Original Article

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

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Abstract

The objective of this open-label, repeated-dose, single-treatment, multicenter study was to evaluate the outcomes associated with a standardized conversion from prior opioid therapy to a novel, once-daily, OROS® osmotic technology, extended-release (ER) hydromorphone formulation in an outpatient population with chronic malignant or nonmalignant pain. The study period was divided into 3 phases: the prior opioid stabilization phase (≥3 days), the conversion and titration phase (3–21 days), and the maintenance phase (14 days). Patients were evaluated at 5 visits during the study period. Analgesic efficacy was measured using the Brief Pain Inventory (BPI). At baseline, patients were required to have daily oral morphine equivalent requirements of ≥45 mg. Prior oral or transdermal opioid therapy was converted to single daily doses of ER hydromorphone (8, 16, 32, and 64 mg tablets) at a 5:1 (morphine equivalent to hydromorphone) ratio. Immediate-release (IR) hydromorphone was given as rescue medication for breakthrough pain. Among the 445 patients who enrolled, 404 received the study medication. Of these, 73 (18.1%) had chronic malignant pain and 331 (81.9%) had chronic nonmalignant pain. Dose stabilization (defined as a 3-day period during which the total daily dose of ER hydromorphone remained unchanged and ≤3 doses of IR hydromorphone per day were required) was attained by 73.8% of patients (298/404), of whom 70.1% (209/298) were stabilized with ≤2 titration steps. The mean ± standard deviation (SD) time to dose stabilization was 12.1 ± 5.7 days (range of 3 to 33 days). The mean ± SD final daily dose of ER hydromorphone was 63.4 ± 129.2 mg. The mean ± SD final daily dose of IR hydromorphone was 11.5 ± 36.4 mg, and the mean ± SD final number of daily doses of IR hydromorphone was 1.7 ± 1.3. Intent-to-treat and completer analysis

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demonstrated significant improvements in BPI ratings from prior opioid therapy to the end of ER hydromorphone therapy ($P < 0.01$ for all pairwise comparisons). Adverse events were consistent with those expected of an opioid agonist in such a patient group, affecting primarily the gastrointestinal and central nervous systems. This uncontrolled study delineates a regimen by which patients with chronic malignant or nonmalignant pain can be readily converted from prior opioid therapy and titrated to an appropriate maintenance dose of ER hydromorphone. Controlled longitudinal studies are required to further evaluate the use of ER hydromorphone in patients with discrete chronic malignant or nonmalignant pain conditions. J Pain Symptom Manage 2002;23:*355–368. © U.S. Cancer Pain Relief Committee, 2002.*

Key Words
Chronic malignant pain, chronic nonmalignant pain, dose conversion, extended-release, hydromorphone, titration

Introduction

Hydromorphone is a semisynthetic congener of morphine that similarly exerts its analgesic effects through μ-opioid receptors in the central nervous system (CNS).[1] First synthesized in 1921 and introduced into clinical practice in 1926, hydromorphone has a well-characterized safety profile and is considered to be an effective alternative to morphine in the treatment of moderate-to-severe pain.[2] On a milligram-per-milligram basis, orally administered hydromorphone is approximately 5 times more potent than orally administered morphine.[2–6] Like morphine, hydromorphone has no intrinsic limit on its analgesic effect; sufficient doses will alleviate even the most severe pain in the majority of patients. However, dose-related side effects, such as nausea, vomiting, and, in rare instances, respiratory depression, limit upward titration. Side effects associated with hydromorphone are similar to those associated with morphine, with the exception of nausea, sedation, and pruritus, which may occur less frequently with hydromorphone.[2] Various dosage forms of hydromorphone exist for oral, parenteral, intraspinal, and rectal administration.

The use of oral hydromorphone in conventional immediate-release (IR) formulations is encumbered by a short elimination half-life (2 to 3 hours)[7] that necessitates 4-to-6-hourly dosing. Frequent dosing may be inconvenient for many patients, and clinical experience indicates that the multiple dosing requirements of IR opioids may be associated with poor adherence to therapy, resulting in inadequate analgesia and diminished quality of life.[8] To reduce the need for repeated administration, a novel, once-daily, extended-release (ER) hydromorphone formulation[9–11] was developed that utilizes the OROS® (Alza Corporation, Mountain View, California) osmotic technology. An ER hydromorphone formulation is currently not available in the United States, although 12-hour ER hydromorphone formulations are marketed in the United Kingdom and Canada.[12–14] ER formulations exist commercially in the United States for morphine (with 12- and 24-hourly dosing)[15,16] and oxycodone (with 12-hourly dosing).[17]

Designed to deliver medication at a controlled rate for up to 24 hours for once-daily dosing, the OROS® osmotic technology ER hydromorphone formulation consists of an osmotically active bilayer core enclosed in a semipermeable tablet shell membrane (Figure 1). The bilayer core is comprised of a drug layer containing hydromorphone and excipients and a push layer containing osmotically active components. The surrounding membrane is pervious to water, but not the drug or osmotic components, and has a laser-drilled orifice on the drug-layer side of the tablet. In the gastrointestinal (GI) tract, water flows across the membrane at a rate determined by membrane properties and the osmolality of the core constituents, causing the drug to go into suspension and the push layer to expand. As the push layer expands, it presses on the drug layer, slowly releasing hydrated hydromorphone through the laser-drilled orifice. The rate of drug release equals that at which water enters the tablet

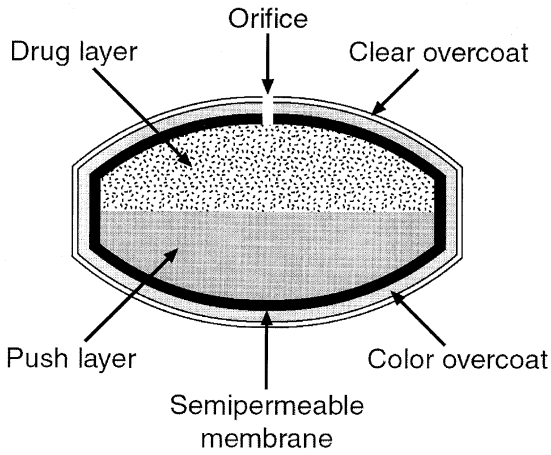

Fig. 1. The OROS® osmotic technology, extended-release hydromorphone formulation tablet. This formulation consists of a drug layer and a push layer enclosed in a semipermeable tablet shell membrane that is pervious to water but not the drug. As water is absorbed from the gastrointestinal tract, the push layer expands and presses on the drug layer, slowly releasing hydrated hydromorphone through a laser-drilled orifice in the tablet shell.

core and is independent of GI motility or pH. Since the osmotic gradient remains constant, the drug release rate is constant and then gradually falls to zero. After release of the drug, the non-absorbable tablet shell is passed in the stool.

Over the past decade, the OROS® osmotic technology has been applied commercially to a variety of marketed drugs, such albuterol,[18] glipizide,[19] isradipine,[20] nifedipine,[21] verapamil,[22] oxybutynin,[23] and methylphenidate.[24] This method of drug delivery is intended to minimize peak-trough plasma concentration fluctuations associated with conventional IR formulations, while providing convenient dosing. The OROS® osmotic technology has been shown to either preserve or enhance the efficacy of drugs available in only multiple-dose IR formulations.[19,21,23]

The objective of this open-label, repeated-dose, single-treatment, multicenter study was to evaluate the outcomes associated with a standardized conversion from prior opioid therapy to a stable dose of ER hydromorphone in an outpatient population with chronic malignant or nonmalignant pain. This study pooled patients taking part in two separate trials that were identical in design, with the exception of type of chronic pain (malignant or nonmalignant). This is the first published report with OROS® osmotic technology ER hydromorphone to involve patients with chronic pain conditions. Previous studies with this formulation involved healthy volunteers and examined pharmacokinetics with single-[10] and repeated-dosing[9] and pharmacodynamics in an experimental electrical pain model.[11]

Methods

Patients

The combined study group was composed of patients participating separately in a chronic malignant pain trial and a chronic nonmalignant pain trial. Patients included in this study were ≥18 years of age; were receiving long-term opioid therapy for chronic pain; had a daily oral morphine equivalent requirement of ≥45 mg; and were expected to have stable opioid requirements. Exclusion criteria consisted of hypersensitivity to hydromorphone or other opioid agonists; gastrointestinal (GI) disorders that might affect the intake, absorption, or transit of the study medication (e.g., dysphagia, daily vomiting, constipation, or pre-existing severe GI narrowing); any significant CNS disorder; respiratory compromise; the risk of serious decreases in blood pressure with an opioid analgesic; significant organ or metabolic dysfunction; pregnancy or lactation; the requirement for radiation treatment during the study; the use of an investigational drug within 30 days prior to initiating the study; and a history of drug or alcohol abuse. Before enrollment, patients were informed of the nature of the study and gave written informed consent.

Study Design

This open-label, repeated-dose, single-treatment, multicenter study was conducted at 48 sites in the United States and Canada. The protocol was approved by an Institutional Review Board for each site. Patients were treated on an outpatient basis. The study period was divided into 3 phases: the prior opioid stabilization phase (≥3 days), the conversion and titration phase (3–21 days), and the maintenance phase (14 days). The study period included 5 office visits (Visits 1 through 5) for patient evaluation

and study medication dispensing. The prior opioid stabilization phase began at Visit 1, when patient baseline evaluations were performed. The conversion and titration phase began at Visit 2, when ER hydromorphone was first administered. The maintenance phase began at Visit 3, included Visit 4 at midpoint, and ended with Visit 5 (termination visit).

During the prior opioid stabilization phase, patients were stabilized on their baseline oral opioid or transdermal (TTS) fentanyl therapy. A patient was considered stabilized when, for a minimum of 3 consecutive days, the total daily dose of baseline opioid medication was unchanged and ≤3 doses per day of rescue medication for breakthrough pain were administered. Patients could have taken more than one opioid during this phase, and any appropriate opioid was allowed. In addition, nonopioid and adjuvant analgesics were permitted.

During the conversion and titration phase, each patient's 24-hour baseline opioid dose was converted to a single daily dose of ER hydromorphone at a conversion ratio of 5:1 (morphine sulfate equivalent to hydromorphone hydrochloride).[2–6] There was no protocol-mandated washout period for prior opioids, and there was no overlap between administration of prior opioids and the study medication. ER hydromorphone therapy was initiated after prior opioid therapy was discontinued. ER hydromorphone hydrochloride (Abbott Laboratories, Abbott Park, IL) was provided in 8, 16, 32, and 64 mg tablets. Patients using IR hydromorphone were converted directly to ER hydromorphone at the dose most closely approximating their prior requirement. Patients using fentanyl TTS were converted to ER hydromorphone at a starting dose of 8 mg for each 25 μg/hr of fentanyl, which conservatively approximates the 5:1 conversion ratio (i.e., 25 μg/hr of fentanyl is approximately equivalent to 45 mg/day of IR morphine[25]). The lowest possible starting dose of ER hydromorphone was 8 mg/day. Patients were instructed to take ER hydromorphone at about the same time each morning and to swallow the tablet whole with 8 ounces of water. Furthermore, patients were told to avoid chewing, dividing, or crushing the tablet and advised that the non-absorbable shell would pass in the stool.

In addition to once-daily ER hydromorphone, IR hydromorphone hydrochloride (Dilaudid®; Abbott Laboratories, Abbott Park, IL) was provided in 2, 4, and 8 mg tablets as needed as rescue medication for breakthrough pain. The recommended dose of rescue medication generally ranged from 10% to 17% of the daily dose of ER hydromorphone, but was as high as 25% for the lowest (8 mg) dose of ER hydromorphone. These variations in rescue medication dose were due to limitations in available IR hydromorphone dosage strengths. As a guide, a 2 mg dose of IR hydromorphone was recommended for 8 and 16 mg/day of ER hydromorphone, a 4 mg dose for 24, 32, and 40 mg/day of ER hydromorphone, and an 8 mg dose for 48, 56, and 64 mg/day of ER hydromorphone. No other opioid was permitted, although nonopioid and adjuvant analgesics were allowed.

Patients were evaluated for dose titration by frequent phone contact with study coordinators. Dose adjustment was considered after two days of therapy with each dose step of ER hydromorphone to ensure that steady-state blood levels of hydromorphone were reached.[9] After the 2 days, upward titration was considered if ≥ 3 doses of IR hydromorphone were required in a 24-hour period. Titration increments of 25% to 100% of the current total daily dose were recommended, as used in clinical practice. Most patients were expected to achieve a stable dose of ER hydromorphone within 3 titration steps (approximately 6 days). A patient was considered stabilized when, for 3 consecutive days, the total daily dose of ER hydromorphone remained unchanged and ≤ 3 doses of IR hydromorphone per day were given for breakthrough pain. Patients stabilized for a 3-day period during the conversion and titration phase were permitted to enter the maintenance phase. Patients not stabilized after 21 days of therapy with study medication were to be discontinued from the study.

During the maintenance phase, patients were followed while receiving ER hydromorphone along with supplemental IR hydromorphone for breakthrough pain. If necessary, dose titration was permitted during this phase using the same criteria used in the conversion and titration phase. During both the conversion and titration phase and the maintenance phase, patients recorded their use of ER and

IR hydromorphone in diaries, while investigators recorded the amount of ER and IR hydromorphone dispensed and returned by each patient at each visit.

Analgesic efficacy was assessed using the short form of the Brief Pain Inventory (BPI),[26] which patients completed at Visits 2, 3, 4, and 5. Pain intensity at its worst, at its least, and on average in the last 24 hours and pain intensity right now were rated on a scale from 0 (no pain) to 10 (pain as bad as you can imagine). Pain relief was rated on a scale from 0% (no relief) to 100% (complete relief). Pain interference of general activity, mood, walking ability, normal work, relationships with others, sleep, and enjoyment of life was rated on a scale from 0 (no interference) to 10 (complete interference).

Safety and tolerability were evaluated through adverse events reported by patients spontaneously or via non-suggestive questioning by investigators, as well as the number of patients discontinuing treatment due to adverse events. At baseline (Visit 1) and at study termination, patients underwent a physical examination.

Patient discontinuation was considered if an inadequate analgesic response was achieved with ER and IR hydromorphone, the patient's condition became unstable, or a serious adverse event occurred. Patients who were discontinued early may have been converted to another opioid-containing therapy at an appropriate dose. If patients were to be discontinued from opioid therapy entirely, it was recommended that the dose of ER hydromorphone be reduced gradually over several days to prevent signs and symptoms of withdrawal. These patients were to have their ER hydromorphone dose reduced by 50% every 2 days, until the lowest possible dose (8 mg) was reached, at which time therapy could be discontinued. Patients who successfully completed the study and reached the termination visit (Visit 5) were given the option to continue receiving ER hydromorphone under a long-term extension protocol.

Statistical Analysis

The statistical analysis pooled patients participating in the two trials. Changes in mean BPI pain intensity, pain relief, and pain interference ratings from pretreatment (Visit 2 at the end of the prior opioid stabilization phase) to endpoint (Visit 5 or the last observation carried forward during treatment, whether at Visits 3 or 4) were assessed using the Wilcoxon signed rank test. In addition to the intent-to-treat analysis, a completer analysis (for those patients with complete data) was performed in which changes in mean BPI ratings from Visit 2 to Visit 5 (termination visit) were assessed using the Wilcoxon signed rank test. To detect the smallest differences in BPI ratings, a type I (α) error of 0.05 was assumed. Statistical significance was set at $P \leq 0.05$. Data are presented as mean $\pm$ standard deviation (SD), unless stated otherwise.

Results

Patient Disposition

Patient disposition is shown in Figure 2. A total of 445 patients with chronic malignant pain (n = 87) or chronic nonmalignant pain (n = 358) enrolled in this study. Of these, 41 patients withdrew from the study prior to receiving the study medication for various reasons, including consent withdrawal (15 patients), administrative reasons (10 patients), disease progression (6 patients), lost to follow-up (5 pa-

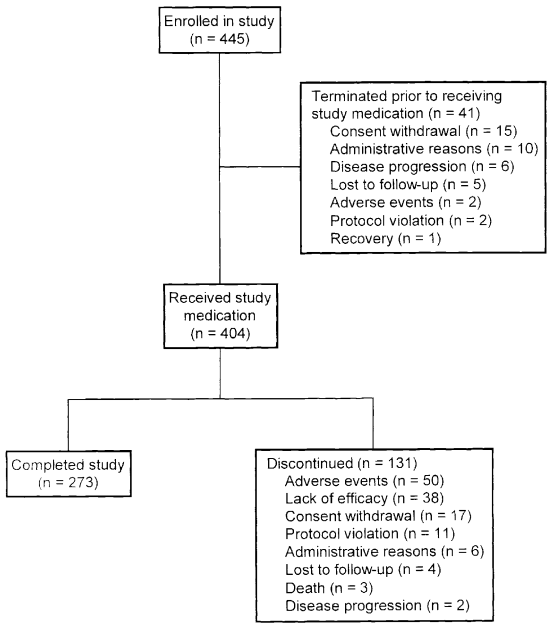

Fig. 2. Patient disposition.

tients), adverse events (2 patients), protocol violation (2 patients), and recovery (1 patient).

Of the 404 patients who received study medication, 273 (67.6%) completed treatment and had a termination visit (Visit 5), while 131 (32.4%) were prematurely discontinued during the study period. Among these 131 patients, 104 were discontinued during the titration and conversion phase, and 27 were discontinued during the maintenance phase. Patient discontinuation was due to adverse events (50/404; 12.4%), lack of efficacy (38/404; 9.4%), consent withdrawal (17/404; 4.2%), protocol violation (11/404; 2.7%), administrative reasons (6/404; 1.5%), lost to follow-up (4/404; 1.0%), death (3/404; 0.7%), and disease progression (2/404; 0.5%). The 3 deaths were unrelated to the study medication and were due to progressive disease states (bacteremia/sepsis secondary to pancytopenia and nasopharyngeal cancer; liver failure secondary to liver metastasis of small cell lung cancer; and GI emergency due to a perforated ulcer possibly related to naproxen treatment). Of the 404 patients who received study medication, 366 (90.6%) were administered ER hydromorphone for at least 7 days. On average, patients were exposed to ER hydromorphone for 24.2 days.

Demographic and Baseline Characteristics

Demographic and baseline characteristics for the 404 patients who received the study medication are presented in Table 1. The mean age of these patients was 50.8 ± 13.0 years. Both women (216/404; 53.5%) and men (188/404; 46.5%) participated. Chronic malignant pain was experienced by 73 patients (18.1%), whereas chronic nonmalignant pain was experienced by 331 patients (81.9%). Chronic malignant pain was characterized as somatic (38/404; 9.4%), visceral (22/404; 5.5%), neuropathic (9/404; 2.2%), treatment-related (1/404; 0.3%), and other miscellaneous types (3/404; 0.7%). Chronic nonmalignant pain was characterized as musculoskeletal (172/404; 42.6%), neuropathic (132/404; 32.7%), sympathetically maintained (16/404; 4.0%), and other miscellaneous types (11/404; 2.7%). At baseline (Visit 1), the mean daily oral morphine equivalent requirement was 150.3 mg for the total patient group, 166.4 mg for chronic malignant pain patients, and 146.8 mg for chronic nonmalignant pain patients. Of the 404 patients, 326 (80.7%) were being treated with single-entity opioids, while 78 (19.3%) were being treated with combination opioids. Prior opioid treatment included oxycodone (155/404; 38.4%), morphine (98/404; 24.3%), hydrocodone (64/404; 15.8%), fentanyl TTS (37/404; 9.2%), hydromorphone (34/404; 8.4%), methadone (29/404; 7.2%), codeine (13/404; 3.2%), propoxyphene (5/404; 1.2%), butorphanol (1/404; 0.3%), and meperidine (1/404; 0.3%).

Dose Stabilization

Dose stabilization was reached by 73.8% of patients (298/404). Among these patients, 20.8% (62/298) required no dose increases, 49.3% (147/298) required ≤1 titration steps, 70.1% (209/298) required ≤2 titration steps, 82.2% (245/298) required ≤3 titration steps, and 90.3% (269/298) required ≤4 titration steps (Figure 3). For the first 4 titration steps, the mean changes in ER hydromorphone dose from 1 step to the next ranged from 12.0 mg to 12.5 mg (Table 2). Although there was a large mean percent increase in dose for the first titration step (59.2%), there were very similar mean percent increases for the subsequent 3 titration steps (27.3% to 30.1%) (Table 2). The percent increases in dose for the first 4 titration steps were well within the 25% to 100% increment recommended in the protocol. There were approximately 3 days between each of the first 4 titration steps. Overall, the mean time to dose stabilization was 12.1 ± 5.7 days (range of 3 to 33 days).

The mean daily doses of ER and IR hydromorphone at the end of the maintenance phase (mean for last 2 days of this phase) for total patients, chronic malignant pain patients, and chronic nonmalignant pain patients are presented in Table 3. The mean daily dose of ER hydromorphone for total patients at the end of the maintenance phase was 63.4 ± 129.2 mg. The median daily dose at that time was 40 mg. The first quartile had a final dose of ≤24 mg, whereas the fourth quartile had a final dose ranging from 64 mg to 1,984 mg. The mean daily dose of IR hydromorphone for total patients at the end of the maintenance phase was 11.5 ± 36.4 mg. The mean daily number of doses of IR hydromorphone for total patients at the end of the maintenance phase was 1.7 ± 1.3.

Table 1
Demographic and Baseline Characteristics (n = 404)

Age, mean ± SD, years	50.8 ± 13.0
Sex, number (%) of patients	
Female	216 (53.5)
Male	188 (46.5)
Chronic malignant pain, number (%) of patients	
Overall	73 (18.1)
Somatic	38 (9.4)
Visceral	22 (5.5)
Neuropathic	9 (2.2)
Treatment-related	1 (0.3)
Other miscellaneous	3 (0.7)
Chronic nonmalignant pain, number (%) of patients	
Overall	331 (81.9)
Musculoskeletal	172 (42.6)
Neuropathic	132 (32.7)
Sympathetically-maintained	16 (4.0)
Other miscellaneous	11 (2.7)
Mean daily oral morphine equivalent requirement, mg	
Total patients	150.3
Chronic malignant pain patients	166.4
Chronic nonmalignant pain patients	146.8
Prior opioid class, number (%) of patients	
Single-entity opioid	326 (80.7)
Combination opioid	78 (19.3)
Prior opioid treatment, number (%) of patients	
Overall	404 (100)
Oxycodone	155 (38.4)
Morphine	98 (24.3)
Hydrocodone	64 (15.8)
Fentanyl TTS	37 (9.2)
Hydromorphone	34 (8.4)
Methadone	29 (7.2)
Codeine	13 (3.2)
Propoxyphene	5 (1.2)
Butorphanol	1 (0.3)
Meperidine	1 (0.3)

SD = standard deviation.

During treatment with ER hydromorphone, the following therapies with adjuvant analgesic activity were used: amitriptyline (14.9%; 60/404), gabapentin (13.9%; 56/404), fluoxetine (9.4%; 38/404), sertraline (7.9%; 32/404), trazodone (6.9%; 28/404), clonazepam (5.9%; 24/404), doxepin (2.7%; 11/404), valproic acid (2.5%; 10/404), clonidine (2.2%; 9/404), nortriptyline (2.2%; 9/404), phenytoin (2.0%; 8/404), carbamazepine (1.7%; 7/404), desipramine (1.5%; 6/404), imipramine (1.5%; 6/404), and clomipramine (0.3%; 1/404). Patients could have used more than one adjuvant analgesic.

Analgesic Efficacy

Mean pain intensity ratings for pain at its worst, at its least, and on average in the last 24 hours and for pain right now decreased significantly from pretreatment to endpoint ($P < 0.01$ for all pairwise comparisons) (Figure 4). Mean pain relief ratings increased significantly from pretreatment (56.2 ± 23.6%) to endpoint (61.1 ± 24.4%) (n = 372) ($P < 0.001$). Mean pain interference ratings decreased significantly from pretreatment to endpoint for each category ($P < 0.0001$ for all pairwise comparisons) (Figure 5). The completer analysis performed on data from patients having a termination visit (Visit 5) yielded similar results, with significant improvements in BPI ratings from Visit 2 to Visit 5 ($P < 0.01$ for all pairwise comparisons) (data not shown). Among the patients withdrawing due to a lack of efficacy, 78.9% (30/38) reported no pain relief or slight pain relief, while 21.1% (8/38) reported at least moderate pain relief. Although permitted to titrate as necessary for up to 21 days, 22 of the 38 patients (57.9%) left the study after only ≤2 titration steps.

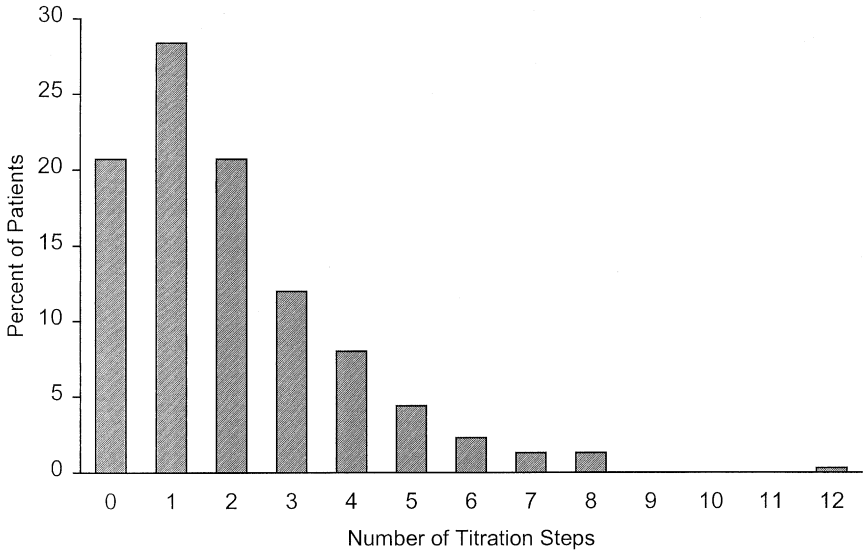

Fig. 3. Percent of patients by the number of titration steps required in reaching a stable dose of ER hydromorphone. Dose stabilization was attained by 73.8% of patients (298/404). Among these, 70.1% (209/298) were stabilized with ≤2 titration steps.

Safety and Tolerability

Adverse event results are summarized in Table 4. Among the 404 patients, 316 (78.2%) experienced adverse events. The most frequent (≥5%) adverse events were nausea (86/404; 21.3%), constipation (70/404; 17.3%), headache (69/404; 17.1%), somnolence (60/404; 14.9%), dizziness (59/404; 14.6%), vomiting (50/404; 12.4%), and asthenia (35/404; 8.7%). Fifty patients (12.4%) withdrew due to adverse events. The most frequent adverse events leading to patient withdrawal were nausea (18/404; 4.5%), headache (8/404; 2.0%), vomiting (7/404; 1.7%), constipation (5/404; 1.2%), and somnolence (5/404; 1.2%).

Adverse events were considered to be serious in 25 patients (6.2%). Three patients (0.7%) experienced adverse events that were considered to be serious and related to the study medication. These adverse events were an overdose in two patients and hallucinations in one patient. One of the patients who experienced an overdose was discontinued from the study after 13 days of treatment with the study medication, while the other continued; both recovered without sequelae. The patient who developed hallucinations was discontinued from the study after 16 days of treatment with the study medication and recovered without sequelae.

Table 2
Titration Step Analysis with Extended-Release (ER) Hydromorphone

Titration Step[a]	Mean ± SD Prior Daily Dose of ER Hydromorphone, mg	Mean ± SD Subsequent Daily Dose of ER Hydromorphone, mg	Mean ± SD Change in ER Hydromorphone Dose, mg	Percent Change in ER Hydromorphone Dose,[b] %	Mean ± SD Days for Each Titration Step
0 to 1 (n = 236)	30.0 ± 36.4	42.0 ± 44.4	12.0 ± 15.2	59.2	2.5 ± 2.1
1 to 2 (n = 151)	42.8 ± 44.2	54.8 ± 55.6	12.0 ± 18.3	30.0	3.2 ± 2.0
2 to 3 (n = 89)	60.4 ± 60.3	72.9 ± 74.9	12.5 ± 27.0	30.1	3.1 ± 1.9
3 to 4 (n = 53)	68.2 ± 59.5	80.8 ± 66.2	12.5 ± 21.0	27.3	3.0 ± 1.9

SD = standard deviation.
[a]A titration step was defined by any change in dose of ER hydromorphone. Titration step 0 to 1 was the first change in dose of ER hydromorphone. Titration step 1 to 2 was the second change, and so on.
[b]The mean percent changes in daily doses of ER hydromorphone were calculated by summing the percent changes for each patient at each titration step and then dividing by the number of patients.

Table 3
Daily Doses of Extended-Release (ER) and Immediate-Release (IR) Hydromorphone at the End of the Maintenance Phase[a]

	Total Patients	Chronic Malignant Pain Patients	Chronic Nonmalignant Pain Patients
Mean ± SD daily dose of ER hydromorphone, mg/day	63.4 ± 129.2 (n = 298)	47.9 ± 51.2 (n = 56)	66.9 ± 141.1 (n = 242)
Mean ± SD daily dose of IR hydromorphone, mg/day	11.5 ± 36.4 (n = 292)	5.2 ± 6.1 (n = 55)	13.0 ± 40.2 (n = 237)
Mean ± SD daily number of doses of IR hydromorphone, doses/day	1.7 ± 1.3 (n = 289)	1.2 ± 1.0 (n = 55)	1.8 ± 1.4 (n = 234)

SD = standard deviation.
[a]mean for last 2 days of this phase.

Discussion

The goal of pharmacotherapy of chronic pain is to provide sustained, around-the-clock analgesia with minimal side effects. Although nonopioid analgesics are indicated for moderate episodic pain, they may not be effective therapies for severe continuous pain because upward titration is limited by a ceiling effect and dose-dependent toxicities.[27] Pure opioid agonists, in contrast, lack a ceiling effect and can be titrated upward until, in most cases, a favorable balance is attained between efficacy and tolerability.[27] Although opioid therapy may be carried out with IR formulations, clinical experience suggests that ER formulations, which allow decreased dosing frequency, may yield improved adherence, more consistent analgesia, and enhanced quality of life.[8] The novel, OROS® osmotic technology, ER hydromorphone formulation described here can be administered once-daily[9–11] and may be an option for treating chronic pain.

In this study, patients with chronic malignant or nonmalignant pain were stabilized on their previous opioid therapy, converted to ER hydromorphone, titrated in a stepwise fashion to

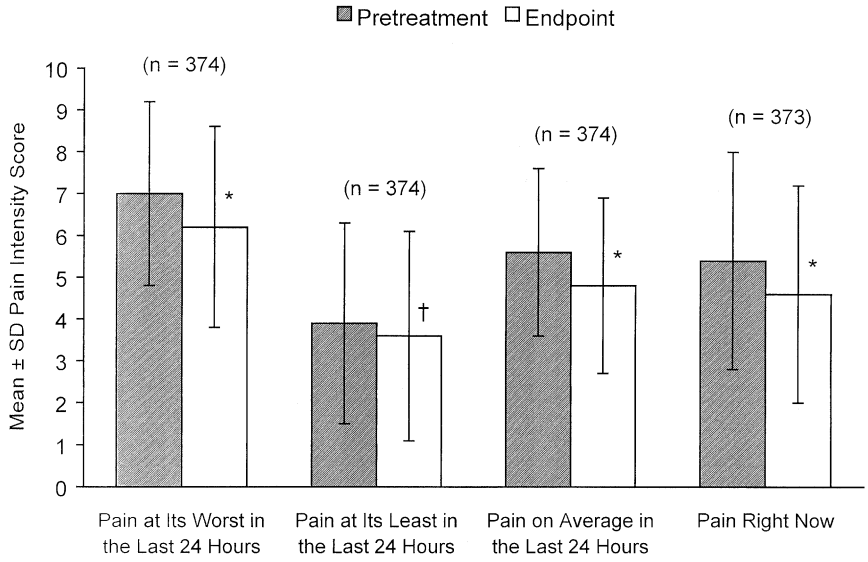

Fig. 4. Comparisons of mean ± standard deviation (SD) pain intensity ratings from the Brief Pain Inventory between pretreatment (Visit 2 at the end of the prior opioid stabilization phase) and endpoint (Visit 5 or the last observation carried forward during treatment, whether at Visits 3 or 4) in the intent-to-treat analysis. Pain at its worst, at its least, and on average in the last 24 hours and pain right now were rated on a scale from 0 (no pain) to 10 (pain as bad as you can imagine). *$P < 0.001$ when comparing pretreatment to endpoint (Wilcoxon signed rank test). †$P < 0.01$ when comparing pretreatment to endpoint (Wilcoxon signed rank test).

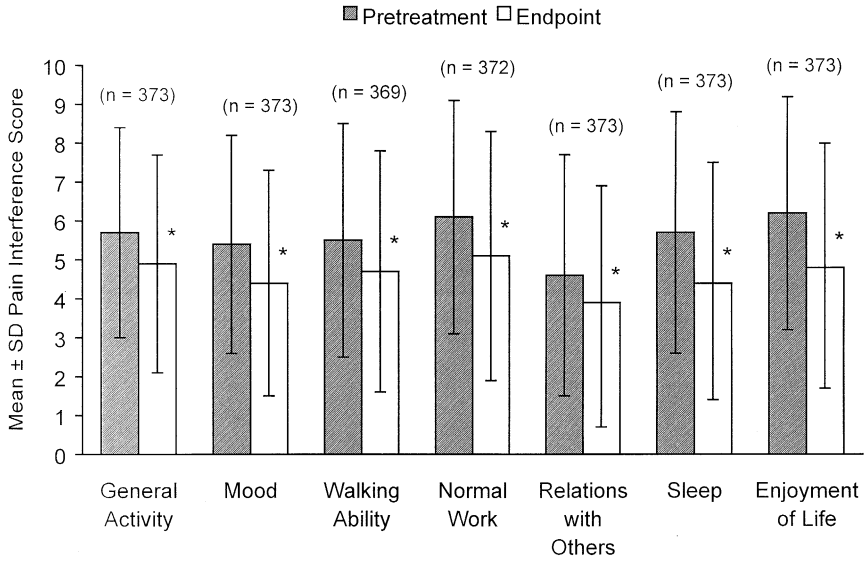

Fig. 5. Comparisons of mean ± standard deviation (SD) pain interference ratings from the Brief Pain Inventory between pretreatment (Visit 2 at the end of the prior opioid stabilization phase) and endpoint (Visit 5 or the last observation carried forward during treatment, whether at Visits 3 or 4) in the intent-to-treat analysis. Pain interference of function (general activity, mood, walking ability, normal work, relationships with others, sleep, and enjoyment of life) was rated on a scale from 0 (no interference) to 10 (complete interference). *$P < 0.0001$ when comparing pretreatment to endpoint (Wilcoxon signed rank test).

an optimal daily dose of ER hydromorphone, and then maintained on ER hydromorphone for a 2-week period. The limitations of this study include the open-label design, the lack of a control or active comparator group, the nonstandardized nature of prior opioid therapy, and the heterogeneity of the patient population with regard to chronic pain etiologies. As such, the study design does not allow conclusions regarding comparative efficacy between ER hydromorphone and other opioid therapies. A study of this type, however, provides insights into the effectiveness of a conversion and titration approach that can be adopted in clinical practice and the safety, tolerability, and acceptability of the study medication.

Conversion from prior opioid therapy and titration to a stable dose of ER hydromorphone was readily performed. The majority of patients (298/404; 73.8%) reached a stable dose of ER hydromorphone, with most requiring no or few titration steps (209/298 or 70.1% with ≤2 titration steps). Dose stabilization was attained with mean titration increments that fell well within the range commonly used in clinical practice (25% to 100%), and dose stabilization was quickly achieved (mean of 12.1 days). ER hydromorphone was well tolerated in the

Table 4
Adverse Events (n = 404)

Number (%) of patients reporting adverse events	316 (78.2)
Number (%) of patients reporting the following most frequent adverse events[a]	
Nausea	86 (21.3)
Constipation	70 (17.3)
Headache	69 (17.1)
Somnolence	60 (14.9)
Dizziness	59 (14.6)
Vomiting	50 (12.4)
Asthenia	35 (8.7)
Number (%) of patients who discontinued treatment due to adverse events	50 (12.4)

[a]Adverse events occurring at a frequency of ≥5%.

patient group; adverse events were consistent with those expected of an opioid agonist administered in such a patient population, affecting primarily the GI system and the CNS.

A 5:1 ratio for conversion from oral morphine equivalent mg to oral hydromorphone, which is often cited in the literature,[2–6] was found to be clinically useful in this study. The appropriateness of the conversion ratio was supported by results showing that the majority of the patients reaching dose stabilization required minimal, if any, dose titration. The methodological decision to forego a modest reduction in the equianalgesic dose, which is often suggested with the intention of avoiding unanticipated side effects related to incomplete cross-tolerance, was supported by the favorable outcomes achieved by most patients. However, clinicians should continue to abide to the recommendation of decreasing the estimated equianalgesic dose of a newly added, long-acting opioid (in this case ER hydromorphone) by 25% to 50%,[27] at least until further large prospective studies with ER hydromorphone address this issue. In addition to suggesting an appropriate conversion ratio, the results of this study suggest that conversion from an alternative opioid to ER hydromorphone can be accomplished directly, without an intermediate IR hydromorphone phase. Previous studies with direct conversion to ER morphine[28] and oxycodone[29] support this notion.

Analgesia was maintained during the transition from prior opioid therapy to ER hydromorphone. Intent-to-treat and completer analysis revealed that BPI ratings improved significantly with ER hydromorphone compared with prior opioid therapy ($P < 0.01$ for all pairwise comparisons). However, although statistically significant, the mean improvements in all the BPI ratings were small in magnitude and may not have been clinically relevant. As such, these data suggest that, at the very least, analgesia with ER hydromorphone was consistent with that of prior opioid therapy. As an additional indication of analgesic efficacy, only a small proportion of patients (38/404; 9.4%) was discontinued from the study due to lack of efficacy. More than half of these patients (22/38; 57.9%) left the study after only ≤2 titration steps, even though the study protocol allowed further titration for up to 21 days.

The mean final daily ER hydromorphone doses of 63.4 mg overall, 47.9 mg in chronic malignant pain patients, and 66.9 mg in chronic nonmalignant pain patients in this study fell within a range of doses reported in previous studies with a 12-hour ER hydromorphone formulation available in the United Kingdom.[12–14] In a randomized, double-blind, cross-over study comparing 12-hour ER hydromorphone to 4-hour IR hydromorphone in 45 patients with stable severe cancer pain, the mean daily dose of hydromorphone was 76 mg.[12] After an open-label, long-term, longitudinal evaluation (8–419 days) of the 12-hour ER hydromorphone formulation in 37 of the 45 patients, the final mean daily dose was 89 mg.[12] In a randomized, double-blind, cross-over, 2-week study comparing 12-hour ER hydromorphone to 4-hour IR hydromorphone in 18 patients with chronic malignant pain, the mean daily dose of hydromorphone was 48 mg.[13] In a randomized, double-blind, cross-over, 1-week study comparing 12-hour ER oxycodone to 12-hour ER hydromorphone in 44 patients with stable chronic malignant pain, the mean daily dose of ER hydromorphone was 30 mg.[14] Additionally, mean doses of IR hydromorphone (11.5 mg/day; 1.7 doses/day) given as rescue analgesia with a stable dose of ER hydromorphone in our study were comparable to those used in previous studies with the 12-hour ER hydromorphone formulation.[12–14]

Most patients utilized maintenance doses below the mean daily dose, indicating that outliers taking relatively high doses may have influenced the results. One patient, in particular, used a very high dose of ER hydromorphone (1,984 mg/day). This patient was a 29-year-old woman with severe chronic nonmalignant pain following multiple occipital neurectomies for debilitating headaches. In general, dose variability is not uncommon with opioid use and may be attributed to a variety of patient-related and pain-related factors, such as prior opioid exposure, underlying pain mechanisms, predisposition to side effects, and psychologic distress.[30] The variability in final ER hydromorphone doses in this study may have been due, in part, to the heterogenous chronic patient population and non-standardized prior opioid therapy.

This study suggests that ER hydromorphone may be effective in treating a variety of chronic pain states. The majority of patients here experienced chronic nonmalignant pain (331/404; 81.9%). Furthermore, a large proportion of

the overall patient group, whether experiencing chronic malignant or nonmalignant pain, had pain of neuropathic origin (141/404; 34.9%). Past experience indicates that the long-term administration of ER opioids can be effective in treating chronic nonmalignant pain[31–34] and that patients with such pain may benefit from opioids without deterioration in function.[35,36] Likewise, well-controlled studies suggest that neuropathic pain may be responsive to opioids.[37–39]

This report describes a regimen by which patients can be easily converted from prior opioid therapy and titrated to an appropriate maintenance dose of ER hydromorphone. Dose conversion from morphine equivalent mg of prior opioid therapy to ER hydromorphone, using a ratio consistent with conversion from morphine equivalent mg to IR hydromorphone, initiated therapy at a dose that was effective and well tolerated for most patients. In light of the results of this study and the convenience afforded by once-daily dosing, we anticipate that the novel, OROS® osmotic technology, ER hydromorphone formulation will be well accepted by patients and physicians in the clinical practice setting. Controlled longitudinal studies are required to further evaluate the use of this ER hydromorphone formulation in patients with discrete chronic malignant or nonmalignant pain conditions.

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