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Oxycodone

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Abstract
Oxycodone has been in clinical use since 1917. Parenteral oxycodone was used mainly for the treatment of acute postoperative pain whereas combinations, for example, oxycodone and acetaminophen, were used for moderate pain. Since the introduction of controlled-release oxycodone, it has been used to manage cancer-related pain and chronic non-cancer-related pain problems. Controlled studies have been performed in postoperative pain, cancer pain, osteoarthritis-related pain, and neuropathic pain due to postherpetic neuralgia and diabetic neuropathy. The pharmacodynamic effects of oxycodone are typical of a μ-opioid agonist. Oxycodone closely resembles morphine but it has some distinct differences, particularly in its pharmacokinetic profile. Being an old drug, the basic pharmacology of oxycodone has been a neglected field of research. J Pain Symptom Manage 2005;29:S47–S56.

Key Words
Oxycodone, oxymorphone

Introduction

Oxycodone has been in clinical use since 1917.[1] It has been administered to human beings intravenously (i.v.),[2,3] intramuscularly (i.m.),[4] intranasally (i.n.),[3] subcutaneously (s.c.),[5] rectally,[6] epidurally,[7] and orally using immediate-release solutions,[4,8–10] and immediate- and controlled-release tablets.[11] The transdermal route of administration has also been tested in animals.[12]

Today oxycodone is mainly used as controlled-release tablets for chronic pain. The immediate- release solution and tablets are used for acute pain or for breakthrough pain. Parenteral oxycodone is a good alternative when opioids cannot be administered orally.

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History

Opium contains two chemical classes of alkaloids, phenantrenes and benzyl-isoquinolines. One of the phenantrene alkaloids, thebaine, present in 0.2–0.8% of the opium derived from *Papaver somniferum* and in 90% of that extracted from morphine-free *Papaver bracteatum*, is extremely toxic and lacks analgesic properties. It is, however, an important precursor of several transformation products, including oxycodone.[13]

Oxycodone was derived from thebaine in 1916[13] and it was introduced into clinical practice in Germany in 1917.[1] It was used in northern Europe mainly for acute pain. In Canada,

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Australia, and the United States, it was used mainly as a combination drug with acetaminophen, phenacetin, and caffeine for moderate pain. In Finland, oxycodone has been used as the main parenteral opioid for acute pain since the 1960s.

Chemistry and Basic Pharmacology

The oxycodone (6-deoxy-7,8-dehydro-14-hydroxy-3-O-methyl-6-oxomorphine) molecule consists of two planar (A and B) and two aliphatic rings (C and D). Important groups for analgesic actions of the phenantrenes are linked to positions C3, C6, and N (Figure 1). Like morphine and methadone, oxycodone may exist in different enantiomers, but the biological effects of the putative isomers have not been studied.

Oxycodone has liposolubility similar to morphine, and both are significantly less lipid soluble than fentanyl.[14] The respective partition coefficients of oxycodone and morphine are 0.7 and 0.5[14] or 1.7 and 1.[15] The protein binding of oxycodone (44–46%) is close to that of morphine (38%) and it is not affected by α1-acid glycoprotein.[14]

Oxycodone is a μ-opioid receptor specific ligand[16,17] with clear agonist properties.[17] The Ki (nM) of oxycodone for the μ-opioid receptor is 18 ± 4 compared with 958 ± 499 for the δ-opioid receptor and 677 ± 326 for the κ-opioid receptor.[17] The μ-opioid receptor binding affinity of oxycodone is, however, less than that of morphine or methadone.[18] Oxymorphone, the active metabolite of oxycodone, has a significantly higher μ-opioid receptor binding affinity.

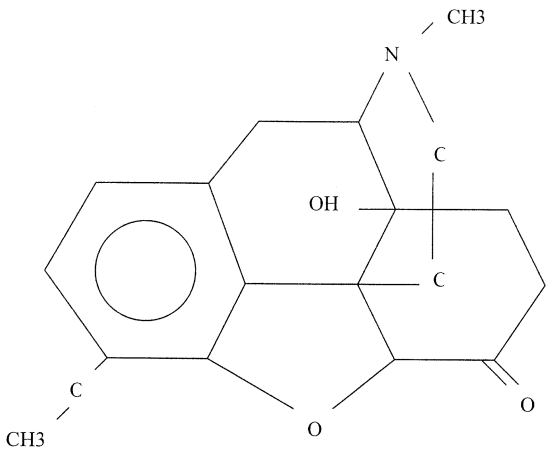

Fig. 1. Chemical structure of oxycodone.

Intramuscular oxymorphone and morphine were compared in patients with chronic pain due to cancer. Intramuscular oxymorphone proved to be 8.7 times as potent as morphine in terms of total analgesic effect and 13 times as potent in terms of peak effect.[19]

In behavioral studies in rats, oxycodone has been compared to morphine and has shown significantly weaker and briefer antinociception in the tail flick and hot plate tests after intrathecal (i.t.) and intracerebroventricular (i.c.v.) administration.[15,20,21] After systemic administration (subcutaneous or intraperitoneal), oxycodone was shown to be 2–4 times more effective than morphine.[20] These results have indicated that the active metabolites of oxycodone (e.g., oxymorphone) could be important in oxycodone-mediated analgesia. Studies using Dark Aguti rats that are deficient in the enzyme CYP2D1, which is required to O-demethylate oxycodone in the rat, and various opioid receptor antagonists have suggested that the antinociceptive effects of oxycodone could be κ-opioid receptor–mediated.[22]

Pharmacokinetics

Healthy Volunteers. The metabolism of oxycodone in humans is still poorly characterized. The main known metabolic pathways of oxycodone are through O-demethylation to oxymorphone and via N-demethylation to noroxycodone.[4,23,24] Noroxycodone concentrations in plasma and urine have been significantly higher after oral than after intramuscular administration, suggesting a prominent role of N-demethylation in the first-pass metabolism of oxycodone. The conversion of oxycodone to oxymorphone, and the conversion of noroxycodone to noroxymorphone, are catalyzed by the liver enzyme P450 2D6 (CYP 2D6). This enzyme has two phenotypes in the white population: 5–10% are poor metabolizers with diminished CYP 2D6 activity.[25] Most of oxycodone and noroxycodone is excreted in urine as the free (unconjugated) form, whereas oxymorphone is mainly excreted in the conjugated form.[4] The role of other metabolic routes such as N-oxidation and 6-ketoreduction[26] in man have not been explored.