-release oxycodone tablets in patients with cancer pain. *J Clin Oncol.* 1998;16:3230–3237.

16. Gaertner J, Frank M, Bosse B, et al. Oral controlled-release oxycodone for the treatment of chronic pain. Data from 4196 patients. *Schmerz.* 2006;20:61–68.

17. Biancofiore G. Oxycodone controlled release in cancer pain management. *Ther Clin Risk Manag.* 2006;2:229–234.

18. International Conference on Harmonisation (ICH) Guideline E9: Statistical Principles for Clinical Trials. (1998). Available online at http://www.ich.org/LOB/media/MEDIA485.pdf (last accessed April 3, 2009).

19. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain.* 2001;94:149–158.

20. Hale M, Tudor IC, Khanna S, Thipphawong J. Efficacy and tolerability of once-daily OROS hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: results of a 6-week, randomized, open-label, noninferiority analysis. *Clin Ther.* 2007;29:874–888.

21. Sabatowski R, Giesecke T. Pharmacotherapy of chronic, non-tumour related pain. Efficacy, tolerability and patient benefit of an oral osmotic system with hydromorphone. *MMW Fortschr Med.* 2007;149(Suppl 3):119–124.

22. Wallace M, Skowronski R, Khanna S, Tudor IC, Thipphawong J. Efficacy and safety evaluation of once-daily OROS hydromorphone in patients with chronic low back pain: a pilot open-label study (DO-127). *Curr Med Res Opin.* 2007;23:981–989.

23. Hanna M, Thipphawong J. 118 Study Group: a randomized, double-blind comparison of OROS hydromorphone and controlled-release morphine for the control of chronic cancer pain. *BMC Palliat Care.* 2008;7:17.

24. Coluzzi F, Mattia C. Oxycodone. Pharmacological profile and clinical data in chronic pain management. *Minerva Anestesiol*. 2005;71:451–460.

25. Morin CM, Gibson D, Wade J. Self-reported sleep and mood disturbance in chronic pain patients. *Clin J Pain*. 1998;14:311–314.

26. Kundermann B, Lautenbachter S. Effects of impaired sleep quality and sleep deprivation on diurnal pain perception. In: Lavigne G, Sessle BJ, Choiniere M, Soja PJ, eds. *Sleep and Pain*. Seattle: IASP Press; 2007:137–152.

27. Gajria K, Kosinski M, Schein J, Kavanagh S, Dubois D. Health-related quality-of-life outcomes in patients treated with push-pull OROS hydromorphone versus extended-release oxycodone for chronic hip or knee osteoarthritis pain: a randomized, open-label, parallel-group, multicenter study. *The Patient: Patient-Centred Outcomes Research*. 2008;1:223–238.

28. Sessle BJ. Pain Mechanisms. In: Lavigne G, Sessle BJ, Choiniere M, Soja PJ, eds. *Sleep and Pain*. Seattle: IASP Press; 2007:23–43.

29. Allan L, Richarz U, Simpson K, Slappendel R. Transdermal fentanyl versus sustained release oral morphine in strong-opioid naïve patients with chronic low back pain. *Spine*. 2005;30:2484–2490.

30. Portenoy RK, Farrar JT, Backonja MM, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. *Clin J Pain*. 2007;23:287–299.