

Results of an Open-label Dose Conversion and Titration Study of Once-Daily Hydromorphone ER in Opioid-Tolerant Patients With Chronic Low Back Pain

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Purpose

This analysis was designed to assess successful dose conversion and titration for once-daily hydromorphone extended-release (ER) in opioid-tolerant patients with moderate to severe chronic low back pain. This study was conducted as part of a placebo-controlled trial employing an enriched enrollment randomized withdrawal (EERW) design. The conversion and titration phase employed individualized conversion and titration over 2-4 weeks in order to identify patients with an effective dose of once-daily hydromorphone ER for continuation into the double-blind phase of the study. An effective dose was a dose that provided meaningful pain relief with tolerable adverse effects. The subsequent placebo-controlled trial was used to assess the ability of once-daily hydromorphone ER to sustain efficacy over 12 weeks compared with placebo in the group of patients for whom active treatment was withdrawn. This analysis describes the results of the conversion and titration phase of this trial, in which a large group of opioid-tolerant patients with moderate to severe chronic low back pain were converted from other opioids to once-daily hydromorphone ER.

Method

In this 2- to 4-week open-label study, opioid-tolerant patients with chronic moderate to severe low back pain received once-daily hydromorphone ER tablets at doses of 12-64 mg/d. Patients were initially converted to a dose of once-daily hydromorphone ER that was approximately 75% of the equianalgesic dose of their previous total daily opioid dose. Two dose titration increases were permitted per week based on investigator evaluations of daily pain intensity as well as tolerability. Pain intensity was assessed by Numeric Rating Scale (NRS) scores recorded in patient diaries (0=no pain; 10=worst possible pain). Hydromorphone immediate-release rescue medication was permitted throughout the study. The definition of stable dose included all of the following: (1) daily dose of 12-64 mg; (2) no dose change for ≥ 7 days (stable dose period); (3) ≤ 2 tablets/day of rescue medication during the stable dose period; (4) mean NRS pain intensity score ≤ 4 during the stable dose period; (5) answer of "yes" to whether the medication helped pain enough to continue taking the medication; and (6) no adverse events that were intolerable or could impact patients' ability to complete the study.

Results

A total of 447 patients (mean age, 49.0 \pm 10.43 y; 50.8% male; 85.7% white) enrolled in the study and took at least 1 dose of once-daily hydromorphone ER. Of these, 27 patients (6.0%) were 65 years of age or older. The overall mean duration of exposure to once-daily hydromorphone ER was 20.1 \pm 9.58 days. A total of 60.0% of patients achieved a stable dose (n=268), with a mean duration of exposure of 23.4 \pm 7.84 days in this group. The most common initial dose of study medication was 12 mg/d (42.5%), and the most common final dose was 64 mg/d (21.8%). Mean dose at the end of the conversion and titration phase was 37.8 \pm 17.4 mg. The mean number of rescue medication tablets per day by patient was 2.7 over the first 3 days of the conversion and titration phase; by the time stable dose was achieved, the mean was < 1 tablet per day. Mean NRS pain intensity scores were reduced by 50% at the end of the conversion and titration phase compared with scores at screening (3.2 \pm 1.0 vs 6.4 \pm 1.91). Adverse events (AEs) occurred in 55.3% (n=247) of patients. The most common AEs were constipation in 15.4% (n=69) of patients, nausea in 11.9% (n=53), somnolence in 8.7% (n=39), and headache in 7.8% (n=35). There were no deaths; 1.3% (n=6) of patients had a serious AE; and 13.0% (n=58) of patients discontinued due to an AE.

Conclusions

This study in opioid-tolerant patients with moderate to severe chronic low back pain demonstrated that these patients can be safely and effectively converted to once-daily hydromorphone ER. Hydromorphone ER reduced NRS pain intensity scores by 50% during this open-label study. Hydromorphone ER was well tolerated, with no unexpected safety concerns.