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Oxymorphone: a review

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Abstract Oxymorphone (oxymorphone hydrochloride) (14-hydroxydihydromorphinone), a semisynthetic μ -opioid agonist, was first approved by the US Food and Drug Administration in 1959. Oxymorphone is considered a more potent opioid than its parent compound, morphine. Recently, an immediate-release and long-acting oral formulation of this drug was developed that makes oxymorphone a new option in treating moderate to severe pain. This article reviews the pharmacodynamics,

pharmacology, and clinical efficacy for this new option in treating moderate to severe pain.

Keywords Oxymorphone · Opioid receptors · Opioid · Pharmacokinetics

Introduction

Pain is a common experience in patients with advanced cancer. Approximately 80% of cancer patients experience moderate to severe pain in the advanced stages of their illness [1]. The World Health Organization (WHO) has recommended a step-by-step approach to the management of chronic pain based on the intensity of pain [2]. Strong opioids are considered the agents of choice for moderate to severe pain. Morphine is considered the standard step-3 agent [3]. Inadequate analgesia and/or unmanageable adverse events associated with opioid use frequently result in the need to rotate patients with cancer pain to a different opioid. The approach is based on the clinical observation that intraindividual response varies remarkably from opioid to opioid, and that a change to an alternative drug may yield a far better balance between analgesia and side effects [4]. Available opioids that meet this need are methadone, oxycodone, fentanyl, hydromorphone, and levorphanol. Oxymorphone (oxymorphone hydrochloride) (14-hydroxydihydromorphinone), a semisynthetic μ -opioid agonist, was first approved by the US Food and Drug Administration (FDA) in 1959. Oxymorphone has a greater analgesic

potency than morphine and, until recently, has been available only as parenteral injection and in suppository form [5]. Recently, an immediate-release (IR) and a long-acting oral formulation of this drug were developed that make oxymorphone a new option for treating moderate to severe pain. Trials in malignant and nonmalignant pain confirm the drug's potential as a new step-3 option [6, 7]. As this drug is a promising addition to the current list of step-3 opioids, it is important for practitioners to have a basic knowledge of its properties. This paper will review the pharmacodynamics, pharmacology, uses, and pharmacoeconomics of this opioid. Differences from other step-3 opioids will be illustrated.

Chemistry

Oxymorphone is a pyridine-ring unsubstituted pyridomorphinan [8]. Oxymorphone differs from morphine by having a ketone-group substitution at the C-6 position of morphine and saturation of the seven to eight double bonds [9]. The ketone-group substitution makes the molecule more lipid soluble [10]. Structurally, oxymorphone is more closely related to hydromorphone [9]. Oxymorphone is available as

a hydrochloride salt, which makes it water soluble. It is sparingly soluble in alcohol. The molecular weight is 337.80. The octanol aqueous coefficient is .98 at 37°C and pH 7.4 [11].

Formulation

Table 1 summarizes the various formulations of oxymorphone. It is available in oral, intravenous, and suppository forms. The oral form is now available in an IR and sustained-release form. Both are available as tablets.

Drug release from the sustained-release form is based on a controlled-release technology that involves the rate of penetration of water entering a hydrophilic matrix with subsequent expansion of the gel coating (TIMERx Penwest Pharmaceuticals Co., Danbury, CT) [12]. The matrix consists of locust bean gum and xanthan gum [12]. The fluctuation index of sustained-release oxymorphone is comparable to known fluctuation indices with other long-acting opioids (see below) [12].

Opioid receptor interactions

The opioid drugs produce their biological effects through their interaction with the opioid receptors, which belong to the family of 7 transmembrane G-protein-coupled receptors [8]. The antinociceptive effects of oxymorphone are mediated predominantly through μ and δ opioid receptors [8]. Oxymorphone has a high affinity for μ -opioid receptors. Oxymorphone has a higher binding affinity to μ -opioid receptors than morphine does (K_i 15 vs morphine K_i 38) [13]. Oxymorphone binds to δ receptors with an affinity greater than does morphine (K_i 145 vs morphine 500) [8, 13]. Oxymorphone is characterized as a δ agonist [14]. This is similar to hydromorphone [8]. In contrast, oxymorphone has little κ -receptor activity [8, 13]. An example of an opioid with a high affinity for the κ -opioid receptor is oxycodone. Quantitatively, oxymorphone has tenfold less affinity for the κ receptor than the μ or δ receptor [8]. The advantages of δ affinity may be twofold. Agonist actions at the δ receptors potentiate μ -mediated analgesic effects. They also may lessen the development of tolerance.

The lesser affinity for the κ opioid receptor may explain the decreased sedation seen in previous studies compared

with morphine [15]. This has not been substantiated by recent trials.

Pharmacology/routes of administration

Oxymorphone can be administered orally, intravenously, subcutaneously, and rectally. Other routes that have been examined are the intranasal, intrathecal, and transdermal routes.

Oral route

Pharmacology of IR oxymorphone

Table 2 compares the pharmacokinetics of oxymorphone with other step-3 opioids. In healthy volunteers, the single-dose and steady-state pharmacokinetic profiles of oxymorphone IR tablets were linear and dose-proportional across the dose range from 5 to 20 mg [16]. Following a single dose of 5, 10, or 20 mg, the oxymorphone IR mean area under the plasma concentration vs time curve from time 0 to infinity was [AUC (infinity)] 4.5, 9.1, and 20.1 $\mu\text{g h}^{-1} \text{ l}^{-1}$, respectively, and maximum plasma concentration [C_{max}] 1.1, 1.9, and 4.4 $\mu\text{g h}^{-1} \text{ l}^{-1}$, respectively] confirmed dose proportionality [16]. Similar results were observed for the plasma concentration of chief metabolites [16]. The oral bioavailability of oxymorphone is approximately 10% [7]. This is the lowest of the oral step-3 opioids. In healthy volunteers, the half-life ranges from 7.2 to 9.4 h [16]. The half-life of IR oxymorphone is longer than that of morphine, hydromorphone, and oxycodone. Food does not affect the shape of concentration time curve [16]. Time to peak concentration is 30 min, which is equivalent to oral morphine. Protein binding is 20–40% [17]. The half-life is influenced by the route of administration (see below). The recommended dosing has been every 6 h, which is longer than most IR opioids. Steady-state conditions are achieved after 3–4 days. Oxymorphone is subject to hepatic first-pass effects and is renally excreted (see “Biotransformation”). Oxymorphone undergoes extensive hepatic metabolism via conjugation with glucuronic acid to create oxymorphone 3-glucuronide, and the keto group is reduced to form 6-OH-oxymorphone [16]. Studies on the relationship between sex, age, and metabolism are lacking.

Pharmacology of extended-release oxymorphone

In healthy volunteers, the extended-release (ER) form of oxymorphone has a lower C_{max} and an elevated C_{min} , which is consistent with decreased dose fluctuations. This is characteristic of long-acting opioids [12]. The C_{max} for the long-acting preparation was 0.27 ng ml^{-1} for the 5-mg ER form [12]. This increased linearly with dose [12]. The T_{max}

Table 1 Formulations of oxymorphone

Routes	Formulation	Dose/concentration
Oral	Immediate-release tablets	5 mg
	Sustained-release tablets	20 mg
Parenteral	Ampules	1 mg ml^{-1} (1-ml vial)
		1.5 mg ml^{-1} (10-ml vial)
Rectal	Suppository	5 mg

Table 2 Pharmacological comparisons (oral route, immediate-release compounds)

Opioid	Oxymorphone (5 mg)	Morphine	Dialudid (4 mg)	Oxycodone	Methadone
AUC infin ng ml ⁻¹ h ⁻¹	4.48	–	28–80		
C _{max} ng ml ⁻¹	1.10		11–20		
T _{max}	0.5	.5–1.5	1 h	1 h	2.5–4
T _{1/2}	7.3–9.4 h	2–3 h	2–4	3.5–5.65 h	Acute 14.3 h, secondary 54.8 h
Bioavailability (%)	11	30–40	10–65	60	80
Metabolism	Liver, intestine	Liver	Liver	Liver	Liver, intestine
Chief metabolites	6-hydroxyoxymorphone (6-OH-OXM) and oxymorphone-3-glucuronide (OXM-3-G)	M6G, M3G, normorphine	Dihydromorphine dihydroisomorphine hydromorphone-3- glucuronide	Noroxycodone, oxymorphone (10%)	No known active metabolites
Protein binding (%)	20–40	35	7	38–45	90

was 3.00 h (range 1–12 h) [12]. AUC values demonstrate linearity and dose-proportionality for oxymorphone and its metabolites, 6-OH-OXM and OXM-3-G, under single-dose and steady-state (12-h) conditions [12]. Steady state was achieved after 3 days of dosing [12]. The mean fluctuation index [defined as $(C_{\max} - C_{\min}) / (C_{\text{ss}} - \text{average})$] was less than 1 for the parent compound and metabolites at all dose ranges [12]. A reduced fluctuation in oxymorphone concentration during the dosing interval keeps oxymorphone blood levels more centered within the theoretical “therapeutic window.” The $\text{time} = 0.75 C_{\max}$ parameter is an index of the control that the formulation exerts over drug-release rate and thus represents a measure of the effectiveness of the respective technologies used to modify the release characteristics of a long-acting formulation [12]. The $\text{time} = 0.75 C_{\max}$ parameter has not been reported for ER oxymorphone. However, measurement of plasma concentrations suggests that peak plasma concentrations observed at 4 h decrease by only 30% at 12 h [12]. The fluctuation index of ER oxymorphone compares favorably to other long-acting compounds [18]. In clinical studies with other formulations (i.e., 12- and 24-h), differences in pharmacokinetic variables (e.g., fluctuations in plasma morphine concentration and time to maximum concentration) have not been shown to translate into differences in extent of pain relief or the incidence or severity of adverse effects [18].

Intravenous oxymorphone/subcutaneous route

After i.v. administration, onset of action is rapid; initial effects are usually perceived within 5–10 min [19]. Its duration of action is approximately 3–6 h [17]. After an i.v. dose, the steady-state volume of distribution was $3.08 \pm 1.14 \text{ l kg}^{-1}$ in healthy male and female subjects [17]. The half-life after i.v. dosing is 1.5 h [19]. Onset of action after

subcutaneous or intramuscular injection is 10–15 min [17]. One half was $1.3 \pm 0.7 \text{ h}$ [17]. There is no information of the bioavailability after subcutaneous administration.

Intranasal oxymorphone

Animal studies suggest that oxymorphone HCl appears to have the solubility, potency, and absorption properties required for efficient nasal delivery. In one study, rats were surgically prepared to isolate the nasal cavity, into which a solution of oxymorphone was administered [20]. A reference group of rats was administered oxymorphone HCl intravenously [20]. Plasma oxymorphone concentrations were determined by high-performance liquid chromatography (HPLC) [20]. Nasal absorption was rapid, nasal bioavailability was 43%, and the i.v. and nasal elimination profiles were similar [20]. In rats, intranasal oxymorphone was well absorbed, and T_{\max} was 0.4 h. The half-life after nasal administration was 1.3 h [20].

Spinal

Oxymorphone has been administered via epidural and intrathecal routes. No information exists regarding peak cerebrospinal fluid (CSF) levels or appropriate dose conversions from i.v./p.o. to epidural and intrathecal doses. Duration of action may be shorter than that of morphine [21]. For epidural block, oxymorphone may be three times as potent as morphine [21]. One report associated intrathecal oxymorphone with the development of leg edema. Five of 23 patients who had intrathecal infusions of opiates for longer than 24 months developed leg and feet edema [22]. Three of the five patients were receiving oxymorphone at doses ranging from 6 to 13 mg day^{-1} [22]. The mechanism

of edema was explained as resulting from opioid-induced vasodilatation [22].

Buccal

Absorption at this site is favored by a drug that is poorly ionized at pH 6 (the pH of saliva, which has high lipophilicity), neither of which applies to oxymorphone [23]. Therefore, buccal or sublingual routes are unlikely to be preferable routes of administration.

Rectal

Oxymorphone suppositories are well absorbed. Rectal administration results in lower and more delayed peak analgesia and a longer duration of action than intramuscular administration. Following rectal administration, onset of action usually occurs within 15–30 min. Analgesia is maintained for 3–6 h following rectal administration [17].

Transdermal route

The octanol aqueous coefficient is 0.98, which is much lower than drugs considered optimal for transdermal delivery such as fentanyl (octanol/aqueous coefficient, 714) [24]. When tested on human skin, as predicted, permeability rates were low unless skin permeation enhancers were included in the vehicle [25].

Biotransformation

Xenobiotics such as opioid drugs are, in general, metabolized and excreted largely as glucuronides by the liver and kidney. Oxymorphone is metabolized by uridine diphosphate glucuronosyl transferase (UGT) enzymes, enzymes 1A3 and 2B7, with UGT 2B7 being the predominant enzyme [9]. At the 3 position, oxymorphone undergoes conjugation to creating oxymorphone 3-glucuronide. The keto group at position 6 is reduced by an unknown enzyme forming 6-OH-oxymorphone (6-OH-OXM). In animal studies, 6-OH-OXM has been shown to have analgesic bioactivity [16]. 6-OH-OXM has an elimination half-life of 7–18 h depending on the dose [12]. The OXM-3-G has a half-life of 8–9 h [12]. Another potential area of biotransformation is via the CYP450 system. The CYP450 system has well-known implications in the biotransformation of many opioids such as oxycodone and methadone. Oxymorphone (ER) was studied in a randomized, open-label, parallel-group study examining the effects on CYP2C9 or CYP3A4 metabolic activities in healthy subjects. Oxymorphone ER exhibited minimal potential for causing meta-

bolic drug–drug interactions mediated by CYP2C9 or CYP3A4 [5].

Elimination

Less than 2% of the parent compound is excreted in the urine [12]. For oxymorphone 3-glucuronide, 33–38% is excreted in the urine in patients with normal renal and hepatic function, and its AUC is 90 times higher than that for oxymorphone [12]. After a 10-mg oral dose, 49% was excreted in the urine during a 5-day period. Of this, 82% was excreted in the first 24 h after administration [12]. The recovered drug-related products contained oxymorphone (1.9%), the glucuronic acid conjugate of oxymorphone (44.1%), the 6 (β)-carbinol product produced by 6-keto reduction of oxymorphone (0.3%), and the conjugates of 6 (β)-carbinol (2.6%) and 6 (α)-carbinol (0.1%) [17]. There is no information on its metabolism in other extrahepatic sites.

Effects of kidney and liver disease and drug interactions

Kidney disease

Oxymorphone accumulates in renal failure. A pharmacokinetic study evaluating the pharmacokinetics of oxycodone and the excretion of oxycodone and its metabolites noroxycodone and oxymorphone in ten uremic patients undergoing renal transplantation. In all ten patients, the mean elimination half-life of oxymorphone (a metabolite of oxycodone) was prolonged [26]. The dosing interval should be increased, as with any opioid that depends on renal excretion.

Liver disease

Data regarding hepatic extraction and clearance are not available. One would expect bioavailability to vary in pathological conditions where hepatic blood flow and liver metabolic function are impaired. In the setting of hepatic insufficiency, it is advisable to consider an increased dosing interval.

Drug interactions

In vivo drug–drug interaction studies involving oxymorphone have not been studied [9]. The potential for drug interactions exists for opioids at both CYP450 system and the glucuronidation pathways. Very little has been published about the potential for pharmacokinetic drug inter-

actions with oxymorphone [9]. Oxymorphone ER did not induce or inhibit CYP2C9 or CYP3A4 activity in healthy adults during steady-state administration. This differs from methadone, which is a substrate for CYP3A4, or oxycodone, which is dependent on CYP2D6.

Cimetidine can potentiate opioids presumably by altering hepatic blood flow and/or extraction ratio. Barbiturates, phenytoin, and rifampicin induce hepatic metabolism. Monoamine oxidase inhibitors delay metabolism and increase the number of adverse effects. Phenothiazines, including promethazine and chlorpromazine, potentiate opioids.

Adverse effects

Overall, the adverse effects that have been observed with oxymorphone are similar to those seen with potent μ agonists. Beaver et al. found that the occurrence of adverse effects was qualitatively and quantitatively similar for intramuscular oxymorphone and morphine, and oral oxymorphone and intramuscular morphine [27]. When administered via patient-controlled analgesia (PCA), oxymorphone was found to cause more nausea and vomiting but less sedation when compared with morphine [28]. This has not been confirmed in recent studies. Quality of life with the use of oxymorphone has been shown to be as good as, or better than, that with morphine [7]. The pilot study conducted by Sloan and coworkers [7] showed no difference in nausea or sedation scores when oxymorphone was compared with either morphine or oxycodone ER. Flatulence has been reported with the oxymorphone ER [12]. A less antitussive effect has been reported with oxymorphone [17]. The American Academy of Pediatrics has not yet rated the safety of oxymorphone in breastfeeding [17]. Available evidence suggests that there are insufficient data to establish safety during breastfeeding; however, caution is advised [17].

Clinical studies

Nonmalignant pain

Lower back pain

Hale et al. [10] conducted a multicenter, randomized, double-blind, placebo-, and active-controlled trial comparing the analgesic efficacy and safety of oxymorphone ER with placebo and oxycodone controlled release (CR) in ambulatory patients with moderate to severe chronic lower back pain requiring opioid therapy. Patients ($N=213$) aged 18–75 years were randomized to receive either oxymorphone ER (10–110 mg) or oxycodone CR (20–220 mg) every 12 h during a 7- to 14-day dose-titration phase. Patients achieving effective analgesia at a stable opioid dose entered an 18-day double-blind treatment phase and either

continued opioid therapy or received placebo. With stable dosing throughout the treatment phase, oxymorphone ER (79.4 mg day⁻¹) and oxycodone CR (155 mg day⁻¹) were superior to placebo for change from baseline in pain intensity measured on a visual analog scale ($P=.0001$). The mean daily dosage of rescue medication was significantly lower for patients receiving oxymorphone ER (25.5 mg; $P=.0068$) or oxycodone CR (24.4 mg; $P=.0024$) than for those receiving placebo (34.8 mg). Adverse events for the active drugs were similar; the most frequent were constipation and sedation. Oxymorphone ER and oxycodone CR were generally safe and effective for controlling lower back pain. Oxymorphone ER was equianalgesic to oxycodone CR at half the milligram daily dosage, with comparable safety.

Postoperative pain

Gimbel and Ahdieh [29] conducted a double-blind, parallel-group study in patients receiving primary total hip or knee replacement surgery (including an osteotomy) and scoring I–III on the ASA physical status classification system. There were two treatment phases, an 8-h single-dose phase and a multiple-dose phase that extended the study to 48 h. During the 8-h single-dose phase, patients received a single dose of oxymorphone IR 10, 20, or 30 mg; oxycodone IR 10 mg; or placebo. In the double-blind, parallel-group study, three oxymorphone IR doses were compared with placebo for efficacy and with oxycodone IR and placebo for safety in patients with acute moderate-to-severe postsurgical pain. All oxymorphone IR doses were superior in providing pain relief for 8 h ($P<0.05$), with a significant analgesic dose response ($P<0.001$). Significant pain intensity differences occurred by 45 min (20- and 30-mg doses; $P<0.05$). Discontinuation for lack of efficacy was 42% among placebo-treated patients and 27% among those treated with oxymorphone IR. Patients requiring rescue medication after 3 h were allowed to receive additional study drug every 4–6 h as needed during the multiple-dose phase ($n=164$). Analgesia was maintained for patients in all oxymorphone groups for 48 h. The median dosing interval was greater than 9.5 h for oxymorphone IR 30 mg and 7 h or more for the other groups. Opioid-related adverse events, similar among groups, were generally mild or moderate. Oxymorphone IR 10, 20, or 30 mg provided significant dose-related pain relief compared with placebo, and this relief was maintained over several days with a safety profile comparable to that of oxycodone IR.

Ahdieh and colleagues [6] conducted a multicenter, double-blind, parallel-group, placebo-controlled, multiple-dose study incorporating two measures of analgesic efficacy: a standard analgesic evaluation and a PCA, opioid, dose-sparing analgesic evaluation. Patients with moderate or severe pain following knee arthroplasty and washout from standard PCA were randomized to receive 20 mg of

oxymorphone ER ($n=65$) or placebo ($n=61$) 12 h for 1 day. Oxymorphone PCA was used as rescue analgesic. Oxymorphone ER provided significant improvements over placebo for most standard single-dose analgesic parameters, including mean total pain relief over 0–12 h ($P=0.0056$) and for all multiple-dose (24-h) efficacy assessments. Oxymorphone-treated patients used significantly less rescue PCA than did those who received placebo ($P<0.02$). Adverse events such as nausea and constipation were typical of opioids, and laboratory and physical findings were similar between groups.

Cancer pain

Sloan and coworkers [7] conducted a pilot study comparing oxymorphone ER and oxycodone CR in patients ($n=86$) with moderate to severe cancer pain. This randomized, multicenter, double-blind, two-period crossover study included adult out-patients (≥ 18 years of age) with moderate or severe cancer pain who first stabilized for 3 days or longer on morphine CR or oxycodone CR. Those who attained stable analgesia for at least 3 days (three or fewer rescue doses of opioid per day) entered the first 7-day treatment period (period 1) at the stabilized dose of the titrated medication with no dosage adjustments. All patients who were treated for 7 days at their stabilized dose of either morphine CR or oxycodone CR were then crossed over to oxymorphone ER at an estimated equianalgesic dosage and treated for an additional 7 days (period 2). During periods 1 and 2, the oral IR formulation of the study medication was available as rescue medication. Each dose of rescue medication was approximately 10% of the total daily dose of scheduled medication. Patients recorded assessments of analgesia, nausea, drowsiness, sleep quality, the use of regularly scheduled medications, and use of rescue medication. Similar daily pain intensity scores during the last 2 days of the initial treatment phase (morphine CR or oxycodone CR) compared with those during the last 2 days of the oxymorphone ER treatment phase indicate that equivalent analgesia was achieved after patients had been rotated to oxymorphone ER. This also suggests that the long-acting formulation can maintain drug levels in a stable fashion. Patients taking oxymorphone ER needed less breakthrough medication than patients taking morphine CR. The tolerability/safety profiles (e.g., nausea, drowsiness, and somnolence) were similar between the two drugs. There were no significant differences in daily pain intensity scores between oxymorphone ER and either morphine or oxycodone.

Dose conversions

Intramuscular oxymorphone proved to be 8.7 times as potent as intramuscular morphine in terms of total analgesic effect (duration and intensity) and 13 times as potent in

terms of peak effect [27]. When both duration and intensity of analgesia are considered (total effect), oral oxymorphone was one sixth as potent as the intramuscular form. In terms of peak effect, however, oral oxymorphone was only 1/14 as potent [27]. Following subcutaneous administration, 10 mg morphine was found to be approximately equivalent in analgesic effects to 1–1.5 mg oxymorphone [7]. Sloan and coworkers [7] found that equianalgesic dose ratios of morphine CR and oxycodone CR to oxymorphone ER were 1.8:1 and 1.2:1, respectively. Hale and colleagues found a 2:1 dose ratio for oxycodone (CR) relative with oxymorphone (ER) [10]. Total analgesic effects of rectal oxymorphone (2- to 12-mg single doses) have been reported to be one tenth as potent as those resulting from intramuscular administration (0.5- to 1.5-mg single doses) [17].

Schedule of administration

Oxymorphone IR tablets may be given at 6-hour intervals. Oxymorphone ER and oxycodone CR offer the convenience of twice-daily dosing. The recommended initial intravenous dose of oxymorphone is 0.5 mg. This may be repeated if necessary every 4–6 h [17]. If the analgesic history is unknown, or if the patient is opioid naïve, intermittent i.v. doses may be given with normal saline over 10–15 min as required (p.r.n.), which can be repeated as needed until the pain is controlled. The intramuscular or subcutaneous dosage of oxymorphone is 1–1.5 mg every 4–6 h intramuscularly or subcutaneously [17]. Recommended rectal dosage of oxymorphone is 5 mg every 4–6 h [17].

Pharmacoeconomics

AWP (Red Book 2004) prices are as follows:

Oxymorphone	Morphine	Hydromorphone
1 mg/1 ml × 10 ampules, \$32.56	10 mg/ml × 1-ml vial, \$0.67	10 mg/ml × 1-ml vial, \$3.54
15 mg/10 ml ampules, \$38.06	15 mg/ml × 1-ml vial, \$0.81	2 mg/ml × 20-ml vial, \$10.63
5-mg suppository × 6 suppositories, \$32.19	–	–

There is no pricing available for oxymorphone IR or ER tablets.

Conclusions

Oxymorphone is a potent opioid, whose antinociceptive effects are mediated predominantly through μ and δ opioid receptors. Oxymorphone is subject to hepatic first-pass effects and is renally excreted. Oxymorphone undergoes extensive hepatic metabolism via conjugation with glucu-

ronic acid to create oxymorphone 3-glucuronide, and the keto group is reduced to form 6-OH-oxymorphone. 6-OH-oxymorphone has been shown to have analgesic bioactivity. Oxymorphone ER exhibits minimal potential for causing metabolic drug–drug interactions mediated by CYP2C9 or CYP3A4. Oxymorphone accumulates in renal failure, and there is little data regarding its disposition in hepatic insufficiency. Overall, the adverse effects that have been observed with oxymorphone are similar to those seen with potent μ agonists. The half-life of IR oxymorphone is

longer than that of morphine, hydromorphone, and oxycodone. Equianalgesic dose ratios of morphine CR and oxycodone CR to oxymorphone ER were 1.8:1 and 1.2:1, respectively. The long half-life of the IR formulation combined with the drug's potency makes it an attractive option for breakthrough pain. Its ability to provide equianalgesia in patients already receiving other step-3 opioid such as morphine and oxycodone make it another option for opioid rotation. The cost of oxymorphone may be prohibitive for most hospices, where the budget is capitated.

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