REVIEW ARTICLE

The Role of OROS® Hydromorphone in the Management of Cancer Pain

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■ **Abstract:** The vast majority of cancer patients experience pain, and treatment with opioids offers the most effective option for pain management. Long-lasting opioid formulations are usually used as cancer pain management strategies. This review surveys the available literature on the only available once-daily sustained-release formulation of hydromorphone, and its use in cancer pain management. Sustained-release (SR) formulations have a more consistent opioid plasma concentration, thereby minimizing the peaks and troughs associated with immediate-release opioid formulations. OROS® hydromorphone (Jurnista™, Janssen Pharmaceuticals, NV, Beerse, Belgium) releases hydromorphone over a 24-hour dosing period. Studies comparing its efficacy with other opioids such as morphine and oxycodone found comparable results overall. Recent trials have provided evidence of decreased rescue medication use for breakthrough pain, a good safety profile, and quality of life benefits. It appears to be an efficacious and well-tolerated treatment. The pharmacokinetics of OROS® hydromorphone are linear and dose-proportional, and only minimally affected by the presence or absence of food. In addition, the SR properties of OROS® hydromorphone are maintained in the presence of alcohol, with no dose dumping of hydromorphone. This formulation shows promise as an addition to cancer pain management strategies, although further randomized, double-blind trials are needed to confirm this. ■

Key Words: cancer pain, opioid analgesics, hydromorphone, sustained-release

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INTRODUCTION

Pain, a common complication of cancer, can affect patients at any stage of the disease. 25% to 30% of patients with recently diagnosed cancer suffer from pain. This rises as cancer progresses, so that 60% to 90% suffer pain at advanced stages.[1–7] Inadequately controlled pain can adversely impact on patients' lifestyles and relationships.[8] Organizations such as the American Cancer Society and the World Health Organization (WHO) have highlighted the importance of pain management as part of routine cancer care.[8] Treatment with opioid analgesics remains the cornerstone of cancer pain management. This review discusses OROS® hydromorphone (Jurnista™, Janssen Pharmaceuticals, NV, Beerse, Belgium) in the field of opioid management of cancer pain.

Opioids in Pain Management

Opioid analgesics are highly effective for the treatment of pain, enabling 85% to 95% of patients to gain functional control of their lives.[9,10] Given their proven effectiveness and safety, opioids should be routinely administered to patients with moderate to severe cancer

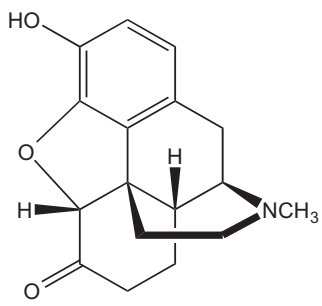
pain.[8] They are the mainstay of chronic cancer pain therapy, as most cancer pain can be controlled with ≤240 mg of oral morphine per day.[11] Morphine is generally accepted as the reference drug for chronic cancer pain,[12] and WHO recommendations list oral morphine[13] as the drug of choice for chronic cancer pain, owing to its global availability and extensive clinical experience.

The WHO has provided recommendations for the pharmacological management of pain in the form of a three-step "analgesic ladder",[13] which is widely accepted as the basis of treatment guidelines. There are recommendations to either skip the second step of the ladder or combine it with the third step,[14] as this step can be unnecessary practice.[15] The second step introduces the use of codeine and combination analgesics, but small doses of other, stronger opioids may be more useful with fewer side effects if they are available. In addition, codeine is a pro-drug for morphine, and some people lack the necessary enzyme to convert it.[15] The third step, for patients with severe pain, is to prescribe strong opioids such as morphine, hydromorphone, methadone, fentanyl, or oxycodone, sometimes in parallel with other medications. These treatments have their own pharmacological profiles, but are usually effective and well tolerated, and one recent study found only minimal efficacy differences between morphine, transdermal fentanyl, and methadone used in cancer pain management.[16] Opioids are usually administered at a low starting dose, and then titrated upwards on an individual basis according to patient requirements, thereby attaining the best possible balance between pain relief and side effects.[17] It is preferable to use slow titration techniques where possible to minimize treatment-emergent adverse events, especially in opioid-naïve patients.

Hydromorphone

The semi-synthetic opioid hydromorphone is a hydrogenated ketone of morphine,[18] its structure only differing by the presence of a 6-keto group and the hydrogenation of the double bond at the 7 to 8 position[19] (Figure 1). After being first synthesized in Germany in 1921, it was introduced into clinical practice in 1926, and has since been used extensively in various indications including postoperative pain[20,21] and cancer pain.[22–24]

Hydromorphone is approximately 5 times more potent on a milligram basis than morphine,[25] is more soluble in water allowing concentrated solutions, and is better absorbed orally. Hydromorphone has a shorter half-life than morphine, and so must be administrated every 4 to 6 hours to provide continuous pain relief if no sustained-release (SR) formulation is used. It is a potent analgesic, with dose-related clinical effects, and is included in the WHO Guidelines for Cancer Pain Treatment.[13]



Hydromorphone

Figure 1. Structure of hydromorphone.

Hydromorphone acts primarily on μ-opioid receptors, which mediate not only the pain-relieving properties of supraspinal analgesia, euphoria, and sedation, but also the unwanted side effects of respiratory depression, decreased gastrointestinal motility, and physical dependence.[22,26] The adverse event profile of hydromorphone is similar to that of other μ-opioid receptor agonists like morphine. The most frequently observed adverse effects are lightheadedness, dizziness, sedation, nausea, vomiting, constipation, sweating, and pruritis.[27] Indeed, for chronic cancer pain, the studies available suggest that there is little difference between morphine and hydromorphone in terms of analgesic efficacy, adverse event profile, or patient preference.[18] Although reports have shown that high-dose hydromorphone in the presence of renal failure is associated with nausea and delirium,[19] reports have shown that hydromorphone may be administered safely to patients with chronic or end-stage renal failure and may be particularly useful in those who have intolerable side effects from other opioids.[28,29] This makes hydromorphone a valuable option when other opioids are best avoided.[30]

The structural difference has a significant impact on metabolism. Hydromorphone is metabolized to the major metabolites hydromorphone-3-glucuronide, hydromorphone-3-glucoside, and dihydroisomorphine-6-glucuronide, which are then usually excreted in the urine along with other metabolites.[31] The presence of multiple metabolites may mean that hydromorphone is less susceptible to the blocking of one pathway. Oxida-

tive metabolism of hydromorphone by the cytochrome P450 enzymes appears to be minor.[32] Morphine, the prototypical opioid analgesic, is metabolized in vivo primarily to morphine-3-glucuronide and morphine-6-glucuronide. These metabolic products account for ~65% of a dose of morphine, with the remaining drug biotransformed to multiple minor species or excreted unchanged.[33] These primary metabolites have been the focus of extensive basic and clinical evaluation for more than 25 years as investigators seek to better understand factors that contribute to opioids' analgesic effect and side effects.[34] The morphine-6-glucuronide metabolite, which does have analgesic properties, has been found to accumulate in the presence of renal failure, and may also cause respiratory depression among other side effects.[35,36] This aspect is less well studied for hydromorphone, but to date there is no evidence that there is an analgesically active 6-glucuronide metabolite.[22,37]

OROS® Push-Pull Technology

Stable drug concentrations are important for balancing treatment efficacy and tolerability. Increased trough levels ensure that the plasma concentrations remain in the optimal range for drug efficacy, while decreased peak concentrations can reduce the incidence of side effects. ORal OSmotic (OROS) Push-Pull technology is a new advanced drug delivery system which relies on the principle of osmosis to control drug release over an extended period of time. Each OROS Push-Pull technology tablet consists of an osmotically active bilayer core within a semipermeable tablet shell membrane. The bilayer core consists of two osmotically active layers, a single drug layer (the "pull" layer) and a hydrophilic expanding compartment (the "push" layer). When ingested, fluid is absorbed from the gastrointestinal tract, forming a drug suspension and causing the push layer to expand. This exerts force on the pull layer and pushes the suspended drug out of the tablet through a laser-drilled orifice in the semipermeable tablet shell membrane. The rate of release from the osmotic system is actively controlled by the dosage form, and is not significantly affected by environmental factors such as pH, presence of food, alcohol[38,39], or gastric motility.[40]

OROS® hydromorphone is a unique long-acting opioid formulation that maintains consistent hydromorphone plasma concentrations throughout a 24-hour period, providing long-lasting analgesia.[25,41,42] Using this delivery system, hydromorphone is steadily released, and has a half-life of approximately 12 hours, thereby allowing more constant pain control. When treating patients with chronic pain, it is often preferable to have a stable low dose for around-the-clock medication rather than only giving treatment when the pain becomes intense. This compares very favorably with other immediate-release (IR) and SR opioid analgesics, which typically have a duration of action of 4 to 6 hours, and require dosing intervals of between 3 and 12 hours.[43,44]

In addition to the reduction in peak–trough variability compared with standard oral IR preparations, the simplified once-daily dosing regimen can potentially improve medication adherence and long-term compliance. One of the major causes of suboptimal therapy outcomes is poor adherence to prescribed treatment regimens.[45] Non- or partial adherence is common in patients with chronic disease requiring long-term maintenance treatment[46] and poor adherence rates as high as 90% have been reported for both psychiatric illness and physical disorders.[47] Treatment-related factors contributing to poor adherence besides side effects of medication and the route of administration also include complex dosing regimens.[46] Oral drug delivery systems have been developed to specifically address treatment-related issues with the intention of improving patient acceptability of the treatment, thereby improving adherence to therapy. The European Association for Palliative Care[12] and the American Pain Society[48] now recommend the use of long-acting oral agents for maintaining analgesia once individual dose requirements have been established.

Trials with OROS® Hydromorphone

There have been a number of trials investigating the efficacy and tolerability of OROS® hydromorphone in different patient groups, pain classifications, and in different settings. These trials have been either placebo controlled, or have compared OROS® hydromorphone with other opioids in clinical use.

A systematic review of studies using hydromorphone showed the majority of studies investigated cancer pain.[18] Two randomized, double-blind studies compared SR hydromorphone with SR morphine; one ($n = 100$) found no difference in pain relief, adverse events, or patient preference.[49] The second study ($n = 47$) reported significantly higher pain scores with hydromorphone, and the hydromorphone group required significantly more doses of rescue analgesia. However, there were no significant differences in other adverse effects among groups.[18] Oral SR hydromorphone was compared with oral SR oxycodone in patients with chronic cancer pain

and both treatments were equally effective and well tolerated, with no differences between rescue analgesia or pain outcomes.[50]

The pharmacokinetics of intravenous, oral, IR hydromorphone, and OROS® hydromorphone were compared, and OROS® hydromorphone was found to produce continued release of medication over 24 hours, thereby allowing once-daily dosing.[42] The pharmacokinetics of OROS® hydromorphone are linear and dose-proportional.[51] The presence or absence of food has only a minimal effect on the bioavailability of hydromorphone from OROS® hydromorphone,[52] and a recent study reported that the SR properties of this formulation are maintained in the presence of alcohol, with no evidence of dose dumping of hydromorphone.[53] This is of particular importance because SR hydromorphone capsules (Palladone) were withdrawn in the U.S. on the advice of the FDA owing to problems with increased, potentially fatal concentrations after dose-dumping occurred when combining the drug with alcohol.

One study evaluated the outcomes in subjects who converted from previous opioid therapy to OROS® hydromorphone in subjects with either chronic malignant ($n = 73$, 18.1%) or nonmalignant ($n = 331$, 81.9%) pain, and found that a regimen of conversion to OROS® hydromorphone and titration to an optimum dose was relatively straightforward and well tolerated.[25] This agrees with findings from another study investigating conversion of standard opioid therapy to once-daily OROS® hydromorphone treatment.[54]

Hanna et al.[55] compared the efficacy and safety of once-daily OROS® hydromorphone with a twice-daily SR formulation of morphine in patients ($n = 200$) with chronic cancer pain. This bi-phasic, short-term, double-blind, comparative study aimed to show equivalence between twice-daily morphine and once-daily OROS® hydromorphone in relieving chronic cancer pain. The study involved both IR and SR phases of treatment for each compound. Equivalence was not demonstrated for the SR formulations for the primary endpoint of Brief Pain Inventory "worst pain in the past 24 hours;" however, the direction of the mean difference between the treatments was in favor of OROS® hydromorphone (least-squares mean [95% confidence interval] difference between the groups of –0.8 points [–1.6, –0.01]). OROS® hydromorphone also provided significantly better pain relief in the evening (Brief Pain Inventory "pain now PM") compared with morphine (least squares mean difference [95% confidence interval], –0.77 [–1.49, –0.05]; $P = 0.0372$), probably owing to its long duration of action. The frequency of breakthrough medication use remained stable throughout both phases in the morphine group, but decreased significantly from the IR phase to the SR phase in the OROS® hydromorphone group.

According to http://www.clinicaltrials.gov at the time of writing, there were 17 trials involving OROS® hydromorphone, three of which were specifically cancer orientated.

CONCLUSIONS

Opioids are currently the most effective treatment option for cancer pain. Long-acting formulations can improve chronic pain management by providing stable plasma concentrations resulting in around-the-clock analgesia with fewer daily doses. Once-daily OROS® hydromorphone has the advantages of convenience, effectiveness, a good safety profile, decreased use of rescue medication which may suggest a reduction in overall breakthrough pain, and quality of life benefits (patient satisfaction, quality of sleep). One trial has shown some superiority for OROS® hydromorphone over another SR opioid formulation; however, further trials are needed to provide evidence for its use as a treatment for cancer pain relief.

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