Ketorolac, Oxymorphone, Tapentadol, and Tramadol

A Comprehensive Review

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KEYWORDS

• Ketorolac • Oxymorphone • Tapentadol • Tramadol • Analgesia • Pain

KEY POINTS

- Ketorolac is primarily used for the treatment of postoperative pain and has been shown to have opioid-sparing effects and reduces opioid-related side effects.
- Oxymorphone is a powerful opioid used for the treatment of moderate to severe pain in both malignant and nonmalignant-related pain.
- Tapentadol functions as both a weak μ-receptor agonist and a norepinephrine reuptake inhibitor, offering a more favorable side-effect profile compared with pure opioids.
- Tramadol is a μ-receptor agonist, and a serotonin and norepinephrine reuptake inhibitor indicated for management of moderate to severe pain.

INTRODUCTION

Affecting more than 50 million people in the United States alone, pain remains a tremendous burden not only for patients but also for the health care system as well.[1] Uncontrolled pain is the leading cause of disability in the country, and it may also delay patient recovery from surgery, increase the risk of life-threatening events, and increase the risk of developing chronic pain. With the advent of several novel analgesics over recent years, there has been a widespread effort to develop novel drugs

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with differing mechanisms of action in an attempt to best manage the pain epidemic in the United States and worldwide. In this regard, various classes of analgesics currently are available, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioid medications, muscle relaxants, antidepressants, and anticonvulsant medications. This review focuses on 4 medications: ketorolac, oxymorphone, tramadol, and tapentadol, and their role as analgesic agents in different pain states.

KETOROLAC

Background

Ketorolac tromethamine is the first NSAID approved for parenteral use. It is used for a variety of clinical indications, but is mainly administered for the management of postoperative pain. It can also be used for treatment of cancer-related pain, for pain after cesarean delivery, and in the emergency department for treatment of migraine headaches, renal colic, musculoskeletal pain, and sickle cell crisis.[2] Ketorolac has been used safely and effectively in select pediatric populations but at present is not recommended for use in children under the age of 17.[3] It has strong analgesic properties, with a dose of 30 mg intramuscular (IM) offering similar analgesia as 12 mg of morphine.[4] The strong analgesic properties reduce opioid requirements and thus decrease opioid-related side effects. These side effects can be associated with significant morbidity and mortality, in particular, related to dose-dependent opioid mediated respiratory and CNS depression. Routes of administration include intravenous (IV), IM, oral (PO), ophthalmic, and intranasal (IN).

Pharmacology

Ketorolac primarily exerts its effects through inhibition of the cyclo-oxygenase (COX) -1 and -2 isozymes, with a greater affinity for COX-1. COX inhibition decreases the production of prostaglandins, thromboxane, and prostacyclin from arachidonic acid. Prostaglandins are involved in the nociceptive pathway by sensitizing afferent nerves.

All forms of ketorolac are rapidly absorbed with a mean half-life for absorption of 3.8 minutes, and duration of action of approximately 6 to 8 hours. It is the tromethamine moiety that renders the compound hydrophilic, augmenting its solubility and absorption. There is complete bioavailability of both IM and IV administration, and the half-life is approximately 5 hours.[3,5] Absorption of PO ketorolac is slower than parenteral forms, and the bioavailability is between 80% and 100%.[5,6] The bioavailability of 15 and 30 mg IN ketorolac is 75% and 67%, respectively. The 30 mg IN dose achieves a plasma level similar to that of 20 mg IM. Maximum plasma concentration is reached on average within 30 to 45 minutes with a terminal half-life of 5 to 7 hours.[7]

Once absorbed, the drug is 99% protein bound in the plasma. Ketorolac is metabolized by the liver into hydroxylated and conjugated forms. The primary route of excretion is renal with 92% of the administered dose being found in the urine. The drug found in the urine is approximately 40% metabolites, and 60% is excreted unchanged. The remaining 6% to 8% of the drug is excreted in the feces.[3]

Ketorolac crosses the placenta and is also excreted into breast milk in small quantities. The hydrophilicity and high protein binding of ketorolac prevents large concentrations of the drug from entering the breast milk. Administrations of ketorolac and other NSAIDs during the third trimester are contraindicated because they can cause premature closure of the ductus arteriosus.

Adverse Events

The adverse events associated with ketorolac are similar to those of other NSAIDs, which include gastrointestinal (GI) bleeding, renal impairment, liver dysfunction, and