

Clinical application of extended-release hydromorphone for pain management

The osmotic controlled-release oral delivery system (OROS®) is being utilized more frequently for once-daily dosing of a variety of medications. While sustained-release formulations of other opioids are currently available in the USA, at present there is no extended-release hydromorphone product on the market. With regard to OROS hydromorphone, a candidate to fill this niche, there is growing evidence to suggest that stable plasma levels can be achieved with tolerable side effects. Furthermore, the drug-delivery system appears to provide reliable opioid release when dosed with food and alcohol.

KEYWORDS: chronic pain ■ hydromorphone ■ opioids ■ OROS® ■ sustained-release hydromorphone

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Hydromorphone is a semi-synthetic μ -agonist commercially available in oral, rectal and injectable formulations for the control of acute and chronic pain [1]. Hydromorphone is typically used for moderate-to-severe pain, and is an effective alternative to morphine [1]. Like other μ -agonists in the opioid family there is no ceiling effect for hydromorphone, and cross-tolerance with other opioids is incomplete [1,2].

In clinical practice, opioids are used for a variety of persistent painful conditions including, but not limited to, those involving the axial spine, arthritis and neuropathic pain. Opioids are also a central agent for the treatment of severe cancer-related pain [2]. For both benign and oncologic pain, stable plasma levels of opioid are achieved through use of long-acting sustained-release opioid preparations [3]. While extended-release formulations of oxycodone, morphine, oxymorphone and fentanyl are commercially available in the USA, there is currently no extended-release formulation of hydromorphone [4]. Earlier this decade, Purdue Pharmaceuticals (CT, USA) produced an extended-release formulation of hydromorphone (Palladone™) that was withdrawn from the market because of concerns regarding accelerated drug release when used in combination with alcoholic beverages. Since the withdrawal of Palladone, there have been no subsequent attempts to bring to market a sustained-release form of hydromorphone in this country [3]. The osmotic controlled-release oral delivery system (OROS®) hydromorphone, a patented drug-release formulation produced by the ALZA Corporation (CA, USA) and marketed in Europe under the trade name Journista™ (Janssen Pharmaceutica, NV, Beerse, Belgium), is a potential candidate to fill this niche [3].

OROS® drug delivery

The OROS osmotic drug-delivery system has been employed to provide extended release of at least 13 drugs, including prazosin, verapamil, oxybutynin, glipizide and albuterol [5]. OROS provides stable plasma concentrations and uniform dosing regimens, which in turn may lead to better patient acceptance of therapy [3]. In the past 30 years, four different systems have been described: the elementary osmotic pump, the two-layer osmotic push-pull tablet, the advanced longitudinally compressed tablet multilayer formulation and the L-OROS system [5]. Using osmosis, the OROS formulations are reported to provide stable drug release for up to 24 h [6].

While beyond the scope of this article, Rathbone *et al.* provide an excellent review of the mechanisms underlying this technology [5]. Current formulations of sustained-release hydromorphone using the OROS technology are designed to deliver medication for up to 24 h using an osmotically active bilayer surrounded by a semi-permeable membrane [4]. The intrinsic properties of this semi-permeable membrane regulate the flow of water into the 'push' layer of the tablet causing it to expand. As the push layer expands, the drug-containing compartment is compressed, resulting in release of drug through a laser-drilled orifice for precise pharmaceutical delivery to the gastrointestinal tract mucosa, resulting in presumably uniform absorption secondary to uniform release [4]. The semi-permeable membrane that acts as an outer shell is subsequently excreted intact in the feces [4,5].

Hydromorphone overview

Hydromorphone is a semi-synthetic congener of morphine, which exerts analgesic effects as a μ -receptor agonist [1]. This opioid was first introduced into clinical practice in the 1920s, and has a well-described safety profile and history of patient acceptance for moderate-to-severe pain [1]. As with other morphine-like drugs, hydromorphone has no ceiling effect, meaning that dose titration may continue to the end point of analgesia [1]. Although opioid tolerance is described with hydromorphone, as with other opioids, hydromorphone has incomplete cross-tolerance [4]. A traditional strategy frequently utilized when rotating from hydromorphone or to hydromorphone in the opioid-tolerant patient employs a 25–50% dose reduction, because the newly introduced μ -agonist will likely have improved efficacy [4]. Oral hydromorphone is generally considered to be 5–7.5-times more potent than orally administered morphine on a milligram-per-milligram basis [1,3]. Parenterally administered hydromorphone has likewise been shown to be approximately seven- to nine-times more potent than parenteral morphine [3].

Hydromorphone side effects are consistent with those traditionally associated with opiates. These include nausea, vomiting, respiratory depression, pruritis and adverse endocrinologic effects (decreased testosterone levels), although hydromorphone has been associated with less nausea and pruritis when compared with morphine [1]. As with other opioids, these side effects are often dose related. In contrast to morphine, hydromorphone does not have metabolites with analgesic activity; however, hydromorphone-3-glucuronide does have neuroexcitatory activity, which has resulted in myoclonic activity and agitation in animal studies [1]. Multiple dosage forms exist for oral, rectal, intravenous and intraspinal drug delivery [1,3].

Immediate-release oral formulations of hydromorphone, while well-tolerated, are complicated by the frequent dosing required owing to the relatively short half-life (2–3 h) of this preparation [6]. The frequent dosing required may be inconvenient for patients, and the peak–trough effect results in varying analgesia [6]. Hydromorphone is extensively metabolized by the liver, with approximately 62% elimination of an oral dose on first pass [1]. The bioavailability is not appreciably different for immediate-release and modified-release preparations.

In addition to OROS hydromorphone, there are other preparations of extended-release hydromorphone currently available in selected

countries. For example, there is a 12-h formulation available in Canada (Hydromorph Contin) and the UK and Germany (Palladone SR) [1]. Additionally, Palladone XL, a 24-h preparation, was approved for use in Canada [1]. Like OROS hydromorphone, the advantages of the Palladone formulations are a similar bioavailability to an immediate-release formulation, without fluctuation in plasma levels [1].

OROS hydromorphone

Produced by the ALZA Corporation and marketed under the trade name Jurnista, OROS hydromorphone utilizes the push–pull form of the osmotic pump for release of hydromorphone [3]. This drug-delivery system is not altered by gastrointestinal motility or pH, and the tablet is excreted intact devoid of opioid in the feces [1,3]. Recent studies have demonstrated the safety and efficacy of this drug-delivery system with respect to hydromorphone.

For example, OROS hydromorphone was demonstrated to provide superior analgesia when compared with immediate-release formulations of both hydromorphone and morphine in cancer patients [7]. Furthermore, this randomized, double-blinded study of 118 patients suggested that the OROS hydromorphone formulation continued to provide acceptable analgesia throughout the day, as determined by the Brief Pain Inventory scores obtained in the evening [7]. Likewise, using a 5:1 conversion factor with a dose titration over 3–21 days, acceptable analgesia was achieved with OROS hydromorphone in patients previously receiving oral morphine [8]. Similarly, chronic nonmalignant pain patients who rotated from previous opioid therapy to OROS hydromorphone reported improved pain control and decreased use of rescue medications [9].

Equivalence with extended-release oxycodone was demonstrated in 138 patients with moderate-to-severe osteoarthritis pain [10]. In this study, side effects for OROS hydromorphone and extended-release oxycodone were similar [10]. An economic impact comparison of OROS hydromorphone compared with extended-release oxycodone for treatment of osteoarthritis pain patients in Germany suggested that in this patient population analgesia could be obtained at a reasonable cost [11]. Its use in the treatment of patients with chronic low back pain in a short-term open-label study suggested efficacy in this patient population without an increased risk of adverse effects [12].

Among the largest studies to date, an open-label, single-treatment study of conversion to OROS hydromorphone from other opioids

Executive summary**Drug delivery**

- The osmotic controlled-release oral delivery system (OROS[®]) drug delivery system is currently used to provide sustained-release formulations of several medications.
- The OROS system relies on what is referred to as an 'osmotic pump' to provide uniform release of a drug for gastrointestinal absorption.
- OROS hydromorphone utilizes the 'push-pull' version of the osmotic pump, with uniform release of hydromorphone independent of gastrointestinal motility or pH.

Hydromorphone general characteristics

- Hydromorphone is an opioid analgesic that has been in use for greater than 80 years for the treatment of moderate-to-severe acute and chronic pain.
- Hydromorphone, like all other opioids, has no ceiling effect with regards to efficacy, and cross-tolerance with other opioids is incomplete.
- Side effects are those common to opioids; nausea, vomiting, constipation, decreased endocrine function and so on.

OROS[®] hydromorphone safety & tolerability

- The OROS extended-release formulation of hydromorphone has been shown to have a similar side-effect profile to the immediate-release form of the drug.
- The drug-delivery system is stable with concomitant food consumption.
- In contrast to the extended-release formulation, Palladone™, which was withdrawn from market, OROS hydromorphone appears to provide stable drug release with concomitant alcohol consumption.
- Stable plasma levels resulted in less need for rescue medication use.

Clinical efficacy

- Extended-release OROS hydromorphone provided comparable and, in many cases, superior analgesia when compared with other sustained-release opioid formulations.
- The extended-release hydromorphone was superior in most cohorts to immediate-release opioids.
- It has a 5:1 conversion factor for oral morphine conversion to oral hydromorphone was validated for the OROS formulation.

Pharmacokinetics

- One study suggested that there may be less first-pass metabolism with this drug-delivery system; otherwise, pharmacokinetics are similar to other hydromorphones.
- OROS tablets are excreted intact in the feces.

demonstrated improved analgesia with OROS hydromorphone versus the prestudy opioid analgesic. In this 400-patient trial of subjects taking opioids in a morphine equivalent of greater than 45 mg per day, side effects were consistent with those seen with opioid therapy alone and not unique to the OROS system [4].

From a pharmacodynamic and pharmacokinetic standpoint, several studies suggest that OROS hydromorphone is well-tolerated. The presence or absence of food does not appear to alter the pharmacokinetic profile of OROS hydromorphone [13]. Likewise, the presence of alcohol does not alter absorption or the integrity of the drug-delivery system, alleviating a prior concern about Palladone – the previous extended-release formulation available in the USA, which was withdrawn from the market by the US FDA for concerns owing to interactions with alcohol [14]. The OROS formulation has been implicated in an earlier achievement of analgesia with less need for dose titration and, therefore, enhanced patient compliance [15]. This may be owing to the demonstrated increased bioavailability of the OROS formulation due to decreased first-pass metabolism, although this remains speculative [16].

Steady-state plasma levels were achieved at approximately 16 h following administration of a single dose and remained at or near maximum values throughout a 30-h period [6]. Importantly, there also appeared to be no gender differences in plasma levels [4,6]. The apparent postdosing half-life of OROS hydromorphone was estimated to be 10 h, significantly longer the 2–3 h half-life of immediate-release hydromorphone, once again helping to prevent the peak–trough effect [6].

In conclusion, OROS hydromorphone appears to be a safe, well-tolerated, alternative to sustained-release morphine and oxycodone. The benefits of steady plasma concentrations with less fluctuation of plasma levels of opioid should provide enhanced clinical effectiveness when compared with immediate-release hydromorphone. In addition, in contrast to Palladone, OROS hydromorphone does not appear to be affected by alcohol consumption. While further studies in differing patient populations are needed, the OROS drug-delivery system and its application to oral hydromorphone therapy for benign and malignant pain appears promising.

Future perspective

Hydromorphone is safe and effective for the treatment of moderate-to-severe acute and chronic pain. At present, at least in the USA, the lack of an extended-release formulation for this opioid limits clinical ability to treat resistant chronic pain if patients have cardiac issues, making methadone a less attractive alternative if they are needing to rotate from fentanyl, morphine or oxycodone ER formulations. The introduction of OROS hydromorphone can potentially fill this need.

While this drug-delivery system appears to be safe and effective in the preliminary studies reviewed, clearly more extensive work needs to be carried out. For instance, larger patient populations are likely to be required to ensure that the drug-delivery system is safe across a range of applications. The experience with Palladone demonstrates the principle that only on wider

distribution can some of these issues be discovered. In addition, efficacy in a variety of benign chronic pain conditions needs to be demonstrated. Finally, long-term benefit in terms of decreased pain experience, increased involvement in daily activities of living and improved functional capacity needs to be determined for this and other extended-release formulations, as most trials are relatively short-term (weeks to months).

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