Hydromorphone: Evolving to Meet the Challenges of Today's Health Care Environment

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ABSTRACT

Background: Hydromorphone, a potent analogue of morphine, has long had an important role in pain management and is included in several international guidelines for managing pain. Advances in hydromorphone formulations and the ways in which hydromorphone is being used clinically today warrant a review of the drug's pharmacotherapeutic utility.

Objective: The history and recent advances in hydromorphone pharmacotherapy are reviewed. Areas covered include the pharmacologic and metabolic profile of hydromorphone, the role of hydromorphone in pain management, formulations and routes of administration, and issues related to relative opioid potencies, equianalgesic ratios, and opioid rotation. Because hydromorphone, like all opioids, carries a risk of misuse, abuse, and illicit diversion, the related issues of tamper-resistant formulations and "dose-dumping" of extended-release formulations are discussed.

Conclusions: Due to the epidemic of prescription opioid overdoses associated with prescription opioid abuse in the United States, development of tamper-resistant opioid formulations that avoid dose-dumping issues has become a significant goal of pharmaceutical manufacturers. The current formulation of hydromorphone extended-release potentially provides the benefits of long-acting hydromorphone (ie, continuous pain control, increased quality of life, freedom to perform daily activities) to appropriate patients, while reducing the risks of abuse and without compromising safety. (*Clin Ther*. 2013;35:2007–2027)

Key words: extended-release, hydromorphone, opioids, pain.

INTRODUCTION

Hydromorphone, a hydrogenated ketone analogue of morphine, is widely used as an alternative to morphine for the relief of acute and chronic pain[1,2] and has a long history in pain treatment. Hydromorphone was first synthesized in Germany in 1921 and has been available for clinical use since 1926.[2] The first immediate-release (IR) oral formulation of hydromorphone* was approved by the US Food and Drug Administration (FDA) in 1984.[3] Twenty years later, an extended-release (ER) formulation of hydromorphone was approved,† only to be removed from the market in 2005 because of the risk of immediate release of hydromorphone through interaction with alcohol (ie, "dose-dumping"), which could result in possible overdose.[4,5]

An ER hydromorphone tablet, formulated with an osmotic oral delivery system,‡[6] was approved in Denmark in 2004§ and marketed in several countries for the treatment of moderate to severe pain.[7] Postmarketing experience with the osmotic oral delivery system has shown a safety profile consistent with other μ-opioid agonist analgesics.[7] In 2010, the FDA approved an ER hydromorphone tablet‖ identical to the version approved in Denmark.[7,8]

The present article reviews the history of and recent advances in hydromorphone pharmacotherapy, including the drug's place in guidelines; pharmacologic and metabolic profile; role in pain management; formulations and routes of administration; and issues

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

†Trademark: Palladone™ (Purdue Pharma LP).

‡Trademark: OROS® Push-Pull™ (Alza Corporation, Mountain View, California).

§Trademark: Jurnista® (Janssen-Cilag Pty Ltd, Auckland, New Zealand).

‖Trademark: Exalgo® (Mallinckrodt Inc, Hazelwood, Missouri).

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related to relative opioid potencies, equianalgesic ratios, and opioid rotation. Because hydromorphone, like all opioids, carries a risk of misuse, abuse, and illicit diversion, the related issues of tamper-resistant formulations and dose-dumping of ER formulations are discussed.

METHODS

A literature search was conducted to find published articles relating to the pharmacologic properties, metabolic profile, formulations, and routes of administration of hydromorphone, as well as clinical studies of the drug in the management of pain. MEDLINE searches were restricted to articles in English, did not restrict date of publication, and included the search terms *hydromorphone, pharmacokinetics, metabolism, administration, equia- nalgesic ratio, and opioid rotation*. A separate search included the search term hydromorphone, with a filter for clinical trials and reviews. Bibliographies from articles retrieved were manually reviewed for additional relevant publications.

PHARMACOLOGIC AND METABOLIC PROFILE

Hydromorphone has a pharmacologic profile similar to that of morphine, although hydromorphone is more potent on a milligram-comparable basis.[9] Hydromorphone is among the most potent of the prescribed morphinan opioids (eg, morphine, oxycodone). As with all full μ-opioid agonists, when the dose of hydromorphone is increased, analgesia increases in a log-linear fashion. The analgesic dose of hydromorphone has no ceiling effect, and increases are limited only by intolerable, dose-dependent adverse effects.[10] Hydromorphone possesses the effects of endogenous opioid peptides by interacting primarily with the μ-opioid receptor and exerts classic opioid effects such as analgesia, respiratory depression, sedation, nausea, vomiting, constipation, pupillary constriction, and euphoria or dysphoria.[11,12] Hydromorphone is 10 times more lipid-soluble than morphine[11]; most equianalgesic tables indicate that hydromorphone is 7 times more potent than morphine when given parenterally and between 4 and 8 times more potent than morphine when given orally.[9]

Although hydromorphone has these notable characteristics in common with morphine and other opioids, the manner in which hydromorphone is metabolized is an important differentiating characteristic. Hydromorphone is largely metabolized in first-pass phase II metabolism by glucuronidation.[13] Unlike other opioids, such as oxycodone and codeine, hydromorphone is not metabolized by the cytochrome P-450 enzyme pathway, thus reducing the potential for significant drug–drug interactions.[14,15] Metabolites of hydromorphone are dihydromorphine, dihydroisomorphine, hydromorphone-3-glucuronide (H3G), and hydromorphone-6-glucuronide (H6G).[16] H6G, to which hydromorphone is largely metabolized, seems to lack analgesic activity, whereas the analgesic activity of the other metabolites of hydromorphone is uncertain.[13,16] Animal studies have shown that H3G causes neuroexcitatory effects.[17,18] This mechanism may be responsible for the occurrence of myoclonus and seizures, which have been described in a small number of patients who received extremely high doses of parenteral hydromorphone.[19,20] Total hydromorphone doses administered for the 24 hours before the seizures occurred were equianalgesic to the equivalent of ~400 to 450 mg/kg of morphine.[20]

Hydromorphone is an important metabolite of hydrocodone.[21] In extensive metabolizers, who constitute ~90% of the white population in the United States, a 10-mg dose of hydrocodone yields appreciable plasma levels of hydromorphone.[21,22] The extent to which the analgesic and nonanalgesic effects of hydrocodone are attributable to the hydromorphone metabolite remains to be clarified.

REPRESENTATION IN INTERNATIONAL GUIDELINES

Hydromorphone is represented in several international guidelines for the treatment of pain. For the management of chronic cancer pain, including breakthrough pain, the World Health Organization uses a model of a 3-step ladder, in which step 1 therapy consists of nonopioid analgesics with or without adjuvant therapy. For persistent or increasing pain, an opioid for mild to moderate pain (eg, tramadol, codeine) might be added. If this combination fails to relieve the pain or if the pain increases, an opioid for moderate to severe pain (eg, morphine, methadone, hydromorphone, oxycodone, fentanyl) should be substituted.[23,24]

Recommendations issued by Italian Society of Anesthesia, Analgesia, and Intensive Care largely agree with the approach of the World Health Organization; however, the organization proposes conflating steps 1 and 2 into a single step and adding a fourth