INTRODUCTION

Oxymorphone Status

This is the second in a hoped-for series of *Pain Medicine* supplements that will deal with medications of interest to the pain medicine clinician. The first of these was in references to duloxetine [1]. The editors of *Pain Medicine* have decided to launch these supplements because research information about specific medications is often scattered among various journals and some early information may only be in poster form presented at various meetings. As such, it is difficult for the busy clinician to get an overall impression of the status of this research. Therefore, the purpose of these supplements is to provide this information to the pain clinician in one volume, which could be used as a reference. In addition, the articles within the supplement are designed, if possible, to compare the medication in question with similar medications and/or to review a topic of relevance to the medication in question. The topic of this supplement is oxymorphone and the clinical research issues related to this medication.

Oxymorphone is a semi-synthetic agonist of the μ- and δ-opioid receptors first approved by the United States Food and Drug Administration (FDA) in 1959. The proposed advantage of the δ-opioid receptor activity is to possibly potentiate or enhance μ-opioid receptor analgesic effects [2]. Oxymorphone has greater analgesic potency than morphine and until recently was only available in parenteral injection or suppository form. Oxymorphone differs from morphine by having a ketone-group substitution at the C-6 position of morphine, which makes the molecule more lipid soluble and structurally more closely related to hydro-morphine [3]. Recently, oxymorphone became available in immediate-release (IR) and extended-release (ER) formulations. Subsequently, oxymorphone obtained FDA approval for the treatment of moderate to severe acute pain (IR) and for relief of moderate to severe pain in patients requiring continuous around-the-clock opioid therapy for an extended time period (ER).

Drug release from the ER form is based on a controlled-release technology that involves the rate of penetration of water entering a hydrophilic matrix with resultant expansion of the gel coating (TIMERx, Penwest Pharmaceuticals Co., Danbury, CT) [4]. This technology has been reported to confer the following to the ER preparation: proportionality; linear pharmacokinetics; an extended release profile lasting more than 4 hours with a half-life of 9–12 hours; a reduced fluctuation in oxymorphone concentration during the dosing interval, which keeps blood levels more centered within the theoretical “therapeutic window”; and no dose dumping [2,4–6]. The effect of ingestion of oxymorphone ER with a high-fat meal has been evaluated in two studies. In both, the mean peak drug concentration (C_{max}) was increased by 50% in fed vs fasted subjects [6]. Thus, the ER formulation should be dosed on an empty stomach (at least 1 hour before or at least 2 hours after eating). Ingestion of 40% alcohol can increase the C_{max} of oxymorphone ER by a mean of 70% [6]. This appears to be unrelated to the direct effect of alcohol on ER tablets [6,7] as alcohol has no effect on the ER preparation in vitro studies [8]. On the basis of these data, the manufacturer cautions against coadministration of both formulations with alcohol. Finally, the ER preparation is subject to the same abuse potential as other available opioids, as the TIMERx technology offers no protection against methods of abuse such as crushing the tablet [9].

Oxymorphone is extensively metabolized, undergoing oxidation and reduction with subsequent conjugation of parent compound and metabolites to glucuronic acid [2,6]. Cytochrome P450 enzymes do not catalyze the conversion of oxymorphone to 6-hydroxy-oxymorphone (the actual metabolite) [6]. As such, it is not metabolized by CYP2D6 [2,9] and does not have any clinically significant interactions with CYP3A4 and CYP2C9 [2,6,9,10]. In addition, it does not inhibit or induce enzymes within the P450 system [9]. Most patients with chronic pain are on multiple medications that are metabolized by P450 enzymes, or inhibit or induced P450 enzymes. Thus, in these patients there is significant potential for drug interactions with the addition of a drug that impacts on the P450 system. As such, drugs such as oxymorphone, which do not have a significant effect on the P450 system, are useful in...
populations taking multiple drugs because no dosage adjustments would perhaps be necessary to prevent drug interactions [9].

The efficacy and safety of oxymorphone ER for chronic pain have been evaluated in six published randomized controlled trials covering a variety of indications and three published open-label studies, two of which lasted up to 1 year [11,12]. The durability of response to oxymorphone ER in opioid-experienced and opioid-naive patients was demonstrated in two 12-week trials [8,9]. Interestingly, in the two 52-week open-label studies [11,12], there was little or no dose escalation with attainment of meaningful pain relief for patients remaining in the studies (there were a significant number of patients who dropped out). In the 6-month nonrandomized open-label study [13], oxymorphone ER was demonstrated to improve quality of life (QOL) as measured by seven QOL indicators.

Adverse events reported to the FDA from placebo-controlled clinical trials (a greater than placebo) for oxymorphone ER in order of decreasing frequency were as follows: nausea, constipation, dizziness, somnolence, vomiting, pruritus, headache, increased sweating, dry mouth, sedation, diarrhea, insomnia, fatigue, decreased appetite, and abdominal pain [6]. It has also been reported that rotation from oxycodone to oxymorphone ER did not lead to a greater incidence of adverse events [14].

The articles/reviews in this supplement will expand on some of the research data summarized above. In the first article, Dr. Smith reviews the clinical pharmacology of oxymorphone. The second article, by Dr. Brennan, reviews the short-term and long-term efficacy studies for oxymorphone. In the third article, Dr. Holmquist, reviews the P450 enzyme system and the effects of oxymorphone on the P450 enzyme system in comparison to other opioids. The fourth article, by Dr. Smith, reviews all the current enteral controlled-release opioid delivery systems. In the final article, Dr. Pergolizzi reviews the evidence for the concept of opioid rotation from oxymorphone studies and from other opioids.

Disclosures

Consultant, Advisory Board, and Speaker’s Bureau: Eli Lilly.

References


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