Oxymorphone HCl (Opana) for the Relief of Moderate-to-Severe Pain

Jennifer Lind, PharmD Candidate, Jaclyn Lennard, PharmD Candidate, Patty Ghazvini, PharmD, Marlon Honeywell, PharmD, and Phillip Treadwell, PharmD

INTRODUCTION

Pain is an unpleasant sensory and emotional sensation that ranges in intensity, and it has the potential to cause patients unnecessary emotional and physical distress. It is a primary reason for seeking medical attention for 50 million Americans who might be partially or totally disabled by pain.[1] The management of pain costs Americans billions of dollars annually, and the demand for appropriate pain management is expected to escalate even further as many Americans plan to work until older ages and live longer.

Pain management depends on the classification of the pain. *Acute* pain is described as sharp or shooting; it is usually localized and temporary. It responds well to treatment and usually subsides when the pain-producing stimulus resolves. *Chronic* pain can last for six months or longer. The etiology may be multifactorial, but the cause might not be evident. Commonly associated with adverse effects on quality of life, chronic pain is more difficult to manage and warrants comprehensive medical treatment.

Although advances in the pathophysiology of pain have led to improved pharmacological therapies, a multidisciplinary approach to the treatment of pain leads to better outcomes.[2–4] Appropriate pharmacological therapy—as well as attention from a health care network consisting of, but not limited to, pharmacists, physicians, physical therapists, and psychiatrists or psychologists—is required. Each patient should be managed individually based upon the cause of the pain and various comorbidities. Unfortunately, because of its subjective nature, pain is often mistreated or undertreated. Severe, unremitting, undertreated pain can erode a patient's well-being.

Ms. Lind and Ms. Lennard are sixth-year pharmacy students at Florida A&M University College of Pharmacy in Tallahassee, Florida. Dr. Ghazvini is Assistant Professor of Pharmacy Practice and Dr. Honeywell is Associate Professor of Pharmacy Practice, both in the university's College of Pharmacy. Dr. Treadwell is Assistant Director of Clinical Pharmacology at the Family Medicine Residency Clinic at Tallahassee Memorial Hospital in Tallahassee. Drug Forecast is a regular department coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi & Associates in New York.

PATHOPHYSIOLOGY OF PAIN

The most common type of pain is *nociceptive*. Clinically, pain can be classified as "nociceptive" if it can be determined that the pain is related to the degree of receptor stimulation by processes that cause tissue injury.[5] Potential causes of the tissue injury include a cut, bruise, bone fracture, crush injury, a burn, or cancer.[6]

Nociceptive pain involves the activation of peripheral pain receptors (nociceptors) by active tissue damage or noxious stimuli and includes somatic and visceral pain.[6–8] *Somatic pain* originates from damage to the skin, muscle, or bone; it presents as an aching, throbbing, stabbing pain, with or without a pressure sensation.[7] *Visceral pain* results from damage to internal organs; it is characterized by a gnawing, cramping, aching, sharp pain, with or without a stabbing sensation.[7]

Normal somatosensory processing of pain involves the interaction between afferent systems activated by the tissue injury and the accompanying inflammation.[5] The primary afferent system includes nociceptors (sensory neurons), signal processing in the dorsal horn of the spinal cord, ascending neural pathways, and thalamic and other specialized brain structures.[5] Peripheral nociceptors are located in the skin, muscle, joints, and some visceral tissues.

In the pathophysiology of nociceptive pain, nociception consists of four steps:[5,9]

1. The process begins with *transduction (depolarization)*, which is the response of peripheral nociceptors to noxious stimuli.
2. *Transmission* is the process by which the stimuli proceed along the primary afferent nociceptive axons to the spinal cord and then on to the brain.[5]
3. After the impulses reach the brain, they are intellectually recognized by the patient as pain in the process known as *perception*.
4. The final process is *modulation*, in which nociceptive impulses are inhibited. Pain modulation is determined by activity in the endorphinergic system and other pain-modulating systems.[5]

In the endorphinergic system, pain relief is mediated by the binding of endogenous opioid compounds to the subset of mu, delta, and kappa receptors.[5] Endorphins are widely distributed in the body and are closely related to systems that regulate homeostasis, response to stress, and pain.[5]

PAIN MANAGEMENT

Available options for the treatment of moderate-to-severe pain include *non-opioid* and *opioid* analgesics. Non-opioid analgesics approved for moderate-to-severe pain are ketorolac (Toradol, Roche) and indomethacin (Indomethacin ER, Sandoz). They work by preventing the formation of prostaglandins produced in response to noxious stimuli, thereby decreasing the number of pain impulses received by the central nervous system (CNS).[1]

Opioids are the most potent analgesics available and are well established for the treatment of acute and chronic pain.[10,11] Opioid analgesics consist of (1) opiate agonists, (2) opiate antagonists, and (3) mixed agonists/antagonists.

Opiate agonists are the most common types. They bind to the opioid receptors in the CNS, leading to analgesia.[12,13]

Examples include hydrocodone (Lortab, UCB Pharma); oxycodone (OxyContin, Purdue); codeine compounds; hydromorphone (Dilaudid, Abbott); methadone; morphine (DepoDur, Endo); levorphanol; meperidine (Demerol, Sanofi-Synthelabo); tramadol (Ultram, PriCara/Ortho McNeil); fentanyl (Duragesic, PriCara/Ortho-McNeil); and oxymorphone (Opana, Endo).

Examples of *opioid antagonists* include naloxone (e.g., Suboxone, Reckitt Benckiser; Talwin NX, Sanofi-Synthelabo) and naltrexone (Vivitrol, Alkermes/Cephalon; ReVia, DuPont/Merck).

Mixed agonists/antagonists include nalbuphine (Nubain, Endo); butorphanol (Stadol, Apothecon); pentazocine (Talwin, Talacen, Sanofi-Synthelabo); and buprenorphine (Suboxone, Subutex, Reckitt Benckiser).

Pure opioid antagonists act by binding competitively to opioid receptors without producing an analgesic or opioid response.[1] They are therefore used most often to reverse the toxic effects of agonist and agonist–antagonist opioids.

Agonist–antagonists stimulate the analgesic portion of the opioid receptors and at the same time minimize the effect on the toxicity portion. They produce analgesia and have a ceiling effect on respiratory depression.[1]

OXYMORPHONE HCl

Oxymorphone HCl immediate-release (IR) tablets (Opana IR, Endo) and extended-release oxymorphone tablets (Opana ER) were approved by the U.S. Food and Drug Administration (FDA) on June 22, 2006 for the relief of moderate-to-severe pain.[14]

Opana ER is indicated for the relief of moderate-to-severe pain in patients requiring continuous opioid treatment for an extended period of time, but it is not intended to be used on an as-needed basis. Opana ER tablets come in 5-mg, 10-mg, 20-mg, and 40-mg strengths.[12]

Opana IR tablets are indicated for the relief of moderate-to-severe acute pain when the use of an opioid is appropriate. They are available in 5-mg and 10-mg strengths.

The Opana products are the only available oral formulations of oxymorphone, which previously was available only in an injectable form (Numorphan, Endo).

Current data indicate that oral oxymorphone does not inhibit or induce the cytochrome P450 (CYP 450) metabolic pathways, and it is not significantly metabolized by CYP 450 enzymes.[15–17]

CLINICAL STUDIES

Adams et al.[18]

A randomized, three-period, four-sequence, crossover study assessed the pharmacokinetics of four dose levels of oxymorphone ER in 24 healthy volunteers. Patients were randomly assigned to receive three of four possible doses of oxymorphone ER tablets: 5, 10, 20, and 40 mg. The three eight-day administration periods were separated by seven-day washout periods.

To protect against potential opioid-related effects, the researchers gave the patients naltrexone 50 mg once a day, beginning on the evening before the first dose of oxymorphone ER on day one and continuing until the evening of day seven. Plasma was collected for up to 48 hours after a single dose on the first day and during a 12-hour dosage interval at steady state.[8]

Dose proportionality and linearity were confirmed after single doses and at steady state. Trough concentrations of oxymorphone and its metabolites, measured before administration of the morning dose on days six to eight, indicated that steady-state conditions were achieved after three days of dosing every 12 hours. After single doses, the mean oxymorphone ER area-under-the-concentration-versus-time curve (AUC) was 4.54 with 5 mg, 8.94 with 10 mg, 17.80 with 20 mg, and 37.90 ng • hour/ml with 40 mg.

The mean terminal elimination half-life of oxymorphone ER was 11.30 hours with 5 mg, 9.83 with 10 mg, 9.89 with 20 mg, and 9.35 hours with 40 mg.

The maximum plasma concentration (C_{max}) for oxymorphone ER, which was the highest level observed during a dosage interval, was 0.27 with 5 mg, 0.65 with 10 mg, 1.21 with 20 mg, and 2.59 ng • hour/ml for 40 mg.

Linear pharmacokinetic parameters at steady state were supported by the nearly linear progression for all concentration-dependent variables as the dosage increased from 5 to 40 mg every 12 hours and by the absence of any meaningful differences in oxymorphone clearance across the four dosages. At steady state, the mean AUC concentration for oxymorphone ER was 5.60 with 5 mg, 9.77 with 10 mg, 19.3 with 20 mg, and 37 ng • hour/ml with 40 mg every 12 hours.

The plasma levels of metabolites also increased in a linear fashion after single-dose administration and at steady state. Therefore, the pharmacokinetic profile of oxymorphone ER demonstrated linearity and dose proportionality under single-dose and steady-state conditions for the parent compound and its metabolites at doses of 5 to 40 mg.[8]

Gimbel et al.[19]

A multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-ranging study compared three oxymorphone IR doses (10, 20, and 30 mg) with placebo for efficacy and safety in patients with acute moderate-to-severe postsurgical pain.

Total pain relief, which was determined via a five-point scale, at all doses of oxymorphone IR was statistically superior to placebo. A dose-dependent relationship was significant for oxymorphone IR, which reached an analgesic plateau at the 20-mg dose.

The median time to pain relief was significantly shorter in all of the oxymorphone IR groups (one hour) than in the placebo groups (1.5 hours) ($P < 0.05$). When dose intervals were averaged from the first to the third day for all patients, the longest median dose interval was observed with a dose of 30 mg: 9 hours, 39 minutes. For the other three active-treatment groups, the median dose intervals ranged from 7 hours to 7 hours, 44 minutes.

The most frequent adverse drug events (ADEs) with oxymorphone IR were mild-to-moderate opioid side effects such as nausea, vomiting, and somnolence. Serious ADEs occurred in 15 of the 464 patients enrolled. Five of these serious ADEs were considered possibly related (hypotension, excessive diaphoresis, somnolence) or probably related (coma) to oxymorphone IR 20 or 30 mg. There were no meaningful changes in any laboratory results, vital signs, or physical examination findings.

This study established the analgesic efficacy and safety of single and multiple doses of oxymorphone IR. All three doses were superior to placebo. Significant pain relief, achieved with oxymorphone IR during the single-dose phase,

was maintained with multiple doses over consecutive days. The median time to pain relief for patients taking oxymorphone IR was one hour, and ADEs were similar to those associated with oxycodone CR.

In conclusion, oxymorphone IR 10, 20, and 30 mg provided effective, dose-related relief of moderate-to-severe acute pain that was maintained over consecutive days with multiple dosing.

Hale et al.[20]

A multicenter, randomized, double-blind, placebo-controlled, active-controlled trial was conducted to compare the analgesic efficacy and safety of oxymorphone ER with placebo and oxycodone controlled release (CR) in ambulatory patients with moderate-to-severe chronic low back pain who required opioid therapy. Patients received oxymorphone ER 10 to 110 mg or oxycodone CR 20 to 220 mg every 12 hours during a seven-day to 14-day dose-titration phase.

Patients who achieved analgesia at a stable opioid dose entered an 18-day double-blind treatment phase. These patients either continued opioid therapy or received placebo.

The use of rescue medication was permitted with oral morphine sulfate 15 mg every four to six hours on an unlimited basis for the first four days to minimize the risk of opioid-withdrawal symptoms in the patients who received placebo. After the first four days, rescue medication was limited to a total of 30 mg/day. No other analgesics—opioid or non-opioid—were permitted during the study.

Because of the titration phase, all of the patients had achieved analgesia at the beginning of the treatment phase. The mean change in pain intensity from baseline to endpoint was significantly greater with the use of placebo than with oxymorphone ER or oxycodone CR. This indicated that the placebo patients, after being stabilized with an opioid in the titration phase, experienced a large increase in pain intensity, compared with patients who continued with opioid therapy.

Patients who continued with either oxymorphone or oxycodone experienced comparable changes in pain intensity. Pain ratings were significantly lower for patients receiving oxymorphone ER than for those receiving placebo ($P = 0.0001$).

ADEs were similar for oxymorphone ER and oxycodone CR; the most frequent ADEs were constipation and sedation. Both drugs were generally safe and effective for controlling low back pain.

Both oxymorphone ER and oxycodone CR provided significant analgesia with comparable ADE profiles. Oxymorphone ER was equianalgesic to oxycodone CR at almost half the milligram dose. Oxymorphone ER offered superior analgesic efficacy compared with placebo.

Fifty-seven percent of patients who received placebo dropped out of the trial because of lack of efficacy, compared with 16% to 20% of those who were treated with an opioid.

McIlwain et al.[21]

A 52-week, multicenter, open-label extension study was performed at 32 centers in the U.S. to evaluate the safety, tolerability, and effectiveness of oxymorphone ER in 153 patients with moderate-to-severe chronic osteoarthritis-related pain. Patients were eligible for this trial only after completing a previous randomized, double-blind, placebo-controlled and active-controlled trial.

The study population for the newer trial included opioid-naive patients from the placebo arm of the original trial. Most patients received an initial dose of 20 mg every 12 hours, but an alternative initial dose was permitted at the discretion of the investigator.

Patients who had received oxymorphone ER or oxycodone CR in the original trial continued at the same milligram dose with oxymorphone ER.

Throughout this study, oxymorphone ER was found to be safe and effective for the relief of moderate-to-severe chronic osteoarthritis-related pain. Patients remained stable, at mild levels of pain intensity, with regular dosing every 12 hours.

More than 80% of the patients rated their overall satisfaction with oxymorphone ER as "excellent," "very good," or "good." Only a small number of patients (7%–8%) withdrew as a result of insufficient therapeutic efficacy.

Opioid rescue medication was not permitted, yet few patients withdrew because of insufficient therapeutic effect. This suggests that oxymorphone ER provided complete 12-hour analgesia for chronic pain on a long-term basis.

Katz et al.[22]

A 12-week, randomized, placebo-controlled study was conducted to determine the efficacy and tolerability of oxymorphone ER in opioid-naive patients with moderate-to-severe chronic low back pain. The study included patients 18 years of age and older. Doses were titrated with oxymorphone ER in 5- to 10-mg increments every 12 hours, every three to seven days, until a well-tolerated, stabilized dose was reached. In 63% of the patients, the dose was stabilized, usually within a one-month time period. Patients were then assigned to continue their oxymorphone ER dose or to receive placebo every 12 hours for 12 weeks.

Oxymorphone IR was also available every four to six hours, as needed, for the first four days and twice daily for the remainder of the study.

After randomization, 68% of the oxymorphone ER and 47% of the placebo patients completed 12 weeks of double-blind treatment. Pain intensity increased significantly more in the placebo group of patients than in the oxymorphone ER group ($P < 0.0001$).

Oxymorphone ER was well tolerated without unexpected ADEs. During titration, 18% discontinued because of ADEs and 1% as a result of a lack of efficacy. After randomization, approximately 8% of patients in each group discontinued therapy because of ADEs. Placebo patients discontinued treatment sooner as a result of a lack of efficacy than those receiving oxymorphone ER ($P < 0.0001$).

Opioid withdrawal was limited to two patients in the placebo group and one in the oxymorphone ER group. Therefore, stabilized doses of oxymorphone ER were generally safe and effective over a 12-week, double-blind treatment period for these patients.

Hale et al.[23]

Another 12-week, randomized, double-blind, placebo-controlled trial demonstrated the efficacy and safety of oxymorphone ER for opioid-experienced patients with chronic, moderate-to-severe low back pain. Patients had to be at least 18 years of age and had to be currently receiving a stable, around-the-clock opioid pain medication equivalent to at least 60 mg/day of oral morphine.

This study consisted of two stages in order to assess efficacy in long-term pain

continued on page 321

continued from page 318

relief. All patients were switched to an almost equianalgesic dose of oxymorphone ER and were entered into an open-label titration period. After they were stabilized with a twice-daily dose that provided adequate pain relief and tolerability, they were entered into a 12-week, double-blind, placebo-controlled treatment period. Stabilized patients (n = 143) either continued with their fixed dose of oxymorphone ER or received placebo. Oxymorphone 5-mg tablets were available as needed for withdrawal symptoms.

The primary efficacy endpoint was the change in average pain intensity from the baseline evaluation to the final study visit.

Pain intensity increased significantly with placebo, whereas oxymorphone ER maintained effective analgesia throughout the entire 12 weeks at the same stabilized dose. Placebo patients were approximately eight-fold more likely than treated patients to stop treatment because of a lack of efficacy ($P < 0.001$). The most frequently reported adverse events were nausea, constipation, headache, and somnolence.

Oxymorphone ER provided efficacious, long-term analgesia and was well tolerated for these patients.

ADVERSE EVENTS

Adverse effects most commonly seen with oxymorphone ER and IR are respiratory depression, hypotension, constipation, nausea, vomiting, fatigue, drowsiness, dizziness, and histamine release.[24] Opana is a Schedule II controlled substance with an abuse potential similar to that of morphine, and there is a potential for physical and psychological dependence.[12,25]

CONTRAINDICATIONS

This product should not be given to:[12]

- patients with a known hypersensitivity to oxymorphone HCl or to any of its ingredients or with a known hypersensitivity to morphine and to morphine analogues like codeine
- patients with respiratory depression unless they are being monitored and resuscitative equipment is at hand
- patients with acute or severe bronchial asthma or hypercarbia
- patients who have or might have paralytic ileus
- patients with moderate or severe hepatic impairment

CONCLUSION

Opana, an oral opioid agonist, is a new option in the armametarium of opioid agonists. In clinical trials, it was found to be safe and effective in relieving moderate-to-severe pain. Opana has been studied clinically for several types of pain, including back pain, postoperative pain, and osteoarthritis pain. All of the trials indicated no significant increase in ADEs, compared with placebo.

Unlike other opioid analgesics, Opana has not been shown to interact with CYP 450 enzymes, a finding that is very beneficial for patients who take several medications, because the risk of drug interactions is reduced. With the FDA's approval of Opana as the first oral formulation of oxymorphone, patients now have a safe alternative and a more convenient route of administration for managing moderate-to-severe pain.

REFERENCES

1. Baumann J. Pain management. *In:* DiPiro JT, Talbert RT, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*, 6th ed. New York: McGraw-Hill; 2005:1089–1104.
2. Goucke C. The management of persistent pain. *Med J Aust* 2003;178(9):444–447.
3. Rasor J, Harris G. Opioid use for moderate to severe pain. *J Am Osteopath Assoc* 2005;105(6)S2–S7.
4. Holdcroft A, Power I. Recent developments: Management of pain. *BMJ* 2003; 326:635–639.
5. American Medical Association: Module 1, Pain Management. Previously available at: www.ama-cmeonline.com. Expired; to be updated: www.ama-assn.org.
6. Merck Manuals Online Library. Types of pain. Available at: www.merck.com/mmpe/sec16/ch209/ch209a.htmlPain. Accessed January 17, 2007.
7. Miller K, Miller M, Jolley M. Challenges in pain management at the end of life. *Am Fam Physician* 2001;64:1227–1234.
8. Nicholson B. Differential diagnosis: Nociceptive and neuropathic pain. *Am J Manag Care* 2006;12:S256–S262.
9. Rice A, Justins D. Pain mechanisms and pathways. *Curr Anaesth Crit Care* 1999; 10:98–104.
10. Furlan A, Sandoval J, Mailis-Gagnon A, et al. Opioids for chronic non-cancer pain: A meta-analysis of effectiveness and side effects. *Can Med Assoc J* 2006;174:1589–1594.
11. Simon S. Opioids and treatment of chronic pain: Understanding pain patterns and the role for rapid-onset opioids. *Medscape Gen Med* 2005;7(4):54. Available at: www.medscape.com/viewarticle/517110. Accessed February 4, 2007.
12. Opana (oxymorphone HCl). Prescribing Information. Chadds Ford, PA: Endo Laboratories; July 28, 2006. Available at: http://opana.com/default.aspx. Accessed January 17, 2007.
13. Prommer E. Oxymorphone: A review. *Support Care Cancer* 2006;14(2):109–115.
14. FDA, Center for Drug Evaluation and Research. Drugs@FDA: Opana label and approval history, July 28, 2006. Available at: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed January 17, 2007.
15. New Drug: Opana/Opana ER (Oxymorphone). *Pharmacist's Letter* 2006;22. Available at: www.pharmacistsletter.com. Accessed January 17, 2007.
16. Adams M, Pieniaszek H, Gammaitoni A, Ahdieh H. Oxymorphone extended release does not affect CYP2C9 or CYP3A4 metabolic pathways. *J Clin Pharmacol* 2005;45:337–345.
17. Sinatra R. Opioid analgesics in primary care: Challenges and new advances in the management of non-cancer pain. *J Am Board Fam Med* 2006;19:165–177.
18. Adams M, Ahdieh H. Pharmacokinetics and dose-proportionality of oxymorphone extended release and its metabolites: Results of a randomized crossover study. *Pharmacotherapy* 2004;24:468–476.
19. Gimbel J, Ahdieh H. The efficacy and safety of oral immediate-release oxymorphone for postsurgical pain. *Anesth Analg* 2004;99:1472–1477.
20. Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: Results of a randomized, double-blind, placebo- and active-controlled phase III study. *J Pain* 2005;6:21–28.
21. McIlwain H, Ahdieh H. Safety, tolerability, and effectiveness of oxymorphone extended release for moderate to severe osteoarthritis pain: A one-year study. *Am J Therapeutics* 2005;12:106–112.
22. Katz N, Rauck R, Ahdieh H, et al. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. *Curr Med Res Opin* 2007;23:117–128.
23. Hale M, Ahdieh H, Ma T, et al. Efficacy and safety of Opana ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: A 12-week, randomized, double-blind, placebo-controlled study. *J Pain* 2007;8:175–184.
24. Lacy C, Armstrong L, Goldman M, et al. *Lexi-Comp's Drug Information Handbook*, 14th ed. Hudson, OH: Lexi-Comp; 2006.
25. Oxymorphone studies. Presented at the 25th Annual Meeting of the American Pain Society: Results from pivotal trials in low back pain and post-surgical pain. San Antonio, TX, May 4, 2006. Available at: www.pslgroup.com/dg/25a6ea.htm. Accessed January 17, 2007. ■