KETOROLAC (Systemic)

Analgesic.
Indications

Accepted

Pain (treatment)¾Ketorolac is indicated for the short-term management of moderately severe acute pain that would otherwise require treatment with an opioid analgesic 37.

It is most commonly used to relieve postoperative pain 8, 10, 18, 20, 37.

The oral dosage form is indicated only for continuation of therapy following initial parenteral administration. Because the risk of gastrointestinal bleeding and other severe adverse effects increases with the duration of treatment, ketorolac should not be administered by any route or combination of routes for longer than 5 days 37.

Before ketorolac is used perioperatively, its platelet aggregation-inhibiting activity, which increases the risk of bleeding, must be considered 37.

Postoperative hematomas and other signs of wound bleeding have been reported in ketorolac-treated patients 37.

Therefore, ketorolac should not be given prior to major surgery to prevent postoperative pain; nor should it be administered intraoperatively when control of bleeding is critical 37.

Also, ketorolac lacks the sedative and anti-anxiety activity usually desired in a preoperative medication 37.

[Pain, postoperative, in pediatric patients (treatment)] *¾Intravenous ketorolac is indicated for short term use in the treatment of postoperative pain in pediatric patients. 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) may be sensitive to ketorolac also 23.

Severe asthmatic 25 and anaphylactoid reactions have occurred in such patients 37.

Tumorigenicity

No evidence of tumorigenicity was found in an 18-month study in mice receiving up to 2 mg per kg of body weight (mg/kg) per day or a 24-month study in rats receiving up to 5 mg/kg per day orally. These doses are considered, on the basis of area under the concentration-time curve (AUC) comparisons, to be

equivalent to 0.9 and 0.5 times, respectively, the human exposure resulting from intramuscular or intravenous administration of 30 mg 4 times a day 37.

Mutagenicity

No evidence of mutagenicity was found in the Ames test, unscheduled DNA synthesis and repair, and forward mutation assays 37.

Also, ketorolac did not cause chromosome breakage in the in vivo mouse micronucleus assay 37.

However, in a concentration of 1590 mcg per mL (mcg/mL)(approximately 1000 times average human plasma concentrations), ketorolac increased the occurrence of chromosomal aberrations in Chinese hamster ovarian cells 37.

Pregnancy/Reproduction

Fertility¾No impairment of fertility was observed in male rats given 9 mg/kg per day or female rats given 16 mg/kg per day, orally (53.1 and 50 mg per square meter of body surface area [mg/m 2] per day) 37.

These doses are equivalent to 0.9 and 1.6 times, respectively, the human exposure resulting from intramuscular or intravenous administration of 30 mg 4 times a day, based on AUC comparisons 37.

Pregnancy¾First trimester¾

Adequate and well-controlled studies have not been done in pregnant women 37.

No teratogenicity occurred in offspring of rabbits receiving oral doses of up to 3.6 mg/kg per day (42.35 mg/m 2 per day; equivalent to 0.37 times the human exposure resulting from intramuscular or intravenous administration of 30 mg 4 times a day, based on AUC comparisons) 37 or rats receiving orally up to 10 mg/kg per day (59 mg/m 2 per day; equivalent to the human exposure, based on AUC comparisons) 37.

Second and third trimesters¾

Although studies in pregnant women have not been done with ketorolac, chronic use of any NSAID during the second half of pregnancy is not recommended because of possible adverse effects in the fetus, such as premature closure of the ductus arteriosus, which may lead to persistent pulmonary hypertension in the newborn 21.

Such effects have been documented in animal studies with other NSAIDs 21.

Chronic administration of 1.5 mg/kg per day (8.8 mg/m 2 per day) of ketorolac to rats after Day 17 of gestation caused dystocia and higher pup mortality 37.

This dose is equivalent to 0.14 times the human exposure resulting from intramuscular or intravenous administration of 30 mg 4 times a day, based on AUC comparisons 37.

Higher doses (9 mg/kg or more per day, administered to rats from Day 15 of gestation) significantly increased the length of gestation, in addition to increasing the incidence of maternal deaths associated with dystocia and decreasing birth weights and survival rates in the offspring 23.

FDA Pregnancy Category C [37].

Labor and delivery¾ When administered during labor, ketorolac crosses the placenta [11, 14] and inhibits platelet aggregation in the neonate [11].

Ketorolac may cause adverse effects on uterine contractility and on the fetal ductus arteriosus, resulting in an increased risk of uterine bleeding and fetal circulatory disturbances, respectively [37].

Therefore, ketorolac should not be used during labor and delivery [37].

Breast-feeding

Because of potential adverse effects in the nursing infant, use of ketorolac by nursing mothers is not recommended [37].

Ketorolac is distributed into breast milk in small quantities [7].

Maximum concentrations of 7.3 nanograms per mL (nanograms/mL) (0.019 micromoles/L) 2 hours after the first dose and 7.9 nanograms/mL (0.021 micromoles/L) 2 hours after the fifth dose were measured in the breast milk of women receiving 10 mg of ketorolac, orally, 4 times a day [7], although the concentration in breast milk failed to reach the lowest detection limit of 5 nanograms/mL (0.013 micromoles/L) in 40% of the subjects tested. 7 Milk-to-plasma concentration ratios of 0.037 and 0.025 have been calculated after administration of a single dose and at steady-state, respectively [37].

Pediatrics

No information is available on the relationship of age to the effects of ketorolac in pediatric patients. Safety and efficacy in patients younger than 16 years of age have not been established [37].

Geriatrics

Studies have shown that clearance of ketorolac is reduced in healthy individuals 65 years of age or older, leading to significant prolongation of the elimination half-life [3, 37].

Also, geriatric patients are more likely to have age-related renal function impairment, which may further reduce ketorolac clearance [3, 16] and increase the risk of NSAID-induced renal [21, 23] or hepatic [21] toxicity. The risk of gastrointestinal ulceration, bleeding, and perforation is higher in elderly patients receiving ketorolac than in younger adults [37].

Also, ketorolac-induced gastrointestinal ulceration and/or bleeding is more likely to cause serious consequences, including fatalities, in geriatric patients [31].

It is recommended that ketorolac be used with caution [21], in the lower of the recommended dosage regimens [37], and with careful monitoring of the patient [21].

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
All of the interactions listed below have not been documented with ketorolac. However, they have been reported with other NSAIDs and should be considered potential precautions to the use of ketorolac also. In addition to the interactions listed below, the possibility should be considered that additive or multiple effects leading to impaired blood clotting and/or increased risk of bleeding may occur if any NSAID is used concurrently with any medication having a significant potential for causing hypoprothrombinemia, thrombocytopenia, or gastrointestinal ulceration or hemorrhage.
Acetaminophen 21