Multicenter, Open-Label, Prospective Evaluation of the Conversion from Previous Opioid Analgesics to Extended-Release Hydromorphone Hydrochloride Administered Every 24 Hours to Patients with Persistent Moderate to Severe Pain

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ABSTRACT

Background: Hydromorphone hydrochloride is a μ-opioid agonist with dose-dependent analgesic properties. Extended-release hydromorphone hydrochloride (ER hydromorphone HCl) capsules have been developed for administration every 24 hours.

Objectives: This prospective evaluation focused on the first (ie, conversion) phase of 2 identically designed, randomized, controlled studies that compared the safety and efficacy of once-daily ER hydromorphone HCl capsules with immediate-release hydromorphone hydrochloride (IR hydromorphone HCl) tablets administered 4 times daily in the treatment of persistent moderate to severe cancer- and noncancer-related pain.

Methods: Patients being treated with opioid analgesics for persistent moderate to severe pain were converted to ER hydromorphone HCl using an 8:1 conversion ratio. The dose was titrated to attain an average pain intensity (API) score ≤4 on a 0- to 10-point numeric rating scale. Supplemental oral IR hydromorphone HCl tablets were used as rescue medication at a dose of one eighth to one sixth of the daily ER hydromorphone HCl dose.

Results: A total of 343 patients (272 [79%] with cancer pain; mean age, 57.8 years) were enrolled and converted to ER hydromorphone HCl from their previous opioids. About half (51%) were women. At baseline, the mean (SD) API score was 5.3 (2.1). Mean (SD) API scores were 4.7 (2.0) after the first 48 hours and 3.4 (2.1) by the end of titration. After 4 to 21 days of titration, 239 (70%) patients reached stabilization defined as a ≥48-hour period with an API score of ≤4, unchanged ER hydromorphone HCl dose, and ≤2 rescue doses per day. The stabilized patients had mean (SD) API scores of 2.7 (1.1) at the end of titration. At stabilization, 102 (43%) of 239 patients remained at their initial conversion dose, 129 (54%) had a dose increase, and 8 (3%) had a dose decrease. Frequent (≥10% of patients) adverse events that occurred within the first 48 hours after conversion and during the entire titration phase were nausea, somnolence, headache, constipation, vomiting, and dizziness.

Conclusion: In this prospective evaluation of the conversion and titration phase of 2 randomized, controlled studies, a conversion ratio of 8:1 mg of oral morphine to oral ER hydromorphone HCl was found to be clinically useful in patients with persistent moderate to severe cancer-related or noncancer-related pain. (*Clin Ther.* 2006;28:86–98)

Key words: analgesics, opioid, hydromorphone, extended-release, conversion, titration.

INTRODUCTION

Opioid analgesia remains the foundation of treatment for moderate to severe cancer-related pain[1–3] and has been increasingly used to manage persistent pain of nonmalignant etiology in selected patients.[4–8] Hydro-

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morphone hydrochloride is a μ-opioid agonist with dose-dependent analgesic properties that has been used to treat pain since the 1920s.[9] Similar to morphine and oxycodone, hydromorphone hydrochloride does not have an analgesic ceiling effect,[3] and doses can be increased as needed to relieve moderate to severe pain. Restrictions to dosing generally depend on the patient's ability to tolerate the typical adverse events (AEs) associated with opioid therapy, such as somnolence, nausea, and vomiting.[3]

The duration of action of oral immediate-release hydromorphone hydrochloride (IR hydromorphone HCl) limits its use for persistent pain; around-the-clock administration every 4 to 6 hours is necessary to maintain adequate analgesia.[10,11] An oral formulation of extended-release hydromorphone hydrochloride* (ER hydromorphone HCl) is available in capsule strengths of 12, 16, 24, and 32 mg for administration every 24 hours.

Pain management guidelines include procedures for conversion from one opioid to another and from one route of administration to another, as well as methods for calculating equianalgesic doses.[3,10,12–15] Equianalgesic doses represent only one consideration in the opioid conversion process. There are many other considerations in the choice of an initial opioid dose, including history of medication use and tolerability of AEs.[12] For the initial opioid conversion, prescribing a conservative dose is an appropriate strategy. Because of incomplete cross-tolerance among opioids,[16] it is also recommended that a higher ratio be used when changing to a new opioid in the tolerant patient. After the conversion, upward titration may be necessary to attain an adequate therapeutic response.[12,15]

A conversion ratio of 8:1 mg of oral morphine to oral hydromorphone was utilized in the open-label conversion and titration phase of 2 identically designed, controlled clinical studies that compared the efficacy and safety of once-daily ER hydromorphone HCl capsules with IR hydromorphone HCl tablets administered 4 times daily in the treatment of patients with persistent moderate to severe cancer- and non–cancer-related pain. This paper presents the results of the open label (first) phase of these studies. The double-blind (second) phase of the studies has been reported elsewhere.[17]

*Trademark: Palladone® (Purdue Pharma LP, Stamford, Connecticut).

PATIENTS AND METHODS

Study Population

Patients aged ≥10 years with persistent cancer-related pain or aged ≥18 years with persistent noncancer-related pain requiring around-the-clock treatment with opioid analgesics were eligible to participate. The diagnosis of persistent noncancer-related pain was based on clinical evidence of osteoarthritis, rheumatoid arthritis, intervertebral disc disease, spondylolisthesis, nerve root entrapment, or similar conditions. Eligible patients had been treated with single-entity or fixed-combination opioid analgesics for ≥2 consecutive weeks before study entry and currently required total daily doses of oral morphine equivalent at ≥90 mg (≥12 mg of oral hydromorphone). If patients were also treated with nonopioid analgesics or nonopioid medications with analgesic properties, patients had to be taking the medication on a regular basis (rather than taking it as needed) and as part of a stable regimen for ≥2 days before entry. Coexisting disease states and related therapy had to be stable for ≥1 week before entry. All patients had to be able to be contacted by telephone and had to be willing and able to participate in all aspects of the study, including taking oral medications, completing subjective evaluations and diaries, and undergoing phlebotomy.

Patients were excluded if they had a history of allergy to hydromorphone or a contraindication to opioid therapy (eg, paralytic ileus, severe pulmonary disease); were pregnant, lactating, or of childbearing potential and did not use contraception; were unable to swallow solid oral formulations; had a planned surgery or other procedures during the 35-day period after the baseline visit that would prevent study completion; were using another investigational drug or device; received strontium chloride 89 within 30 days before study entry; or had concurrent medical conditions that posed an increased risk to the use of the study medication or that could confound or obscure efficacy assessments. Patients with noncancer-related pain were also excluded if they previously or currently abused drugs; were currently involved in any litigation or arbitration related to their pain and/or injury; or had received IM or intra-articular steroid injections to the site of their pain within the past 6 weeks.

Study Design and Drug Treatment

This prospective evaluation focused on the initial, nonrandomized, open-label conversion/titration phase

of 2 studies, as previously noted. These studies were conducted according to the 1964 Declaration of Helsinki, as well as all amendments concerning medical research in humans,[18] and were approved by institutional review boards at each of 37 sites in the United States. All patients provided written informed consent.

Patients were transitioned to ER hydromorphone HCl from their prestudy opioid analgesics and then underwent titration for 4 to 21 days to an individualized dose. A conversion ratio of 8:1 mg of oral morphine to oral hydromorphone was used to estimate the dose of hydromorphone required to convert patients from their previous opioid regimens. This 8:1 conversion ratio is supported by results from reviews and equianalgesic dose tables presented in pain management guidelines.[10,19–21]

All patients discontinued their prestudy opioids and received open-label ER hydromorphone HCl administered once daily at 8 AM ± 1 h. The minimum initial daily dose was 12 mg, the strength of a single ER hydromorphone HCl capsule used in each study. Because of packaging limitations, the maximum daily dose of ER hydromorphone HCl, excluding supplemental (rescue) analgesia, was 84 mg. Rescue medication was supplied as 2-mg IR hydromorphone HCl tablets. Each dose was one eighth to one sixth the daily dose of ER hydromorphone HCl administered every 4 to 6 hours as needed for exacerbations of pain.

There was no washout period between the previous opioid and the initial dose of ER hydromorphone HCl. The interval between the previous opioid dose and the initial dose of ER hydromorphone HCl was based on the duration of action or frequency of administration of the prestudy opioid, and was ≥4 hours. Patients administered controlled-release opioids twice daily received their first ER hydromorphone HCl dose after a 12-hour interval. For patients discontinuing treatment with transdermal fentanyl, ≥17 hours were required before initiation of ER hydromorphone HCl dosing.

For each patient enrolled, the initial daily dose of oral hydromorphone was selected by converting from the prestudy opioid using the 8:1 ratio (**Table I**). If a patient was taking >1 opioid at entry, the calculated total daily dose of hydromorphone was based on the aggregate dose of previous opioids. The calculated dose was then rounded to a multiple of the 12-mg capsule strength of ER hydromorphone HCl according to **Table II**. The investigator's judgment of recent pain intensity and prestudy opioid-related AEs were also considered during the determination of whether the rounded dose should be adjusted upward or downward by 1 increment. If the calculated dose was <10 mg, the investigator assessed whether the patient's pain re-

Table I. Conversion factors for calculating oral hydromorphone equivalent.[10]*

Prestudy Opioid	Oral	Parenteral†	Transdermal
Codeine	0.0375	–	–
Fentanyl‡	–	–	0.225
Hydrocodone	0.225	–	–
Hydromorphone	1.0	5.0	–
Levorphanol	1.875	3.75	–
Meperidine	0.025	0.10	–
Methadone	0.375	0.75	–
Morphine	0.125	0.75	–
Oxycodone	0.25	–	–

*Total daily dose of each prestudy opioid in milligrams was multiplied by the conversion factor indicated to obtain the calculated daily dose of oral hydromorphone. If patients were receiving >1 prestudy opioid, the calculated daily doses of oral hydromorphone for each opioid were added. For transdermal fentanyl, the total prestudy opioid dose, in micrograms per hour, was multiplied by the conversion factor.

†A more conservative conversion ratio was used for patients receiving high-dose parenteral opioids (eg, 0.375 instead of 0.75 for high-dose parenteral morphine).

‡Patients had to receive doses of ≥50 μg/h of transdermal fentanyl before starting therapy with hydromorphone, unless they received fentanyl in combination with other opioids.

Table II. Determination of the rounded dose of extended-release hydromorphone hydrochloride (ER hydromorphone HCl).

Calculated Total Daily Hydromorphone Dose, mg	Rounded Dose of ER Hydromorphone HCl, mg	No. of ER Hydromorphone HCl Capsules for Initial Dose
10–20	12	1
21–32	24	2
33–42	36	3
43–54	48	4
55–66	60	5
67–78	72	6

quired treatment with 12 mg of ER hydromorphone HCl and made no further initial adjustment.

After the start of ER hydromorphone HCl administration, the initial dose could be titrated upward or downward to adjust for pain intensity, for multiple use of rescue medication, or to manage AEs. During the first 48 hours after conversion to ER hydromorphone HCl, the investigator was discouraged from titrating to facilitate assessment of the initial dose and because steady-state concentrations of hydromorphone are achieved within 2 to 3 days after initiation of ER hydromorphone HCl administration.[22] However, the investigator was allowed to prescribe rescue medication, as needed, to manage the patient's pain.

After the first 48 hours, upward titration was usually not performed more than every 48 hours; however, the investigator could increase the ER hydromorphone HCl dose after 24 hours if the patient was receiving ≥4 doses of rescue medication and/or had a average pain intensity (API) score of ≥8 on a 0- to 10-point numeric rating scale (unless AEs precluded upward titration).

On each study day, patients kept a diary in which they recorded their API ratings, the time and number of ER hydromorphone HCl capsules taken per dose, the time and number of IR hydromorphone HCl tablets taken per dose, concomitant medications, and AEs. API was assessed 4 times per day using a numeric rating scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine).[23] Patients assessed their API since their last rating at 8 AM ± 1 h, at 1 PM ± 1 h, at 6 PM ± 1 h, and at bedtime (≥4 hours after the last rating). The content of the diary was reviewed by telephone every evening by site staff. During the interview, patients were asked if any reported AEs were tolerable, according to their subjective assessments.

The objective of the titration phase was to provide stable pain control on the same ER hydromorphone HCl dose for ≥48 hours with ≤2 rescue doses per day, except for patients administered the lowest dose of ER hydromorphone HCl (12 mg), who could receive ≤3 rescue doses per day. For stable pain control, the API score was usually rated as ≤4. If >2 of the 8 API scores during a 48-hour period were 5, 6, or 7, or if ≥1 of the API scores was ≥8, pain was not considered stable. In addition, patients had to report that any AEs at this dose level were tolerable according to their subjective assessments.

All other opioids and opioid-containing medications were prohibited during the study, except for antidiarrheal agents containing the weak opioid diphenoxylate hydrochloride. Nonopioid analgesics and adjuvant medications with analgesic properties administered before the study or begun during the titration phase could be adjusted. As-needed administration of nonopioid antipyretic analgesics for fever and aspirin for myocardial infarction prophylaxis was permitted.

Statistical Analysis

A sample size of 80 patients from each of the 2 studies (160 patients) was needed in the double-blind phase to achieve ≥80% power to have the 90% CI based on the Student *t* statistic for the difference of 2 means to be within the range of –2 to 2.[17] To ensure that 160 patients would be randomized, a sufficient number of patients were enrolled in the open-label conversion/titration phase. This report includes all patients who entered the open-label phase.

Demographic and efficacy data were summarized using descriptive statistics. The mean daily API score at baseline (before administration of ER hydromor-

phone HCl) was compared with mean scores obtained after the first 48 hours and after titration to a stable dose. The number and percentage of patients who attained stabilization were provided; the rounded dose of ER hydromorphone HCl in milligrams was compared with the ER hydromorphone HCl dose after the first 48 hours and at stabilization. In addition, the number of doses and total daily dose in milligrams of rescue medication during the first 48 hours and at stabilization were summarized and presented together with the API scores.

All efficacy end points were examined for the population as a whole, by type of pain, and by previous opioid medication. Patients who were receiving >1 opioid before the study were converted to hydromorphone, based on the total daily opioid equivalents for all prestudy opioids.[10] For categorization purposes, these patients were grouped according to the previous opioid that converted to the highest number of hydromorphone equivalents based on dose and potency. This opioid was designated the predominant prestudy opioid.

Because the analyses were descriptive, observed data were used. The analyses were performed using data from 3 groups of patients: all those enrolled in the open-label phase, to determine the end-of-titration results from all patients (ie, last observation in titration); all those with complete data in the first 48 hours, to determine the results for the first 48 hours; and all those who reached stable pain control, to examine the effect of titration.

All AEs reported by the patient or observed by the investigator during the titration phase were documented and graded by the investigator for severity and probability of relationship to the study drug. AEs included symptoms of intercurrent illnesses. Each AE was counted once, regardless of the duration of the AE. *Treatment-emergent AEs* (ie, AEs that occurred for the first time during treatment or that became more severe after the first dose) were classified by *Coding Symbols for Thesaurus of Adverse Reaction Terms*[24] term and body system. *Serious AEs* were defined as any untoward medical occurrences that, at any dose, resulted in death, persistent or significant disability/incapacity, or a congenital anomaly/birth defect; were life threatening; or required inpatient hospitalization or prolongation of existing hospitalization, or an intervention to prevent permanent impairment or damage.

RESULTS

Patient Demographics and Disposition

A total of 344 patients were enrolled in the 2 studies. One patient was enrolled but did not receive any study drug. The safety population included 343 patients who converted to hydromorphone and received ≥1 dose of study drug. Complete data in the first 48 hours were available for 329 (96%) patients. Two hundred thirty-nine (70%) patients reached stable pain control as defined in the protocol.

The patient population was predominantly white (87% [299/343]) and had a mean age of 57.8 years (range, 22–85 years) (**Table III**). No patients aged <22 years enrolled in the study. One hundred twelve (33%) patients were aged ≥65 years and 41 (12%) were aged ≥75 years. Cancer-related pain was experienced by 272 (79%) patients. Among those with cancer-related pain, the most common predominant pain type was bone in 139 (51%) patients, followed by viscera in 53 (19%) patients and soft tissue in 51 (19%) patients. The remaining 71 (21%) patients had noncancer-related pain. Although noncancer-related pain could have multiple etiologies, the most common causes were osteoarthritis in 34 (48%) patients and intervertebral disc disease in 24 (34%) patients.

One hundred twenty (35%) of 343 patients were receiving >1 opioid before study entry. The predominant prestudy opioids are presented in **Table IV**. Oxycodone, the most frequent prestudy opioid, was used by 110 (32%) patients, followed by morphine in 72 (21%) patients and hydromorphone in 71 (21%) patients. Thirty-one (9%) patients were receiving transdermal fentanyl. Ninety-one (27%) patients were taking fixed-combination opioids as the predominant prestudy opioid.

One hundred twenty-six (37%) patients discontinued study participation during titration because of AEs (57 patients, including 15 whose AE was intercurrent illness not due to drug), ineffective treatment (40 patients, including 3 within the first 48 hours), other reasons (16 patients), protocol violations (10 patients), and death (3 patients). No deaths were related to the study medication; this is discussed in more detail in "Safety and Tolerability."

Assessment of First 48 Hours

Of the 343 patients who received ER hydromorphone HCl, 45 (13%) received a dose on day 1 that was greater than the rounded dose, 17 (5%) received

Table III. Demographic and baseline characteristics of patients with persistent cancer-related and noncancer-related pain who converted to extended-release hydromorphone hydrochloride from other opioids and received ≥1 dose of study drug (N = 343).

Variable	Value
Sex, no. (%)	
Female	174 (51)
Male	169 (49)
Race, no. (%)	
White	299 (87)
Black	32 (9)
Hispanic	8 (2)
Age, y	
Mean (SD)	57.8 (13.0)
Range	22–85
Pain category, no. (%)	
Cancer-related	272 (79)
Noncancer-related	71 (21)
Primary cancer site, no. (%)*	
Thorax	75 (28)
Breast	54 (20)
Digestive system	48 (17)
Genitourinary	41 (15)
Hematopoietic	32 (12)
Gynecologic	15 (6)
Head and neck	14 (5)
Skin	8 (3)
Musculoskeletal	6 (2)
Predominant cancer pain type, no. (%)	
Bone	139 (51)
Viscera	53 (19)
Soft tissue	51 (19)
Nerve	27 (10)
Primary nonmalignant disease, no. (%)*	
Osteoarthritis	34 (48)
Intervertebral disc disease	24 (34)
Nerve root entrapment	13 (18)
Spondylolisthesis	10 (14)
Rheumatoid arthritis	4 (6)

*Not mutually exclusive subcategories. Some patients with cancer had >1 primary cancer site and some patients with noncancer-related pain had >1 cause of pain. Overall, 272 patients had cancer-related pain and 71 had noncancer-related pain.

Table IV. Predominant prestudy opioid used by patients with persistent cancer-related or noncancer-related pain who converted to extended-release hydromorphone hydrochloride from other opioids (N = 343).

Prestudy Opioid*	No. (%) of Patients
Oxycodone	110 (32)
Morphine	72 (21)
Hydromorphone	71 (21)
Hydrocodone	43 (13)
Fentanyl	31 (9)
Codeine	6 (2)
Methadone	5 (1)
Propoxyphene	5 (1)

*In patients receiving >1 opioid at study entry, the predominant prestudy opioid was based on the dose and potency of the opioid whether administered as a single entity or in fixed combination. One hundred twenty (35%) patients were receiving >1 prestudy opioid.

a dose that was less than the rounded dose, and 281 (82%) received a dose that was the same as the rounded dose. The mean (SD) rounded dose of ER hydromorphone HCl was 20.1 (13.5) mg for all 343 patients, 21.3 (14.4) mg for patients with cancer-related pain, and 15.6 (8.0) mg for patients with noncancer-related pain.

Of the 329 patients with complete information on the adjustment of the rounded dose up to 48 hours, 272 (83%) had no change in dose. Adjustments to the rounded dose were based on the investigator's assessment of pain, use of rescue medication, and/or AEs at 48 hours, and were made for 57 (17%) patients: 51 (16%) titrated upward and 6 (2%) titrated downward. Dose adjustments resulted in a slight apparent change from the mean (SD) ER hydromorphone HCl rounded dose of 20.1 (13.5) mg to 21.2 (14.0) mg on day 1 and to 21.9 (14.0) mg on day 2 (**Figure 1**). Due to study design, none of these observations was assessed for statistical significance.

During the first 48 hours, the mean (SD) number of doses of rescue per day was 2.8 (1.6), a number equivalent to a mean (SD) daily hydromorphone dose of 10.7 (10.1) mg. Patients with noncancer-related pain used 3.3 doses of IR hydromorphone HCl compared with 2.7 doses in patients with cancer-related pain. These observations were not assessed for statistical significance.

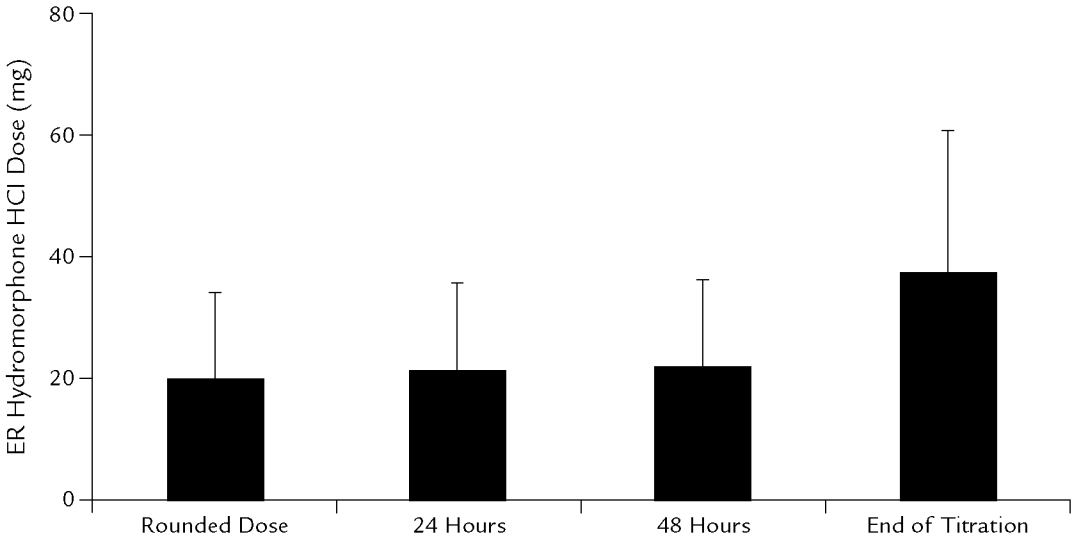

Figure 1. Mean (SD) extended-release hydromorphone hydrochloride (ER hydromorphone HCl) dose at the time of conversion, at 24 and 48 hours after conversion, and at the end of titration among 343 patients with persistent cancer-related and noncancer-related pain who converted to ER hydromorphone HCl from other opioids and received ≥1 dose of study drug.

Mean (SD) API scores for patients decreased slightly from 5.3 (2.1) at baseline to 4.7 (2.0) at 48 hours after conversion to ER hydromorphone HCl (**Figure 2**). These changes were observed in patients with both cancer- and noncancer-related pain, although patients with noncancer-related pain appeared to have higher pain scores than patients with cancer-related pain (6.8 vs 4.9 at baseline and 6.4 vs 4.3 at 48 hours); however, these observations were not assessed for statistical significance.

Assessment of Titration

At the end of 4 to 21 days of titration, 239 (70%) of 343 patients met the criteria for stabilization. The mean time to the protocol-defined criteria for stabilization for those patients who achieved stable pain control was 3.9 days (median, 2.0 days). The majority (90%) of the 239 patients were stabilized after ≤3 titrations. The mean (SD) ER hydromorphone HCl dose in the 239 patients was 32.4 (20.5) mg, an apparent increase from the mean rounded dose of 13.6 (17.8) mg (**Table V**); however, this was not assessed for statistical significance. Interestingly, patients with noncancer-related pain (n = 46) seemed to have a greater dose increase from the rounded dose to stabilization compared with patients with cancer-related pain (n = 193): 24.8 (17.8) mg versus 10.9 (16.8) mg; however, this was not assessed for significance.

One hundred two (43%) of the 239 patients who attained protocol-defined stabilization did not need to have their ER hydromorphone HCl doses adjusted to achieve stable pain control. Upward adjustments to the rounded dose to attain an API score of ≤4 were made for 129 (54%) patients. Eight (3%) patients had their rounded dose titrated downward due to AEs, but they still achieved the protocol-defined criteria for stabilization.

The mean (SD) dose of ER hydromorphone HCl at the end of titration (n = 343) was 37.2 (23.0) mg (**Figure 1**), an apparent increase in dose of 17.1 (19.2) mg from the rounded dose; this was not assessed for significance. Patients with noncancer-related pain (n = 71) appeared to have a greater increase in ER hydromorphone HCl dose than patients with cancer-related pain (n = 272): 26.4 (18.2) mg versus 14.7 (18.8) mg; statistical significance was not assessed. As expected, patients receiving oral IR hydromorphone HCl as the predominant prestudy opioid appeared to have a smaller mean (SD) increase (10.8 [17.2] mg) from the rounded dose compared with patients converted from morphine, oxycodone, hydrocodone, or fentanyl; statistical significance was not assessed.

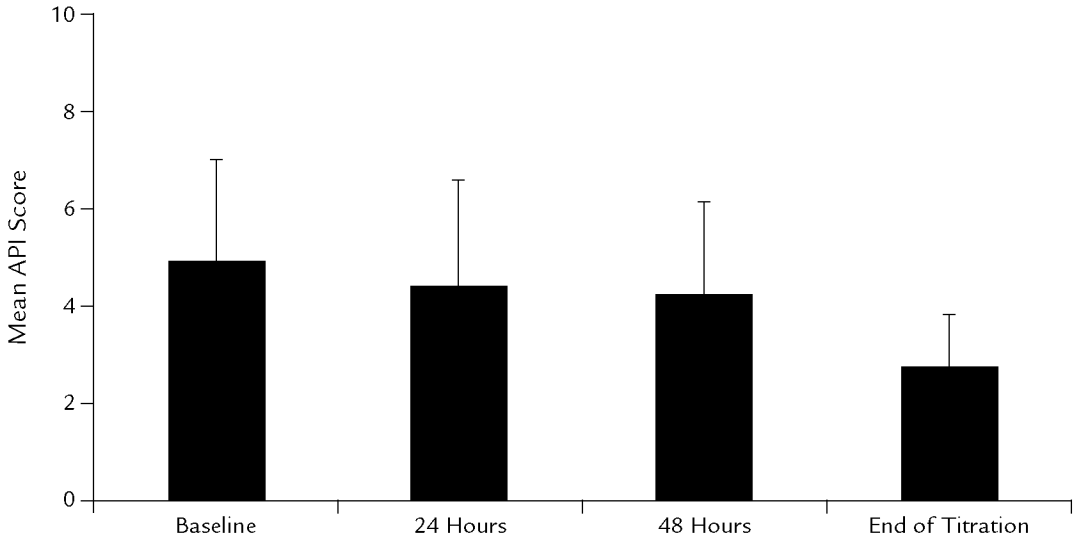

Figure 2. Mean (SD) average pain intensity (API) scores at the time of conversion, at 24 and 48 hours after conversion, and at the end of titration among 339 patients with persistent cancer-related and noncancer-related pain who converted to extended-release hydromorphone hydrochloride from other opioids. Pain was rated on a scale of 0 (no pain) to 10 (pain as bad as you can imagine).

Table V. Mean (SD) average pain intensity (API) scores and mean (SD) extended-release hydromorphone hydrochloride (ER hydromorphone HCl) doses at baseline, at 24 hours and 48 hours after conversion, and at dose stabilization, for patients achieving stable pain control.

Variable	No. of Patients*	Baseline	24 Hours	48 Hours	Stabilization
Mean (SD) API score†	238	4.9 (2.1)	4.4 (2.1)	4.2 (1.9)	2.7 (1.1)
Mean (SD) ER hydromorphone HCl dose, mg					
All patients	239	18.8 (11.6)‡	19.8 (12.4)	20.3 (12.0)	32.4 (20.5)
Patients with cancer-related pain	193	19.7 (12.2)‡	20.5 (12.8)	21.1 (12.5)	30.7 (20.2)
Patients with noncancer-related pain	46	15.1 (7.8)‡	17.0 (9.7)	17.0 (9.3)	39.9 (20.4)
Predominant prestudy opioid§					
Oxycodone	77	16.7 (9.2)	18.7 (11.6)	19.1 (11.7)	32.0 (21.5)
Hydromorphone	56	23.4 (15.3)	23.4 (15.9)	23.1 (15.3)	31.7 (21.9)
Morphine	47	19.7 (11.9)	20.4 (11.2)	20.7 (10.2)	33.5 (20.5)
Hydrocodone	30	13.6 (5.2)	14.4 (5.8)	15.4 (5.8)	33.2 (16.9)
Fentanyl	21	22.9 (11.3)	23.4 (12.3)	24.9 (12.9)	36.6 (20.3)
Codeine	3	12.0 (0)	16.0 (6.9)	18.0 (6.0)	20.0 (6.9)
Propoxyphene	3	12.0 (0)	12.0 (0)	12.0 (0)	12.0 (0)
Methadone	2	12.0 (0)	12.0 (0)	15.0 (4.2)	42.0 (25.5)

Stabilization = period of 48 hours with API score of ≤4, unchanged ER hydromorphone HCl dose, and ≤2 rescue doses per day.
*Number of patients in each subgroup with complete data at baseline and at dose stabilization.
†Pain was rated on a scale of 0 (no pain) to 10 (pain as bad as you can imagine).
‡Rounded dose.
§In patients receiving >1 opioid at study entry, the predominant prestudy opioid was based on the dose and potency of the opioid whether administered as a single entity or in fixed combination.

The mean (SD) number of daily doses of rescue medication used at the end of titration was 1.5 (1.3). The mean (SD) daily dose of IR hydromorphone HCl at the end of titration was 10.6 (12.8) mg. At the end of titration, patients with noncancer-related pain received a mean (SD) IR hydromorphone HCl dose of 12 (10.2) mg compared with a mean dose of 10 (13.4) mg in patients with cancer-related pain.

At the end of titration, the mean (SD) API score was 3.4 (2.1) for the 343 patients, compared with a baseline score of 5.3 (2.1) (**Figure 2**). For the 239 patients who achieved stabilization as defined by the protocol, mean (SD) API scores were 4.9 (2.1) at baseline and 2.7 (1.1) at stabilization (**Table V**). For the 102 patients who required no change in their rounded dose to achieve stabilization, mean (SD) API scores were 4.2 (2.0) at baseline and 2.5 (1.1) at stabilization.

Safety and Tolerability

Treatment-emergent AEs that occurred during the first 48 hours and those that occurred during the entire titration phase are summarized in **Table VI.** The cumulative incidence of AEs was higher during the entire titration phase compared with the first 48 hours (92% vs 75%), probably because patients were monitored for a longer period of time; however, the nature and daily incidence of AEs reported during the 2 periods were similar.

Of the 343 patients who received ER hydromorphone HCl during the titration phase, 315 (92%) experienced treatment-emergent AEs. In 285 (83%) patients, treatment-emergent AEs were considered to be related to the study drug. Most AEs were mild to moderate; 94 (27%) patients experienced severe AEs. The most frequently occurring (≥10% incidence) treatment-emergent AEs were nausea, constipation, somnolence, vomiting, dizziness, headache, and asthenia. These AEs are typically reported with the use of opioid analgesics.[3,12,15] Fifty-seven (17%) patients discontinued because of AEs during the titration phase, including 15 patients whose AE was intercurrent illness not due to the drug; 7 (2%) of the patients discontinued during the first 48 hours after conversion. It should be noted that different AE profiles may be observed when converting from one opioid to another. The most common AEs resulting in discontinuation during the titration phase were typical opioid-associated AEs[3,12,15] and included confusion, somnolence, constipation, nausea, vomiting, dizziness, hallucinations, and headache.

Table VI. Cumulative incidence and most frequently reported (≥10% of patients) treatment-emergent adverse events (AEs) during the first 48 hours and during the entire titration phase among patients with persistent cancer- and noncancer-related pain who converted to extended-release hydromorphone hydrochloride from other opioids and received ≥1 dose of study drug (N = 343).

Variable	No. (%) of Patients
During the first 48 hours	
Patients reporting AEs	258 (75)
Most frequently reported AEs	
Nausea	88 (26)
Somnolence	60 (17)
Headache	48 (14)
Constipation	47 (14)
Vomiting	38 (11)
Dizziness	35 (10)
During the entire titration phase	
Patients reporting AEs	315 (92)
Most frequently reported AEs	
Nausea	154 (45)
Constipation	129 (38)
Somnolence	117 (34)
Vomiting	81 (24)
Dizziness	78 (23)
Headache	73 (21)
Asthenia	52 (15)

Serious AEs occurred in 48 (14%) patients during the titration phase. The most common reason for defining the AE as serious was the requirement of hospitalization. These serious AEs included infection (2 patients), fever (5 patients), pneumonia (5 patients), abdominal pain (1 patient), hematemesis (1 patient), nausea (2 patients), vomiting (1 patient), headache (2 patients), constipation (1 patient), asthenia (2 patients), somnolence (2 patients), pleural effusion (2 patients), thrombocytopenia (1 patient), leukopenia (1 patient), hallucinations (1 patient), liver failure (1 patient), diarrhea (2 patients), skin melanoma (1 patient), confusion (2 patients), pelvic pain (1 patient), thrombophlebitis (1 patient), metastatic lung carcinoma (1 patient), dehydration (7 patients), and death (7 patients). The total number of deaths was greater than the number of discontinuations due to death because

4 patients died after previously discontinuing due to other AEs. The causes of death were progressive malignancy (6 patients) and cardiac arrest (1 patient), and were not considered to be related to the study drug. Some of these serious AEs, such as nausea, constipation, headache, somnolence, and hallucinations, are typical of opioids.[3,12,15] However, most serious AEs were considered by the investigator to be a consequence of or associated with the patient's underlying disease and not related to the study drug. Ten (3%) patients experienced serious AEs in the first 48 hours. No occurrence of opioid-related respiratory depression was observed during the titration phase.

Three (1%) patients discontinued during titration due to death; no deaths occurred during the first 48 hours. One patient was hospitalized for hypercarbia and somnolence and died of respiratory failure secondary to progressive non–small-cell lung cancer. The second patient was hospitalized for the management of anorexia, nausea, vomiting, dehydration, hypovolemia, hypotension, and neutropenia, and died of causes directly related to progression of metastatic cancer involving the lung and liver. The third patient, with a diagnosis of metastatic bladder cancer, was hospitalized for hypercalcemia and died of pulmonary embolus. All deaths were considered by the investigator to have been a consequence of or associated with the patient's underlying malignancy and unrelated to the study drug.

AEs that could be associated with withdrawal symptoms (eg, anxiety, yawning, perspiring, tearing eyes, runny nose, goose flesh, shaking, hot flashes, cold flashes, aching bones and muscles, restlessness, nausea, twitching muscles, cramps) were evaluated. Eight (2%) patients reported ≥3 of these symptoms within the first 48 hours of conversion from their prestudy opioids.

DISCUSSION

Results of the titration phase after conversion from previous opioid regimens to ER hydromorphone HCl suggested that a conversion ratio of approximately 8:1 mg of oral morphine to oral ER hydromorphone HCl was clinically useful and well tolerated in this study population. During the first 48 hours, only 7 (2%) of 343 patients discontinued the study because of AEs and only 3 (1%) because of lack of efficacy. However, it should be noted that the open design may have influenced the assessment of the association and severity of the AEs.

The mean API score at study entry was 5.3 on a 0- to 10-point numeric rating scale. The objective of titration was to control the patient's pain to an API score of ≤4. Seventy percent (239/343) of the patients who received ER hydromorphone HCl fulfilled the criteria for stabilization (ie, a period of 48 hours with an API score of ≤4, an unchanged dose of ER hydromorphone HCl, and ≤2 doses of rescue per day). The overall 45% reduction in pain in the 239 patients who achieved stabilization with a 72% increase in dose is comparable with the 2-fold increase in dose observed in some dose-response studies.[8,25,26] For example, in a randomized, single-dose, double-blind, placebo-controlled study, a 2-fold increase in dose of controlled-release oxycodone from 10 mg to 20 mg led to a 32% increase in overall pain relief.[25] Such dose-response studies typically involve administering various fixed doses of opioid analgesics and measuring the analgesic response.

Calculation of a conversion dose is only a first step in attaining stable pain control with opioid analgesics. Every patient's dose is individualized according to his or her clinical history and present clinical status. The 8:1 conversion ratio provided a well-tolerated initial dose in the population studied. In addition, the rounded dose of ER hydromorphone HCl in 30% (102/343) of the patients was sufficient to attain the goal of stabilization (ie, an API score of ≤4). The rounded dose in these patients resulted in a 40% decrease in pain with no further dose adjustment needed. In 8 (2%) patients, better analgesia was observed at a dose lower than the rounded dose, a finding that is consistent with the wide interindividual responsiveness to opioid analgesics.[12]

Out of 343 patients, 129 (38%) required an increase from their rounded doses. This finding raises the question of whether these patients were undertreated with their initial doses of ER hydromorphone HCl. If patients had not been receiving comparable doses of opioids after conversion, more might have been expected to exhibit symptoms of opioid withdrawal. Only 8 (2%) patients in this study exhibited ≥3 AEs in the first 48 hours that were considered possibly related to withdrawal, a finding that suggests that the 8:1 conversion ratio did not significantly underestimate the necessary dose of oral hydromorphone. Moreover, dose adjustment was encouraged to achieve a higher level of pain control than that obtained prior to enrollment. Ninety-one (27%) patients were receiving fixed-combination opioids as the predominant prestudy opioid, and the conversion calcu-

lation was based on only the opioid component. However, nearly half of these patients did not require dose adjustment after converting to ER hydromorphone HCl and still showed a pain reduction. This finding may be explained by incomplete cross-tolerance between opioids.

Relative potency ratios should not always be strictly followed when substituting one opioid analgesic for another, because the clinical setting and patient status may dictate the use of a dose somewhat different than that suggested by the relative potency ratio alone. Although some conversion ratios are derived from well-controlled relative potency studies, conflicting recommendations, largely based on clinical experience, appear in the literature. For example, the American Pain Society noted that the equianalgesic dose of 3:1 of oral to parenteral morphine in its conversion table was based on clinical observations of repeated administration and was not from data derived from well-controlled, single-dose comparison trials that used a 6:1 ratio.[12]

Single-dose studies are an appropriate method for comparing analgesic efficacy and potency, as are onset, peak, and duration of effect in many cases.[26,27] A well-controlled relative potency study of parenteral morphine and hydromorphone in patients with postoperative pain resulted in ratios ranging from 8.3:1 to 11.1:1.[19] The first study of the equianalgesic dose of morphine and hydromorphone in patients with cancer pain indicated a potency of parenteral morphine to hydromorphone of 7.9:1.[19] If single-dose relative potency studies showed that oral morphine was one sixth as potent as IM morphine[28] and that 10 mg of IM morphine was equianalgesic to 1.3 mg of IM hydromorphone[19] (which is 5 times more potent than oral hydromorphone),[3,20] then 60 mg of oral morphine and 7.5 mg of oral hydromorphone would be approximately equianalgesic. The results of the present analysis suggest a conversion ratio of 8:1 for the oral ER hydromorphone HCl formulation. In a repeated-dose study in patients with cancer-related pain, controlled-release hydromorphone q12h and controlled-release morphine q12h provided equivalent analgesia at a conversion ratio of 7.5:1.[21]

It cannot be overemphasized that conversion ratios are an initial approximation and that individual circumstances for each patient influence the calculation of the new opioid dose.[4,10,12,15] Consistent with published guidelines, close monitoring of patients is recommended with further titration after the initial conversion from one opioid agonist to another.

Qualifications to the present evaluation include the fact that the statistical analyses were descriptive rather than inferential and the study design was open (ie, nonblinded). Regarding the rate of discontinuation (37%), it is comparable with those reported in clinical studies involving opioid analgesics.[29] In clinical studies that detail discontinuations during titration periods, rates >20% have been reported.[30,31]

CONCLUSION

In this prospective evaluation of the conversion and titration phase of 2 randomized, controlled studies, a conversion ratio of 8:1 mg of prestudy opioid to oral ER hydromorphone HCl was found to be clinically useful in patients with persistent moderate to severe cancer-related or noncancer-related pain.

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