Original Article

Comparative Efficacy of Oral Extended-Release Hydromorphone and Immediate-Release Hydromorphone in Patients with Persistent Moderate to Severe Pain: Two Randomized Controlled Trials

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Abstract

Two multicenter, randomized, double-blind, crossover studies with identical designs evaluated the efficacy of oral extended-release hydromorphone (HHER) administered q24h compared with immediate-release hydromorphone (HHIR) dosed four times daily in patients with persistent moderate to severe pain. Patients titrated to a stable HHER dose were randomized to individualized doses of HHER or HHIR for 3 to 7 days before crossover to the second treatment. Primary efficacy end point was the mean of average pain intensity (API) scores, rated on a 0- to 10-point numeric scale, over the last 2 days before the pharmacokinetics/pharmacodynamics day of each double-blind period. Difference between treatments (HHER − HHIR) in study 1 was 0.17 with a 90% confidence interval (CI) (−0.01, 0.34); in study 2, difference was 0.07 with a 90% CI (−0.12, 0.26). There were no significant differences between treatments in API scores or amount of rescue medication used at any time interval within the 24-hour dosing period. No reduction in pain control occurred in patients administered HHER at the end of the 24-hour dosing period. Most treatment-emergent adverse events were opioid-related. In these studies, HHER administered q24h and HHIR dosed four times daily provided comparable analgesia at an equivalent total daily dose. J Pain Symptom Manage 2005;29:584–594. © *2005 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words

Analgesics, opioid, hydromorphone, extended-release, pain

Introduction

Hydromorphone hydrochloride is a μ-opioid agonist with dose-dependent analgesic properties. Hydromorphone has no ceiling effect for analgesia; the dose can be titrated to relieve

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most types of moderate to severe pain with tolerable or manageable side effects.[1–3] Hydromorphone is commonly prescribed as an alternative to morphine, fentanyl, or oxycodone for the management of moderate to severe pain.[4–6] Estimates of the relative analgesic potency of hydromorphone and morphine from single-dose studies indicate that 7.5 mg of oral hydromorphone is equianalgesic to 60 mg of oral morphine.[1] In repeated-dose studies in patients with cancer-related pain, oral controlled-release hydromorphone was 7.5 times more potent than oral controlled-release morphine[7] and 4 times more potent than oral controlled-release oxycodone.[8] Each drug was administered twice daily.

The immediate-release hydromorphone (HHIR) tablet formulation available in the United States is indicated for administration every 4 to 6 hours. A 12-hour controlled-release hydromorphone capsule is available in Canada and has been approved for use in 13 member states of the European Union, in Switzerland, and in several eastern European countries. This formulation has been reported to be effective and safe in randomized controlled studies in patients with moderate to severe pain.[5,7,8]

A new extended-release formulation of hydromorphone hydrochloride (HHER) has been developed in capsule strengths of 12, 16, 24, and 32 mg for dosing every 24 hours. On approval by the Food and Drug Administration, this product will be marketed as Palladone capsules. The steady-state pharmacokinetics of hydromorphone in plasma following q24h HHER administration have been characterized.[9,10] Two studies were conducted to assess the efficacy and safety of HHER in patients who were currently receiving opioids for persistent moderate to severe cancer- or non–cancer-related pain.

Methods

Study Population

Two identically designed multicenter studies enrolled 344 patients with persistent moderate to severe cancer- or non–cancer-related pain. These studies were conducted according to the Declaration of Helsinki and were approved by institutional review boards at each of 37 sites in the United States. All patients gave written informed consent.

Male and female patients ≥10 years of age with persistent cancer-related pain or ≥18 years of age with persistent non–cancer-related pain requiring treatment with opioid analgesics were eligible to participate. The diagnosis of persistent non–cancer-related pain was based on clinical evidence of osteoarthritis, rheumatoid arthritis, intervertebral disc disease, spondylolisthesis, nerve entrapment, or similar conditions. Patients had been treated with single-entity or fixed-combination opioid analgesics for at least the prior 2 weeks. The required total daily dose of the previous opioid analgesics had to be equivalent to ≥90 mg of oral morphine (at least 12 mg of oral hydromorphone) at study entry. If patients also were treated with nonopioid analgesics or nonopioid medications with analgesic properties, the dosage regimens had to be stable (not prn) for at least 2 days prior to entry. Coexisting disease states and related therapy had to be stable for at least the last week. Patients had to be able to be contacted by telephone and had to be willing and able to participate in all aspects of each study including use of oral medications, subjective evaluations, diary completion, and phlebotomy.

Patients were excluded if they had a history of allergy to hydromorphone or a contraindication to opioid therapy including paralytic ileus or severe pulmonary disease; were unable to swallow solid oral dosage forms; were using another investigational drug or device, or received strontium chloride 89 within the previous 30 days; planned surgery or other procedures during the 35-day period after the baseline visit that would prevent study completion; had concurrent medical conditions that posed an increased risk to administration of the study drug, or could confound or obscure efficacy assessments; or were women who were pregnant or lactating, or who were of childbearing potential and did not use contraception. Patients with non–cancer-related pain also were excluded if they had a past or present history of substance abuse; were currently involved in litigation or arbitration related to their pain and/or injury; or had received intra-articular or intramuscular steroid injections to the site of their pain within the last 6 weeks.

Study Design and Drug Treatment

Each study was a multicenter, randomized, double-blind, two-period crossover comparison