Drug Therapy

KETOROLAC

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Ketorolac is a non-steroidal, non-narcotic agent with potent analgesic and modest anti-inflammatory activity. It has a rapid onset of action and is available in parenteral and oral preparations.

Structure

Ketorolac is a new alpha substituted arylacetic acid, structurally related to indomethacin. The chemical name is (±)-5-benzoyl-2,3-dihydro-l H-pyrrolizine-1-carboxylic acid, 2-amino-2-(hydroxymethyl)-l, 3 propanediol. It is the steric and hydrogen bonding properties of this molecule which are essential for the analgesic and anti-inflammatory activity of the drug(l).

Pharmacokinetics

Ketorolac is well absorbed after oral and intramuscular administration achieving peak plasma concentration in 30 to 60 minutes and analgesia is maintained for 6 to 8 hours. Bioavailability is reported to range from 81-100%(2).

Ketorolac is metabolized by glucoronic acid conjugation and para-hydroxylation in the liver. Drug and metabolites are mainly excreted in urine with half life of elimination of 4-6 hours(3). Single dose pharmacokinetics of ketorolac have been investigated in several studies but multiple dose pharmacokinetics are not yet clearly established.

Ketorolac crosses the placenta (10%) and insignificantly into the breast milk (0.2-0.4%).

Pharmacodynamics

It acts at the cyclo-oxygenase pathway of arachidonic acid metabolism, thus inhibiting prostaglandin synthesis and producing marke'd analgesia.

(i) Analgesic activity: In various animal models, the relative analgesic potency of ketorolac was 200 to 800 times greater than that of aspirin. Similarly, ketorolac is also more potent than indomethacin, naproxen and phenylbutazone(4).

(ii) Anti-inflammatory activity: Ketorolac has less anti-inflammatory activity as compared to its analgesic action. Anti-inflammatory action is equal or greater than that of indomethacin, three times than that of naproxen and 36 times of phenylbutazone(5). Currently, ketorolac is also undergoing investigation as a topical anti-inflammatory ophthalmic agent.

(iii) Anti-pyretic activity: The antipyretic

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effect of Ketorolac is still not well established.

(iv) *Effects on platelet function and hemostasis: In vivo* studies on humans receiving Ketorolac have shown inhibition of arachidonic acid and collagen induced platelet aggregation but little effect on ADP induced platelet aggregation. While blood thromboxane B2 levels are markedly decreased and mean bleeding time is prolonged. There is no interaction with heparin. Ketorolac does not affect PT, PTT or KCCT(6).

(v) *Effect on gastrointestinal mucosa:* Dose-related gastrointestinal erosion and mucosal injury is reported to occur with Ketorolac administration but significantly less as compared with aspirin(7).

(vi) *Other effects:* Ketorolac is devoid of causing respiratory depression, withdrawal symptoms and significant hemodynamic changes as observed with morphine and other opioids.

Therapeutic Use

1. *Post operative pain:* Efficacy in post-operative pain is assessed in terms of pain intensity difference (PID), summed pain intensity difference (SPID), total pain relief (TOTPAR) and summed analogue pain intensity difference (SAPID) along with verbal rating and overall patient/physician assessment(4).

In all trials, Ketorolac has demonstrated single dose efficacy superior to that of morphine and pethidine. Ketorolac 30 to 90 mg intramuscular has shown analgesic efficacy superior to morphine (6 to 12 mg), pethidine (50 to 100 mg) and pentazocine 30 mg. Low dose Ketorolac (10 mg) is as effective as opioid analgesics(8,9).

Single dose Ketorolac (20 mg IM) has demonstrated efficacy equal to or greater than that of a combination of opioid and non-steroidal or simple analgesic. Similarly, oral Ketorolac also is reported to be superior to other NSAID in acute pain(10,ll). However, multiple dose studies with oral ketorolac have failed to establish its superiority over placebo or other analgesics in the chronic phase of study(12).

2. *Acute musculoskeletal pain:* In several studies on patients suffering from sprains or strains, oral Ketorolac 10 mg 6 hourly for upto 7 days provided similar pain relief as diclofenac 50 mg thrice daily and better relief than ibuprofen 400 mg, paracetamol 600 mg±60 mg codeine 4 times daily or phenylbutazone 100 mg thrice daily(4).

3. *Other pain states:* Ketorolac has also been evaluated in post extraction dental pain, post traumatic pain, cancer pain and renal colic and the results are promising. The major drawback is that all these studies have been performed in adults.

In a preliminary report of a multicentric double blind trial comparing oral Ketorolac 10 mg 4 times a day with aspirin 650 mg QID in 823 patients with chronic pain, there were less withdrawals from the study because of efficacy in patients receiving Ketorolac(13).

4. *Ocular inflammation:* Ketorolac ophthalmic solution is reportedly superior to placebo and dexamethasone in reducing ocular inflammation after cataract surgery(14).

Adverse Effects

Oral and intramuscular Ketorolac is well tolerated. However, it shares the adverse effect profile of other NSAID. Nausea, headache, drowsiness, somnolence and palpitation are the commonly noticed side

effects after single dose. Multiple intramuscular administration may lead to somnolence (7%), injection site pain (2%), sweating (1%), nausea, headache, pruritus, vasodilatation *etc.* Long term therapy increases the incidence of gastrointestinal pain, dyspepsia, nausea and renal impairment. Ketorolac should be used with caution in patients with liver or kidney disease and those who are at risk by prolongation of bleeding time(4,8,9,13).

Dosage and Administration

Ketorolac is available as tablets containing 10 mg and intramuscular injection containing 30 mg per ml. In adults, single dose administration is 30 mg orally or 30 to 90 mg intramuscular. The drug is under evaluation for use in children and the recommended dosage schedule is 1.5 mg/kg 12 hourly(l5).

Place of Ketorolac in Ameliorating Pain

The available analgesics can be divided into two groups, *i.e., (i)* opioids 'such as morphine, pethidine and pentazocine, and *(ii)* nonsteroidal anti-inflammatory drugs (NSAID) such as paracetamol, ibuprofen, naproxen, *etc.* Opioids mainly act on central nervous system and NSAID have predominant peripheral action. Peripherally acting analgesics have less CNS side effects and less of addictive potentials but most of available NSAID do not satisfy the criterion of being potent, having rapid onset of action and suitability for parenteral administration. Ketorolac possesses most of the above mentioned properties and offers promise as an alternative to opioids and other NSAID in relieving acute pain. Wider clinical experience is required to firmly establish its role in pediatric and neonatal population.

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