A new extended release formulation (OROS®) of hydromorphone in the management of pain

Sharon M Weinstein
University of Utah, Huntsman Cancer Institute, Salt Lake City, Utah, USA

Abstract: Opioid analgesics are essential in the treatment of moderate to severe cancer-related pain. Opioids are also recognized as important in the management of other severe, persistent refractory painful conditions, such as sickle cell disease and arthritis. In the clinical practice of pain management, stable opioid dosing generally depends on achieving maximal analgesia with tolerable side effects typical of opioid analgesics. There is a wide interindividual variability of responsiveness to exogenous opioids both in terms of analgesic efficacy and side effects. Optimizing pain management for the individual patient may require sequential trials of opioid medications until the regimen with the most favorable therapeutic ratio of efficacy to side effects is determined.

Keywords: analgesics, opioid, hydromorphone, OROS®, extended-release

Hydromorphone, a semi-synthetic opioid, is one of a family of closely related μ-agonist opioid drugs with dose-dependent analgesic properties. Hydromorphone has been used clinically to treat pain since the 1920s, and is commercially available in the United States in oral, rectal and injectible formulations.

A new formulation of extended release hydromorphone utilizing the OROS® technology has been demonstrated to provide sustained analgesia in patients with various types of chronic painful conditions. This new formulation may be advantageous to patients who tolerate hydromorphone well and other opioids poorly.

Opioid analgesics are essential in the treatment of moderate to severe cancer-related pain.[1–3] Opioids are also recognized as important in the management of other severe, persistent refractory painful conditions, such as sickle cell disease and arthritis.[4–11] In the clinical practice of pain management, stable opioid dosing generally depends on achieving maximal analgesia with tolerable side effects typical of opioid analgesics.[3] It is well known that there is a wide interindividual variability of responsiveness to exogenous opioids both in terms of analgesic efficacy and side effects. Optimizing pain management for the individual patient may require sequential trials of opioid medications until the regimen with the most favorable therapeutic ratio of efficacy to side effects is determined.

Correspondence: Sharon M Weinstein
Professor of Anesthesiology, Adjunct Associate Professor of Neurology and Medicine (Oncology), University of Utah Huntsman Cancer Institute, 2000 East Circle of Hope – Room 2151
Salt Lake City, Utah, USA 84112
Tel +1 801 585 0112
Fax +1 801 585 0159
Email sharon.weinstein@hci.utah.edu

Hydromorphone

Hydromorphone, a semi-synthetic opioid, is one of a family of closely related μ-agonist opioid drugs with dose-dependent analgesic properties (Figure 1). Hydromorphone has been used clinically to treat pain since the 1920s,[12] and is commercially available in the United States in oral, rectal and injectible formulations. Similar to other opioid agonists, hydromorphone does not have a ceiling effect for analgesia,[3] and doses can be increased as needed to relieve moderate to severe pain. The relatively short duration of action of oral hydromorphone limits its use for persistent daily pain. Around-the-clock

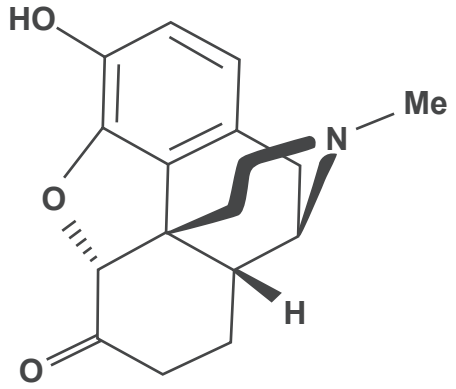

Figure 1 Chemical structure of hydromorphone.

dosing every 4 to 6 hours is often necessary to maintain adequate analgesia with immediate release oral preparations that have a relatively short duration of analgesic action.[13,14] For the treatment of acute post-operative pain, parenteral dosing intervals may be as short as every ten minutes using patient controlled analgesia devices. In the setting of short term acute pain management, parenteral opioids such as hydromorphone are advantageous for rapid titration to analgesia and downward dose tapering as pain improves.

Hydromorphone has been used to treat acute and chronic pain in adults and children. It is routinely administered via the oral, rectal, intravenous, subcutaneous and spinal (epidural and intrathecal) routes. In studies of subcutaneous hydromorphone implants, it was demonstrated that drug was steadily released for weeks in vitro and in vivo, producing plasma levels comparable to subcutaneous infusion.[15] There is no evidence that the abuse potential of hydromorphone differs from that of other opioids.[16–18]

There are several considerations in the choice of an initial opioid agonist medication and dosing schedule, including the personal history of efficacy and tolerability of different opioid analgesic medications.[19] Prescribers should be familiar with the pharmacokinetics and pharmacokinetics of opioid analgesics. Patients with chronic painful conditions are usually best managed with a combination of sustained action and immediate release form of the same opioid drug, for control of "background" and "breakthrough" pain. Clinical pain management guidelines include procedures for converting from one route of drug administration to another and from one opioid analgesic agent to another. When converting hydromorphone from the parenteral to oral route one should use the potency ratio of 1.5:7.5 (conversion factor of 5). Oral and rectal routes of administration are considered equipotent for the purpose of opioid conversions. The intravenous, subcutaneous and intramuscular routes are considered equipotent.[20,21]

Although hydromorphone may confer some advantages, caution should be used when prescribing for patients with renal insufficiency, as there is a potential for toxicity due to accumulation of glucuronidated by-products.[22,23]

Published guidelines also include methods for calculating equianalgesic doses of the different opioid agonist drugs.[3,13,19,24,25,26] For an initial opioid conversion, the use of a conservative dose is an appropriate strategy. Because of incomplete cross-tolerance among opioids,[27] it is recommended that initial doses be reduced to 50%–75% of the calculated equianalgesic dose. After the initial conversion, upward dose titration is usually necessary to attain an adequate analgesic response.[19,22,26,28] The data for the analgesic potency of hydromorphone compared to morphine are summarized in Table 1.

Single-dose comparison studies are an accepted method of establishing relative analgesic efficacy and potency, as well as onset, peak, and duration of analgesic effects.[29,30] A well-controlled relative potency study of parenteral morphine and hydromorphone in patients with postoperative pain resulted in ratios of 8.3–11.1:1 (morphine significantly less potent than hydromorphone).[31] The first study of the equianalgesic dose of morphine and hydromorphone in patients with cancer pain demonstrated an equivalence of parenteral morphine to hydromorphone of 7.9:1.[32] Single-dose relative potency studies showed that oral morphine is 1/6 as potent as intramuscular (IM) morphine,[33] that 10 mg of IM morphine is equianalgesic to 1.3 mg of IM hydromorphone,[19] and that IM hydromorphone is 5 times more potent than oral hydromorphone, suggesting that 60 mg of oral morphine and 7.5 mg of oral hydromorphone are approximately equianalgesic. These results indicate a conversion ratio of 8:1 (morphine:hydromorphone) for the oral formulations. In a repeated-dose study in patients with cancer-related pain, controlled-release hydromorphone and controlled-release morphine administered every 12 hours provided equivalent analgesia at a conversion ratio of 7.5:1.[34]

In two controlled clinical studies of 344 patients that compared the efficacy and safety of hydromorphone hydrochloride extended-release capsules with hydromorphone hydrochloride immediate-release tablets in the treatment of persistent moderate to severe pain (cancer and noncancer related), a conversion ratio of 8:1 mg of oral morphine to oral hydromorphone was used.[13,31,35]

In a retrospective clinical study comparing hydromorphone to morphine potencies, the authors observed a

Table 1 Relative analgesic potency of hydromorphone compared to morphine

Reference	Potency ratio	Comments
Bruera[42]	3.6:1	Converting oral hydromorphone to morphine
Lawlor et al[a,28] Mercandante[61]	3.7:1	Converting oral hydromorphone to morphine
Lawlor et al[a,28]	4.3:1	Average
Lawlor et al[a,28] Mercandante[61]	5:1	Converting oral morphine to hydromorphone
Bruera[42]	5.3:1	Oral morphine to hydromorphone
Grilo[62]	5.7:1	Oral morphine to hydromorphone
Wirz[63]	5:1	Oral morphine to hydromorphone
Lee[35]	7.7:1	Oral morphine to hydromorphone
Wallace[64]	5:1	Oral morphine to hydromorphone
Dunbar[65]	3:1	Comparing intravenous use via patient controlled analgesia
Rapp[66]	5:1	Intravenous patient controlled analgesia
Coda[67]	5:1	Intravenous patient controlled analgesia
Collins[68]	5.1:1	Pediatric; intravenous patient controlled analgesia
Miller[69]	5:1	Subcutaneous at end of life
Hill[70]	10:1	Intravenous morphine to hydromorphone
Mahler[31]	8.3–11.1:1	Intravenous morphine to hydromorphone
Weinstein[45]	8:1	Synthesis of previously published data applied in clinical trial of oral once-daily hydromorphone

[a]Data from oral and subcutaneous routes mixed.

range of 3.7–5:1 (morphine to hydromorphone) depending on the direction of conversion, but independent of initial dose level.[28]

Additional studies have indicated that the conversion ratios may depend on the direction of conversion, that is, to or away from hydromorphone as summarized in Table 1. It is clear that hydromorphone is significantly more potent than morphine on a milligram for milligram basis, regardless of the conversion direction or route of administration.

It cannot be overemphasized that conversion ratios are meant as an initial approximation and that individual clinical circumstances influence the calculation of an opioid dose.[4,13,19,26] Close monitoring of patients is generally recommended during further titration after the initial conversion from one opioid agonist to another.

Hydromorphone yields metabolites, especially the hydromorphone-3-glucuronide, that may contribute to excitotoxic neurologic states. With high dose administration, myoclonus and seizures may occur. The rare syndrome of hyperalgesia may manifest initially as worsening intensity of the pain syndrome and new, discrete allodynia in the saddle region (the author has observed this with high dose intrathecal administration). If these symptoms emerge, patients may respond to opioid rotation, dose reduction and administration of benzodiazepine.[36,37,38]

Modified-, controlled-, sustained- or extended-release formulations of opioids have been in clinical use for over 25 years. Such formulations of hydromorphone hydrochloride have been developed to provide sustained analgesia for patients requiring medication for the control of persistent daily pain. Consistent pharmacokinetics and pharmacodynamics have been demonstrated with formulations designed for every 12- and every 24-hour dosing in patients with cancer and noncancer related pain.[35,39–46]

Palladone™, a 24-hour hydromorphone product, was voluntarily withdrawn from the United States market by the manufacturer due to the potential for "dose dumping" when it was ingested simultaneously with alcohol, although no such adverse events were reported to have occurred during post-marketing surveillance.[47,48]

In summary, hydromorphone is a safe and effective opioid agonist analgesic for the management of acute and chronic pain of various etiologies in patients of all ages.

OROS® hydromorphone

OROS® is a patented technology for the osmotic-controlled release oral delivery of medication. OROS® has been reported to produce stable drug concentrations, uniform drug effects, reduced dosing frequency and an improved safety profile. A review of the technology development over

the past 30 years has indicated that there are four different systems: the elementary osmotic pump, the two-layer osmotic push-pull tablet, the advanced longitudinally compressed tablet multilayer formulation, and the L-OROS™ system. These systems have been applied in several different therapeutic areas.[49] According to the manufacturer, OROS® technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours, can be used with a range of compounds, and may enhance bioavailability due to more efficient drug absorption. There are currently thirteen OROS® commercial products available worldwide.[50] In 2006, Jurnista™, a hydromorphone formulation utilizing the OROS® Push-Pull delivery system, was released in Europe after completing the European Mutual Recognition Program. Four dosage strengths will be available – 8, 16, 32 and 64 mg – for once-daily (every 24 hours) dosing.[51]

Two studies of OROS® hydromorphone formulations have been recently reported. In one study, the pharmacokinetics of intravenous, oral immediate-release and oral extended-release (OROS®) formulations were compared. The OROS® formulation produced continuous release of medication over 24 hours, predicted to allow once daily dosing. The authors concluded that the formulation will produce less fluctuation in plasma concentrations compared with repeated immediate-release equivalent dosing and that the formulation should therefore provide more consistent analgesic effect. The OROS® formulation was noted to have greater bioavailability, possibly related to decreased first-pass effect or enterohepatic recycling of drug.[52]

An open-label, repeated-dose, single-treatment study evaluated the outcomes associated with standardized conversion from prior opioid therapy to the OROS® hydromorphone in patients with chronic malignant or nonmalignant pain. Eligibility criteria included baseline oral morphine equivalent requirement of greater than or equal to 45 mg daily. Over 400 patients received study drug. Significant improvements in pain were noted with OROS® hydromorphone compared to prestudy medications. Adverse events were consistent with those expected, ie, side effects affecting primarily the gastrointestinal and central nervous systems.[53]

Several studies have supported the safety and efficacy of this formulation in the treatment of cancer related and other acute and chronic painful conditions.[54–58]

A recent report revealed that when ingested with alcohol, dissolution of OROS® hydromorphone was not significantly altered, ie, there was no "dose dumping."[59]

Conclusion

With extended-release hydromorphone formulations available, those patients who tolerate hydromorphone far better than other opioids will be able to be treated with single agent opioid pharmacotherapy in a safe and convenient manner. Further research will be needed to establish the cost-effectiveness and advantages of long term treatment with extended-release hydromorphone preparations, particularly the OROS® formulation. One German study anticipated cost-effectiveness of this formulation for the treatment of pain associated with osteoarthritis.[60]

Given the prevalence of chronic painful conditions; the wide interindividual variability in responsiveness to opioids; and our aging population that will have an increasing need for safe and effective analgesics; broader clinical applications of new extended-release preparations of opioids can be anticipated. The OROS® hydromorphone will likely find a therapeutic niche in the treatment of those patients with chronic painful conditions who have a more favorable therapeutic response to hydromorphone compared to other opioids. Clinical practitioners are encouraged to familiarize themselves with the pharmacology of opioids and to follow established guidelines for the management of pain that emphasize individualized treatment for optimal therapeutic outcomes.

Disclosures

The author has no conflicts of interest to disclose.

References

1. Bonica JJ, Ekstrom JL. Systemic opioids for the management of cancer pain: An updated review. In: Benedetti C, Chapman CR, Giron G, (eds.) Opioid Analgesia: Recent Advances in Systemic Administration. New York: Raven Press. *Adv Pain Res Ther.* 1990;14:425–446.
2. World Health Organization. Cancer Pain Relief. Geneva: World Health Organization. 1986.
3. Jacox A, Carr DB, Payne R, et al. Management of Cancer Pain. Clinical Practice Guideline No. 9. Rockville, Md: Agency for Health Care Policy and Research, US Department of Health and Human Services, Public Health Service. AHCPR Publication No. 94-0592. 1994.
4. Schug SA, Merry AF, Acland RH. Treatment principles for the use of opioids in pain of nonmalignant origin. *Drugs*. 1991;42:228–239.
5. Zenz M, Strumpf M, Tryba M. Long-term oral opioid therapy in patients with chronic nonmalignant pain. *J Pain Symptom Manage*. 1992;7:69–77.
6. Portenoy RK. Opioid therapy for chronic nonmalignant pain: A review of the critical issues. *J Pain Symptom Manage*. 1996;11:203–217.
7. A Consensus Statement from the American Academy of Pain Medicine and the American Pain Society. The use of opioids for the treatment of chronic pain. *Clin J Pain*. 1997;13:6–8.
8. Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain. *Arch Intern Med*. 2000;160:853–860.
9. Guidelines for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis, 2nd Edition, 2002. American Pain Society, Skokie, IL.

10. Guidelines for the Management of Acute and Chronic Pain in Sickle Cell Disease, 1999. American Pain Society, Skokie, IL.
11. Shiaova L, Wallenstein D. Outpatient management of sickle cell pain with chronic opioid pharmacotherapy. *J Natl Med Assoc*. 2004;96(7):984–986.
12. Lullies G. Unsere Erfahrungen mit Dilaudid [Our experience with Dilaudid]. *Munch Med Wochenschr*. 1929;70:1463–1464.
13. Foley KM. The treatment of cancer pain. *N Engl J Med*. 1985;313:84–95.
14. Hays H, Hagen N, Thirlwell M, et al. Comparative clinical efficacy and safety of immediate release and controlled release hydromorphone for chronic severe cancer pain. *Cancer*. 1994;74:1808–1816.
15. Lesser GJ, Grossman SA, Leong KW et al. In vitro and in vivo studies of subcutaneous hydromorphone implants designed for the treatment of cancer pain. *Pain*. 199s;65(2–3):265–272.
16. Murray A, Hagen NA. Hydromorphone. *J Pain Sympt Manage*. 2005;29(Suppl 5):S57–66.
17. Quigley C, Wiffen P. A systematic review of hydromorphone in acute and chronic pain. *J Pain Sympt Manage*. 2003;25(2):169–178.
18. Quigley C. Hydromorphone for acute and chronic pain. *Cochrane Database Syst Rev*. 2002;(1):CD003447.
19. American Pain Society. Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain. 3rd ed. Skokie, Ill: American Pain Society. 1992.
20. Durnin C, Hind ID, Ghani SG, Yates DB, Cross M. Pharmacokinetics of oral immediate-release hydromorphone (Dilaudid® IR) in young and elderly subjects. *Proc West Pharmacol Soc*. 2001;44:79–80.
21. Durnin C, Hind ID, Ghani SG, Yates DB, Cross M. Dose proportionality of the pharmacokinetics of oral immediate-release hydromorphone (Dilaudid® IR). *Proc West Pharmacol Soc*. 2001;44:73–74.
22. Lee MA, Leng MEF, Tiernan EJJ. Retrospective study of the use of hydromorphone in palliative care patients with normal and abnormal urea and creatinine. *Palliat Med*. 2001;15:26–34
23. Fainsinger R, Schoeller T, Boiskin M, Bruera E. Cognitive failure and coma after renal failure in a patient receiving captopril and hydromorphone. *J Palliat Care.* 1993;9(1):53–55.
24. Kaiko RF. Commentary: equianalgesic dose ratio of intramuscular/oral morphine, 1:6 versus 1:3. In: Foley KM, Inturrisi CE (ed.) *Adv Pain Res Ther*. New York: Raven, 1986;8:p. 87–94.
25. Cherny NI. Opioid analgesics. Comparative features and prescribing guidelines. *Drugs*. 1996;51:713–737.
26. Gutstein HB, Akil H. Opioid analgesics and antagonists. In: Hardman JG, Limbird LE, (eds.) Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th ed. New York: McGraw-Hill. 2001;p. 569–619.
27. Houde RW, Wallenstein SL, Beaver WT. Evaluation of analgesics in patients with cancer pain. In: Lasagna L, ed. International Encyclopedia of Pharmacology and Therapeutics. Section 6, *Clin Pharmacol*. 1. Oxford: Pergamon Press. 1966;p. 59–97.
28. Lawlor P, Turner K, Hanson J, Bruera E. Dose ratio between morphine and hydromorphone in patients with cancer pain: a retrospective study. *Pain*. 1997;72(1–2):79–85.
29. Max MB, Laska EM. Single-dose analgesic comparisons. In: Max MB, Portenoy RK, Laska EM, (eds.) The Design of Analgesic Clinical Trials. New York: Raven Press. *Adv Pain Res Ther*. 1991;18:p. 55–95
30. Guideline for the Clinical Evaluation of Analgesic Drugs. Rockville, Md: US Dept of Health and Human Services, Public Health Service, Food and Drug Administration. *FDA Publication.* 1992;93–3093.
31. Mahler DL, Forrest WH Jr. Relative analgesic potencies of morphine and hydromorphone in postoperative pain. *Anesthesiology*. 1975;42:602–607.
32. Houde RW. Clinical analgesic studies of hydromorphone. In: Foley KM, Inturrisi CE, (eds.) Opioid Analgesics in the Management of Clinical Pain. New York: Raven Press. *Adv Pain Res Ther*. 1986;8: p. 129–135.
33. Houde RW, Wallenstein SL, Beaver WT. Clinical measurement of pain. In: de Stevens G, ed. Analgetics. New York: Academic Press. 1965;p. 75–122.
34. Moriarty M, McDonald CJ, Miller AJ. A randomised crossover comparison of controlled release hydromorphone tablets with controlled release morphine tablets in patients with cancer pain. *J Clin Res*. 1999;2:1–8.
35. Grosset AB, Roberts MS, Woodson ME, et al. Comparative efficacy of oral extended-release hydromorphone and immediate release hydromorphone in patients with persistent moderate to severe pain: two randomized controlled trials. *J Pain Symptom Manage*. 2005;29(6):584–594.
36. Smith MT. Neurotoxicity effects of morphine and hydromorphone evidence implicating the 3-glucuronide metabolites. *Clin Exp Pharmacol Physiol*. 2000;27(7):524–528.
37. Wright AWE, Mather LE, Smith MT. Hydromorphone-3-glucuronide: A more potent neuro-excitant than its structural analogue, morphine-3-glucuronide. *Life Sci.* 2001;69:409–420.
38. Thwaites D, McCann S, Broderick P. Hydromorphone neuroexcitation. *Palliat Med*. 2004;7(4):545–550.
39. Angst MS, Drover DR, Lotsch J, et al. Pharmacodynamics of orally administered sustained-release hydromorphone in humans. *Anesthesiology*. 2001;94(1):63–73.
40. Hagen N, Thirlwell MP, Dhaliwal HS, et al. Steady-state pharmacokinetics of hydromorphone and hdyromorphone-3-glucuronide in cancer patients after immediate and controlled-release hydromorphone. *J Clin Pharmacol*. 1995;35(1):37–44.
41. Hays H, Hagen N, Thirlwell M, et al. Comparative clinical efficacy and safety of immediate release and controlled release hydromorphone for chronic severe cancer pain. *Cancer*. 1994;74(6):1808–1816.
42. Bruera E, Sloan P, Mount B, et al. A randomized, double-blind, double-dummy, crossover trial comparing the safety and efficacy of oral sustained-release hydromorphone with immediate-release hydromorphone in patients with cancer pain. Canadian Palliative Care Clinical Trials Group. *J Clin Oncol*. 1996;14(5):1713–1717.
43. Hagen NA, Babul N. Comparative clinical efficacy and safety of a novel controlled-release oxycodone formulation and controlled-release hydromorphone in the treatment of cancer pain. *Cancer*. 1997;79(7):1428–1437.
44. Vashi V, Harris S, El-Tahtawy A, et al. Clinical pharmacology and pharmacokinetics of once daily hydromorphone hydrochloride extended-release capsules. *J Clin Pharmacol*. 2005;45(5):547–554.
45. Weinstein SM, Headley DL, Shi MG, et al. Multicenter, open-label, prospective evaluation of the conversion from previous opioid analgesics to extended-release hydromorphone administered every 24 hours to patients with persistent moderate to severe pain. *Clin Ther*. 2006;28(1):86–98.
46. Nadstawek J, Wartenberg HC, Schenk M, Wirz S. Hydromorphone in elderly patients with polypathia and with severe pain. *The Pain Clinic.* 2006;18(5–6):403–413.
47. FDA ALERT: Alcohol-Palladone™ Interaction; www.fda.gov. [07/2005]
48. Health and Drug Alerts: Alcohol-associated rapid release of a long-acting opioid. JAMC. 2005;173(7); www.cmaj.ca
49. Conley R, Gupta SK, Sathyan G. 2006. Clinical spectrum of the osmotic-controlled release oral delivery system (OROS), an advanced oral delivery form. *Curr Med Res Opin*. 2005;10:1879–1892.
50. www.ALZA.com – OROS® Oral Delivery Technology; accessed January 2007.
51. info@prnewswire.co.uk; www.janssen-cilag.com – JURNISTA™; accessed January 2007.
52. Drover DR, Angst MS, Valle M, Ramaswamy B, Naidu S, Stanki Dr, Verotta D. 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.
53. Palangio M, Northfelt DW, Portenoy RK, Brookoff D, Doyle RT Jr, Dornseif BE, Damask MC. Dose conversion and titration with a novel, once daily, OROS osmotic technology, extended-release formulation in the treatment of chronic malignant or nonmalignant pain. *J Pain Symptom Manage*. 2002;23(5):355–368.

54. Sathyan G, Xu E, Thipphawong J, Gupta SK. Pharmacokinetic investigation of dose proportionality with a 24 hour controlled-release formulation of hydromorphone. *BMC Clin Pharmacol*. 2007;7:3.
55. Gupta S, Sathyan G. Providing constant analgesia with OROS hydromorphone. *J Pain Symptom Manage*. 2007;33:2S:S19–S24.
56. Sathyan G, Xu E, Thipphawong J, Gupta SK. Pharmacokinetic profile of the 24-hour controlled release OROS formulation of hydromorphone in the presence and absence of food. *BMC Clinical Pharmacology*. 2007; 7:2.
57. Wallace MS, Thipphawong J. Clinical trial results with OROS hydromorphone. *J Pain Symptom Manage*. 2007;33:2S:S25–S32.
58. Wallace M, Skowronski R, Khanna S, Tudor IC, Thipphawong J. Efficacy and safety evaluation of once-daily OROS hydromorphone in patients with chronic low back pain: a pilot open-label study (DO-127). *Curr Med Res Opin*. 2007;23(5):981–989.
59. Sathyan G, Sivakumar K, Thipphawong J. Pharmacokinetic profile of a 24-hour controlled-release OROS formulation of hydromorphone in the presence of alcohol. *Curr Med Res Opin*. 2008;24(1):297–305.
60. Ward A, Bozkaya D, Fleischmann J, Dubois D, Sabatowski R, Caro JJ. Modeling the economic and health consequences of managing chronic osteoarthritis pain with opioids in Germany: comparison of extended-release oxycodone and OROS hydromorphone. *Curr Med Res Opin*. 2007;23(10):2333–2345.
61. Mercandate S. Opioid rotation for cancer pain: rationale and clinical aspects. *Cancer*. 1999;86(9):1856–1866.
62. Grilo RM, Bertin P, Scotto di Fazano C. Opioid rotation in the treatment of joint pain. A review of 67 cases. *Joint Bone Spine*. 2002;69(5):491–494.
63. Wirz S, Wartenberg HC, Elsen C, Wittmann M, Diederichs M, Nadstawek J. Managing cancer pain and symptoms of outpatients by rotation to sustained-release hydromorphone: a prospective clinical trial. *Clin J Pain*. 2006;22(9):770–775.
64. Wallace M, Rauck RL, Moulin D, Thipphawong J, Khanna S, Tudor IC. Once-daily OROS hydromorphone for the management of chronic nonmalignant pain: a dose-conversion and titration study. *Int J Clin Pract*. 2007;61(10):1671–1676.
65. Dunbar PJ, Chapman CR, Buckley FP, Gavrin JR. Clinical analgesic equivalence for morphine and hydromorphone with prolonged PCA. *Pain*. 1996;68(2–3):265–270.
66. Rapp SE, Egan KJ, Ross BK, Wild LM, Terman GW, Ching JM. A multidimensional comparison of morphine and hydromorphone patient-controlled analgesia. *Anesth Analg*. 1996;82(5):1043–1048.
67. Coda B, Tanaka A, Jacobson RC, Donaldson G, Chapman CR. Hydromorphone analgesia after intravenous bolus administration. *Pain*. 1997;71(1):41–48.
68. Collins JJ, Geake J, Grier HE, Houck CS, Thaler HT, Weinstein HJ, Twum-Danso NY, Berde CB. Patient-controlled analgesia for mucositis pain in children: a three-period crossover study comparing morphine and hydromorphone. *J Pediatr*. 1996;129(5):722–728.
69. Miller MG, McCarthy N, O'Boyle CA, Kearney M. Continuous subcutaneous infusion of morphine vs. hydromorphone: a controlled trial. *J Pain Symptom Manage*. 1999;18(1):9–16.
70. Hill JL, Zacny JP Comparing the subjective, psychomotor, and physiological effects of intravenous hydromorphone and morphine in healthy volunteers. *Psychopharmacology (Berl)*. 2000;152(1):31–39.