

New in Pain Management

OROS® hydromorphone prolonged release. A review of its use in the management of chronic, moderate to severe pain

Carter NJ, Keating GM. *CNS Drugs* 2010; **24**(4): 337-361.

Introduction

Hydromorphone is a semisynthetic derivative of morphine, which may be used as an alternative to morphine in the treatment of severe chronic pain. OROS® hydromorphone prolonged release uses OROS® (osmotic-controlled release oral delivery system) technology, which provides stable plasma concentrations and avoids fluctuating plasma drug levels that may lead to adverse events and breakthrough pain. With once-daily administration, the OROS® delivery system releases hydromorphone at a near constant rate to provide 'around-the-clock' analgesia and reduce the necessity for breakthrough pain medication.

OROS® hydromorphone is indicated for use in patients with severe pain. It is contraindicated in patients with acute or postoperative pain. Like morphine, it acts as an agonist at μ - and (to a lesser extent) δ -opioid receptors, with weak or no affinity for κ -, σ - and ϵ -receptors. Although hydromorphone is a more potent analgesic agent than morphine, differences between individual agents and opioid formulations mean that a fixed dose ratio cannot be relied on when switching patients from other opioids to OROS® hydromorphone and careful patient monitoring and dose titration is required. The manufacturer's prescribing information recommends that the total daily dose of morphine (or the morphine-equivalent daily dose of any opioid) is multiplied by a conversion factor of 0.2 when converting from oral morphine to OROS® hydromorphone. As with other opioids, there is no ceiling effect with hydromorphone and the analgesic efficacy increases with increasing dose. The only restriction on escalating dose is the emergence of adverse effects. Preliminary evidence suggests that OROS® hydromorphone may be associated with a lower risk of opioid abuse than immediate release (IR) hydromorphone, requiring higher doses and a 2- to 12-fold longer time to reach similar peak 'drug-liking' effects.

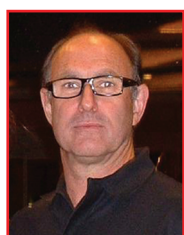
Drug interactions

OROS® hydromorphone is contraindicated with concomitant use of monoamine oxidase inhibitors and the combined opioid receptor agonists/antagonists (e.g. buprenorphine). Concomitant use with CNS depressants may lead to respiratory depression, hypotension and profound sedation. Consequently, if OROS® hydromorphone must be used with a CNS depressant drug, the dose of one or both medications should be reduced. Because of the risk of respiratory depression, OROS® hydromorphone should be avoided in combination with muscle relaxants.

Pharmacokinetics

The pharmacokinetics of OROS® hydromorphone with respect to peak plasma concentration and area under the plasma concentration-time curve are linear over a dose range of 8-64 mg, whereas time to maximum concentration is not dose dependent. Maximum plasma concentrations are reached within 12 to 17 hours and are maintained for up to 30 hours after a single dose. With multiple dosing, steady state plasma concentrations are reached within (3) days of administration.

Pharmacokinetics are not altered by food. OROS® hydromorphone is metabolised by the liver to a principle metabolite, hydromorphone-3-glucuronide, which does not contribute to the analgesic activity of the drug, but which may possess neuroexcitatory properties. Pharmacokinetic analyses have not been performed with OROS® hydromorphone in special populations. However, with IR hydromorphone no clinically significant changes in pharmacokinetics were apparent in elderly patients, and maximum plasma concentrations and area under the curve were increased in patients with hepatic or renal insufficiency. Consequently, patients with moderate hepatic or renal impairment should receive lower doses of hydromorphone and should be monitored carefully during treatment.



Reviewed by:

Dr. Milton Raff obtained his MB ChB at the University of Pretoria in 1979 and his FFA in 1986. He was a consultant anaesthesiologist at Grootte Schuur Hospital from 1986 to 1988 and since then has been in private practice in Cape Town. In 1997 he was responsible for establishing the City Park Pain Clinic, of which he remains a director. He is a consultant at the Grootte Schuur pain clinic and an honorary lecturer at the University of Cape Town. Dr Raff currently holds a number of important positions in his capacity as an anaesthesiologist and specialist in pain management. He is the Chairman of the Acute Pain Committee of WfSA, a member of the Task Team of IASP for Acute Pain Management in Developing Countries and Councilor in the College of Anaesthesia of the SA College of Medicine. He is also President of PAINSA and editor of the PAINSA journal.

Efficacy

The analgesic efficacy of OROS® hydromorphone has been demonstrated in patients with chronic moderate to severe low back pain, cancer pain and non-malignant pain, where patients were converted from standard opioid medication to OROS® hydromorphone using a conversion ratio of 5:1 morphine equivalents to hydromorphone. Where specified, approximately two thirds of patients were stabilised without the need for dose adjustment, indicating that this conversion ratio is suitable to switch patients to OROS® hydromorphone. Once daily administration provided consistent and stable analgesia over a 24 hour period in patients with chronic moderate to severe cancer pain, which was at least equivalent to morphine. Pain scores indicated that pain relief may have been better with OROS® hydromorphone in the evening when morphine was at trough levels and hydromorphone was at the midpoint of the dosing period. A 1-year, open-label study indicated that pain relief could be sustained in the long-term with continued use of OROS® hydromorphone.

In patients with chronic non-malignant pain, OROS® hydromorphone was noninferior to oxycodone ER in the treatment of chronic moderate to severe osteoarthritis pain and both treatments were associated with improvements in health-related quality of life (HR-QoL) and sleep. Noninferiority was also demonstrated in a separate study including patients with moderate to severe low back pain (57%), musculoskeletal pain (24%), neuropathic pain (10%), or other types of non-malignant pain (9%).

Pharmacoeconomics

Pharmacoeconomic analyses suggest that OROS® hydromorphone was a cost-effective treatment option compared to oxycodone CR in patients with chronic, severe osteoarthritis pain and relative to other opioids in patients with severe, chronic malignant or non-malignant pain.

Tolerability

The tolerability profile of OROS® hydromorphone is manageable, with most adverse events being mild to moderate and typical of those expected with an opioid medication. The most commonly reported adverse events in clinical trials included constipation, nausea, somnolence, dizziness, vomiting and fatigue. Adverse events reported with long-term use are similar to those experienced with short-term use. In general, serious adverse events were infrequent. Respiratory depression was rarely reported, occurring in ≥ 1 in 10 000, but < 1 in 1000 patients, but hypotension was more common occurring in ≥ 1 in 100, but < 1 in 10. As with all opioids, there is a potential for the development of tolerance or physical dependence. Abrupt discontinuation of OROS® hydromorphone may result in withdrawal symptoms and to prevent this, dosage should be reduced by 50% every 2 days until the lowest possible dose is reached when the drug may be stopped.

Contraindications

OROS® hydromorphone is contraindicated in patients with severe hepatic insufficiency, status asthmaticus, acute abdominal pain of unknown origin and prior surgery or an underlying pathology that may lead to narrowing of the gastrointestinal tract, the formation of blind loops or obstruction. It is also contraindicated in children, comatose patients and women in labour.

Conclusions

Chronic pain can significantly impair quality of life and interfere with normal daily functioning, both socially and at work. OROS® hydromorphone has been developed with the aim of improving analgesia and providing the convenience of a once daily dose, with a lower potential for abuse or dependence compared with short-acting opioid alternatives.

Reviewer's comments

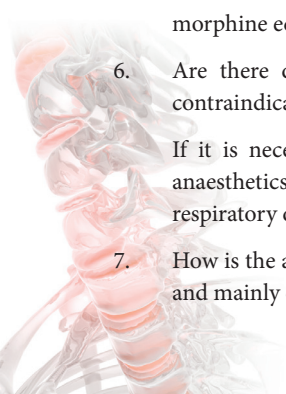
This article is an extensive review by an Adis International review panel. Every aspect about the pharmacology of OROS® hydromorphone is examined and the article serves as an excellent review.

We, as treating physicians, need to extract the relevant facts that are pertinent to our everyday practice. When a new product such as OROS® hydromorphone is released what do we need to know about it?

1. What is this agent? It is a sustained release hydromorphone, which is an opioid acting at the normal μ - and δ - opioid receptors.
2. What is the dose and the dosing interval? The product is supplied as a 4 mg and 8 mg once daily sustained release preparation.
3. What is the starting dose? 4mg.
4. Why do we not rather use morphine? Morphine maybe the drug of choice in patients requiring an opioid for the treatment of moderate to severe cancer pain, but other opioids such as hydromorphone are acceptable alternatives when morphine is not tolerated or is unsuitable. No opioid is recommended over another for the treatment of non-malignant pain.
5. What is the relative strength of hydromorphone when compared to morphine? Most clinical studies used a conversion ratio of 5:1 morphine equivalents.
6. Are there drug interactions? The concomitant use of OROS® hydromorphone with monoamine oxidase inhibitors (MAOIs) is contraindicated, because of the risk of CNS excitation/depression, hypotension or hypertension.

If it is necessary to use OROS® hydromorphone in combination with a CNS depressant drug (e.g. hypnotics, sedatives, general anaesthetics, antipsychotics and alcohol), the dosage of one or both of the drugs should be decreased as the combination may lead to respiratory depression, hypotension, profound sedation and coma.

7. How is the agent eliminated? Hydromorphone is extensively metabolised in the liver. All hydromorphone metabolites are water soluble and mainly excreted in the urine.



8. What about special populations? Initiate treatment cautiously in the elderly, using a lower initial dosage. Similar reduced dosages should be used in patients with hepatic and renal function impairment.
9. Where should we be using hydromorphone? There is good clinical data supporting its use in malignant pain and severe lower back pain. There is also support for its use in severe osteoarthritis of the hip and knee. It has been used for neuropathic pain.
10. What does this agent cost? A single dose 4 mg tablet costs approximately ZAR10.
11. Are there significant side effects? As this is an opioid we must expect similar side effects as for all the agents in this group of drugs. The most common side effects seen with OROS® hydromorphone are constipation, dizziness, somnolence, pruritus and nausea and vomiting. We must always consider respiratory depression as being a major side effect of all opioids and this is true for hydromorphone, albeit not a common side effect.

OROS® hydromorphone is a useful addition to the South African analgesic market and will be of great benefit to patients who have chronic pain and for the physicians who treat this group of patients.

The long-term safety and efficacy of OROS® hydromorphone in patients with chronic low back pain

Wallace, Skowronski R, Khanna, S, *et al.* Poster presented at the 25th Annual Scientific meeting of the American Pain Society, San Antonio, Texas, May 3-6; 2006.

Chronic lower back pain lasting more than 6 months is common, occurring in over 10% of the population. It may be debilitating, interfering with work and normal daily activities.

This study was a six-month extension phase of a seven-week, multicenter, open-label, noncomparative study to assess the efficacy and tolerability of OROS® hydromorphone in adult patients with chronic low back pain. OROS® hydromorphone tablets 8 mg, 16 mg, 32 mg, or 64 mg were administered once daily. Safety and efficacy were assessed using the Brief Pain Inventory (BPI), patient and investigator global evaluations and daily pain diaries in 113 patients who completed the initial seven-week study. Eighty three patients completed the six-month extension phase.

During the seven-week initial phase, diary-based pain relief scores improved from 1.76 at baseline to 2.02 at endpoint (0 = no relief, 4 = complete relief) and BPI improved from 5.1 to 6.4. Pain relief obtained at the end of the seven-week study was maintained for the full six-month extension, with no change in the severity ratings over the duration of the extension phase. Seventy two percent of patients and 82% of investigators rated overall treatment as good, very good or excellent.

Adverse events were generally of mild severity, with the most frequently reported adverse events being nausea (7.1%), constipation (6.2%) and somnolence (4.4%). Less frequent adverse events included diarrhoea, fatigue, headache, hyperhidrosis and vomiting (2.7% each). Twelve patients discontinued the study before six months due to an adverse event.

Reviewer's comment

One of the most frequent conditions seen by medical practitioners in South Africa is lower back pain (LBP). To date no epidemiological figures are available for the South African population. What is well known is that the cost of LBP to the economy is enormous, based on the cost of therapy, hospitalisation and loss of work hours.

Not all LBP can be treated with medical intervention, so medical therapy plays a large role in this condition. It is important to be able to distinguish between somatic and neuropathic components of the pain as therapy will differ for these two components. This article examines the efficacy of OROS® hydromorphone in patients with LBP where the cause of pain was somatic. This is the so called axial lower back pain.

The study seeks to examine efficacy of the therapy based on recognised pain measurement parameters such as the Brief Pain Inventory Score and Patient as well as Physician Global Impression of Change scores.

What we need to learn from this article is that the agent provided rapid and sustained pain relief in an extended trial. To us as practitioners this means that we can prolong the therapy without losing efficacy.

The authors do not evade the issue of adverse effects and advise that this product is no different from other opioids in that opioid side effects are noted. The reported frequency of the side effects is low, but we as treating physicians need to be aware of the possibility of these problems. The most frequent of these side effects are, as would be expected, nausea, constipation and somnolence.

The OROS® hydromorphone does have benefit for LBP sufferers and is a useful addition to the armamentarium of the treating practitioner.



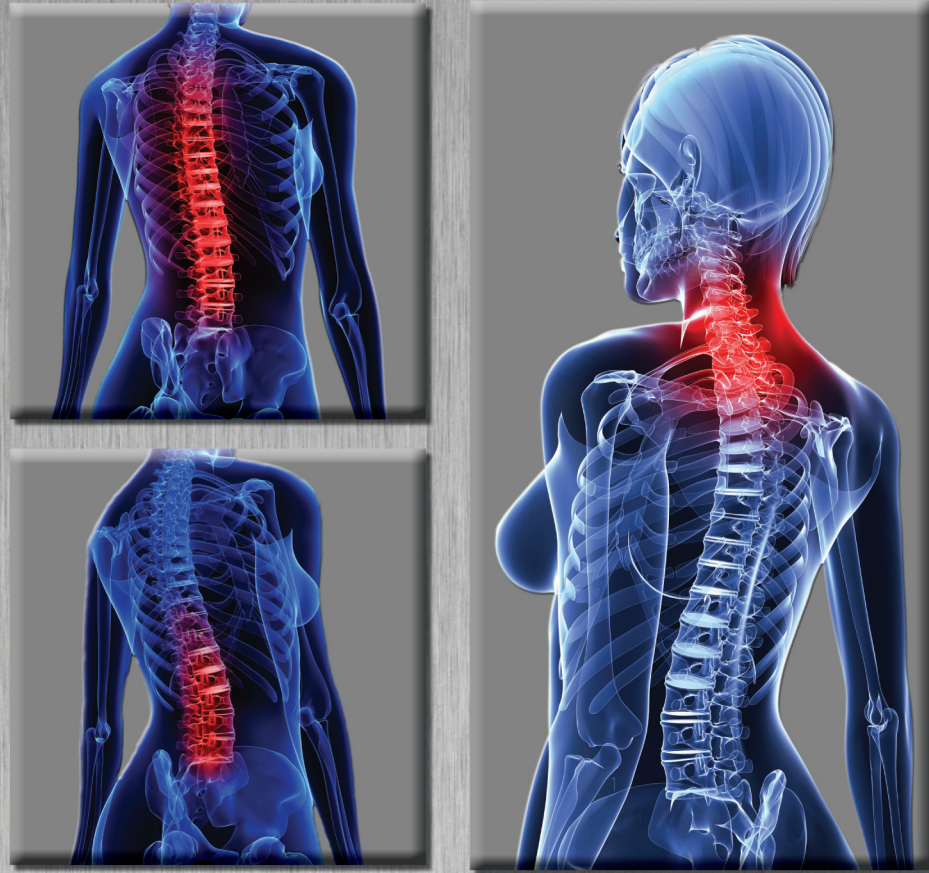
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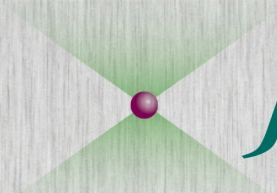
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References: 1. Gupta S, Sathyan G. Providing constant analgesia with OROS[®] hydromorphone. *J Pain & Symp Man* 2007;33(2S):S19-S24. 2. Jurnista[®] package insert. March 2011. 3. Turgeon J, Gröning R, Sathyan G, *et al.* The pharmacokinetics of a long-acting OROS[®] hydromorphone formulation. *Expert Opin Drug Deliv* 2010;7(1):137-144. 4. Drover DR, Angst MS, Valle M, *et al.* Input characteristics and bioavailability after administration of immediate and a new extended-release formulation of hydromorphone in healthy volunteers. *Anesthesiology* 2002; 97(4):827-836.

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