Proceedings of the Symposium "Updates of the Clinical Pharmacology of Opioids with Special Attention to Long-Acting Drugs"

Hydromorphone

Alison Murray, MD, CCFP, MPH and Neil A. Hagen, MD, FRCPC (Neurology)
Department of Family Medicine (A.M.), Division of Palliative Medicine (A.M., N.A.H.), and Departments of Clinical Neurosciences and Medicine (N.A.H.), University of Calgary; and Tom Baker Cancer Center (A.M., N.A.H.), Calgary, Alberta, Canada

Abstract

Hydromorphone is a semi-synthetic opioid that has been used widely for acute pain, chronic cancer pain and to a lesser extent, in chronic nonmalignant pain. Its pharmacokinetics and pharmacodynamics have been well studied, including immediate release oral preparations, a variety of slow release oral preparations, as well as administration through intravenous, subcutaneous, epidural, intrathecal and other routes. It is known to be metabolized to analgesically inactive metabolites that have been associated with neuroexcitatory states and other toxicity. There is no evidence that hydromorphone has any greater abuse liability than other opioids. Further research is needed to address remaining areas of uncertainty: equianalgesic ratios; relative risk of toxicity compared with other opioids, its use in nonmalignant pain, and the role of specific hydromorophone metabolites in the development of toxicity, particularly in association with organ failure. J Pain Symptom Manage 2005;29:S57–S66.

History

Hydromorphone is a semi-synthetic opioid agonist and a hydrogenated ketone of morphine.[1] It was first synthesized in Germany in 1921 and was introduced into clinical practice by 1926. Although there were over 200 publications supporting its pain relieving qualities within ten years of its introduction to clinical medicine, hydromorphone has commonly been viewed as a second-line drug to morphine in the treatment of both acute and chronic pain.[1] Oral morphine is the drug of first choice for chronic cancer pain as recommended by the World Health Organization,[2] because of its global availability and the extensive clinical experience and pharmacokinetic and pharmacodynamic data available.[3] Despite this recommendation, a significant proportion of patients do not achieve adequate pain relief with morphine, commonly because of unmanageable adverse effects such as nausea, delirium, or myoclonus. It has been shown that rotating from one opioid to another can improve pain control as well as reduce opioid-related toxicity, although the mechanisms are unclear.[4–7] Therefore, hydromorphone has a key role in the area of chronic and acute pain relief as an alternative to morphine. It is included in clinical practice guidelines for the management of pain secondary to cancer[2,8] and has been well studied as an analgesic for post-operative pain.[9–11]

Raymond W. Houde and Ada Rogers started an informal group called the New York Pain Group in the early 1960s and went on to co-found the American Pain Society in the late 1970s. Houde is professor emeritus at Memorial

Address reprint requests to: Neil A. Hagen, MD, FRCPC, 1331-29 St. NW, Calgary, Alberta, Canada T2N 4N2.
Accepted for publication: January 5, 2005.

0885-3924/05/$–see front matter
doi:10.1016/j.jpainsymman.2005.01.007

Sloan Kettering Cancer Institute and has written numerous articles on pain, its physiology, and treatment. He was involved in studies during the 1980s which elucidated the equianalgesic ratio between oral and parenteral hydromorphone, as well as the potency of hydromorphone compared to morphine.[12] However, to this day further research is ongoing to add to understanding of this drug and its clinical applications.

Chemistry

Hydromorphone is structurally very similar to morphine; it differs from morphine by the presence of a 6-keto group and the hydrogenation of the double bond at the 7-8 position of the molecule.[13] Like morphine, it acts primarily on μ opioid receptors, and to a lesser degree on delta receptors. Hydromorphone does not effect kappa, sigma, or epsilon receptors.[14] μ receptors mediate the pain relieving properties of opioids but also mediate unwanted side effects, such as constipation, nausea, and respiratory depression.

Pharmacokinetics

Oral

Hydromorphone is available in the following oral preparations: powder, solution, immediate-release tablet, and modified-release tablet. It is absorbed in the upper small intestine, is extensively metabolized by the liver, and has a variety of renally excreted, water-soluble metabolites. Approximately 62% of the oral dose is eliminated by the liver on first pass, partly accounting for oral bioavailability in the range of 1:2 to 1:8.[15] For orally-administered, immediate-release preparations, the onset of action is approximately 30 minutes with a duration of action of about 4 hours.[14] For modified-release preparations, the bioavailability is similar to immediate-release preparations, with a duration of action of either 12 or 24 hours depending on the particular formulation.[16–18,50]

Parenteral

Hydromorphone can be administered parenterally by intravenous, intramuscular, and subcutaneous routes. The oral to parenteral equianalgesic ratio has been estimated as 5:1, although a range has been described and clearly there is a great deal of interindividual variablility.[15] Subcutaneous administration has been found to have 78% of the bioavailability of intravenous dosing.[19] Onset of action of hydromorphone after intravenous dosing is approximately 5 minutes, although maximum effect is not achieved for as long as 20 minutes due to the hysteresis (compartment) effect of a partially lipid soluble agent and the delayed penetration of the blood–brain barrier.[20] Because it is more fat soluble than morphine, its onset of action is correspondingly faster than that of morphine, but is slower than highly lipid soluble drugs such as fentanyl. Hydromorphone can be prepared in highly concentrated solutions (up to 100 mg/mL) and because of the smaller volumes, can be easier to administer as a subcutaneous infusion than morphine in the setting of very high dose opioid administration, such as in opioid-resistant cancer pain.[21] However, hydromorphone administered subcutaneously in high concentrations can result in a painful local reaction,[22] although many patients do not experience this toxicity.[23]

Spinal

Hydromorphone can be given via the epidural route. The epidural to parenteral equianalgesic ratio is approximately 1:2.[24] Duration of action after a single epidural dose of hydromorphone has been estimated between 7.7 and 19.3 hours.[25–27]

Hydromorphone Metabolites

Although hydromorphone is chemically very similar to morphine, its minor structural differences have a significant impact on its metabolism.

Morphine undergoes metabolism to its 3-glucuronide, which has no analgesic activity but has been found to have significant neuroexcitatory properties. However, other morphine metabolites, morphine-6-glucuronide and normorphine, do have analgesic activity. Morphine-6-glucuronide has been found to accumulate in the presence of renal failure and may cause respiratory depression and other side effects.[28–30] There are other metabolites present in smaller amounts, including morphine-3-sulfate.