Advances in the Long-Term Management of Chronic Pain: Recent Evidence with OROS® Hydromorphone, a Novel, Once-Daily, Long-Acting Opioid Analgesic

Clinical Trial Results with OROS® Hydromorphone

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Abstract
OROS® hydromorphone is a unique drug delivery system being evaluated for the once-daily oral treatment of moderate to severe chronic pain. Results of dose conversion studies indicate that most patients can be successfully titrated from prior opioid therapy to OROS® hydromorphone using a 5:1 ratio to convert oral morphine equivalents to OROS® hydromorphone in up to two dose titration steps. OROS® hydromorphone is effective in both chronic cancer pain and chronic noncancer pain of moderate to severe intensity. It is at least as effective at controlling chronic pain, reducing the impact of pain on functionality, and improving quality of life as controlled-release morphine (cancer pain) and extended-release oxycodone (osteoarthritis pain). In all studies, OROS® hydromorphone was generally well tolerated, with an adverse event profile similar to that of other long-acting opioid analgesics. J Pain Symptom Manage 2007;33:S25–S32. *© 2007 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Hydromorphone, pain, osteoarthritis, low back pain, opioid analgesics

Introduction

OROS® hydromorphone is an osmotically controlled delivery system that was designed by ALZA Corporation (Mountain View, CA, USA) to provide sustained relief from chronic pain with once-daily oral administration. Early investigations confirmed that hydromorphone is released from this unique delivery system continuously over a 24-hour period,[1] producing sustained, dose-dependent, long-acting analgesia.[2] The use of OROS® hydromorphone has been evaluated in clinical studies involving more than 700 patients with chronic pain in North America and Europe.[3] The populations studied include patients with chronic cancer pain and those with chronic noncancer pain (including low back pain and osteoarthritis). This article reviews recently released data from several short-term studies, including dose conversion studies and comparison studies with other commonly prescribed long-acting opioids (twice-daily controlled-release morphine and twice-daily extended-release oxycodone).

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Dose Conversion Studies

Hydromorphone is a potent opioid analgesic that was introduced clinically for the treatment of pain in 1926;[4] initial doses for patients switching from other oral opioids to oral hydromorphone typically are calculated using conversion ratios of 5:1 to 7.5:1 morphine equivalents to oral hydromorphone (in milligrams).[5] Results of early nonrandomized, open-label, dose conversion studies support a 5:1 ratio to convert oral morphine equivalents to OROS® hydromorphone.[6] These studies were conducted at 48 U.S. and Canadian centers. All studies were conducted in three phases: a prior opioid-stabilization phase, a conversion phase, and a maintenance phase. During the initial phase, doses of opioids were titrated to stability (stable dose requiring ≤3 doses of rescue medication per day for three consecutive days). The duration of this phase ranged from 3 to 40 days. In the second phase, investigators used a 5:1 ratio to convert oral morphine equivalents to once-daily OROS® hydromorphone and titrated doses to stability. The duration of the second phase ranged from 3 to 21 days. OROS® hydromorphone therapy was continued at stable doses for 14 days in the final phase. Efficacy was evaluated using the Brief Pain Inventory (BPI),[7] rescue-medication use, pain relief assessment, and patient and investigator evaluations of overall effect. A total of 404 patients participated in these studies (54% women; mean age, 50 years). Approximately 68% of patients completed the studies, with 38 (9%) and 50 (12%) patients discontinuing prematurely because of lack of efficacy and adverse events, respectively. The studies included 73 (18%) patients with chronic cancer pain as well as 331 (82%) patients with chronic noncancer pain. At baseline, approximately 81% of patients were receiving single-entity opioid therapy, and 19% were receiving multiple opioids (overall, oxycodone [38%], morphine [24%], hydrocodone [16%], fentanyl transdermal therapeutic system [9%], hydromorphone [8%], methadone [7%], or codeine [3%]) at doses equivalent to 15 to 2028 mg of morphine daily (mean, 150.3 mg) (Table 1). The mean initial dose of OROS® hydromorphone was 31.8 mg. Most of the patients (73.8%) underwent successful conversion from prior opioid therapy to stable OROS® hydromorphone doses, with 20.8% of these patients requiring no dose titration, 49.3% requiring one or fewer titration steps, and 70.1% requiring two or fewer dose titration steps. After seven days, significant reductions in the interference of pain with daily function were observed (Fig. 1). These findings indicate that conversion from other opioids (in morphine equivalents) to OROS® hydromorphone should be initiated using a 5:1 ratio.

Table 1
Baseline Characteristics of Subjects Participating in Dose Conversion Studies

	Mean Daily Oral Morphine Equivalent Requirement (mg): Amount (range)
Total patients	150.3 (15–2028)
Chronic cancer pain	166.4 (32–960)
Chronic noncancer pain	146.8 (15–2028)
Prior opioid class	Number (%) of patients
Single entity	326 (80.7)
Combination	78 (19.3)

Data on file, ALZA Corporation.[3]

Efficacy and Safety

Chronic Cancer Pain: OROS® Hydromorphone Versus Sustained-Release Morphine

Results of a randomized, double-blind study conducted in 37 centers in Europe and Canada showed that once-daily OROS® hydromorphone is at least as effective as twice-daily, sustained-release morphine for the management of severe chronic cancer pain.[8] A total of 200 patients with chronic cancer pain participated in this two-phase study, they were assigned randomly to receive either immediate-release hydromorphone for 2 to 9 days followed by once-daily OROS® hydromorphone for 10 to 15 days or immediate-release morphine for 2 to 9 days followed by twice-daily, controlled-release morphine for 10 to 15 days. The primary efficacy outcome measure was the BPI worst pain in the past 24 hours item, which is scored on a scale of 0 to 10 (higher scores indicating greater pain). Equivalence was predefined as a 95% confidence interval (CI) of the treatment difference at end point within −1.5 and 1.5. Secondary outcome