Clinical Pharmacokinetics of Ketorolac Tromethamine

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Summary

Ketorolac is a new chiral nonsteroidal anti-inflammatory drug (NSAID) which is marketed for analgesia as the racemate. The drug is administered as the water soluble tromethamine salt and is available in tablets or as an intramuscular injection. The absorption of ketorolac is rapid, $C_{\text{max}}$ being attained between 20 to 60 min. Its oral bioavailability is estimated to range from 80 to 100%. The drug is extensively bound (>99%) to plasma proteins and has a volume of distribution (0.1 to 0.3 L/kg) comparable with those of other NSAIDs. Only small concentrations of ketorolac are detectable in umbilical vein blood after administration to women in labour. The elimination half-life is between 4 and 6 h and is moderate in comparison with other NSAIDs. The area under the plasma concentration-time curve of ketorolac is proportional to the dose after intramuscular administration of therapeutic doses to young healthy volunteers.

Ketorolac is extensively metabolised through glucuronidation and oxidation; little if any drug is eliminated unchanged. Most of the dose of ketorolac is recovered in the urine as conjugated drug. Although ketorolac is excreted into the breast milk, the amount of drug transferred comprises only a small fraction of the maternal exposure. Little stereoselectivity was present in the pharmacokinetics of ketorolac in a healthy volunteer receiving single intravenous or oral doses. The elderly exhibit reduced clearance of the drug. Renal insufficiency appears to cause an accumulation of ketorolac in plasma, although hepatic disease may not affect the pharmacokinetics.
Ketorolac (fig. 1) is a new racemic nonsteroidal anti-inflammatory drug (NSAID) which is marketed for systemic use as a peripherally acting analgesic agent (Rooks et al. 1982, 1985). The drug was recently introduced into the pharmaceutical markets of several countries, including the US, Canada, New Zealand, Italy and Denmark. The analgesic properties of ketorolac are manifested through its prostaglandin synthetase inhibitory activity (Rooks et al. 1982, 1985) which, like other aryl alkanic acid NSAIDs, is mostly attributable to the $S$ enantiomeric configuration (Guzman et al. 1986; Jamali 1988). Because ketorolac is produced as a tromethamine salt, it possesses sufficient water solubility to allow for its parenteral administration (Rooks 1990). Other NSAIDs which have also been used parenterally are diclofenac sodium (Reynolds 1989), indomethacin sodium trihydrate (Reynolds 1989) and ketoprofen (Debruyne et al. 1987).

Ketorolac seems to be as effective as morphine, but is without potentially troublesome side effects such as respiratory depression or constipation (Resman-Targoff 1990). This may allow ketorolac a useful role in the short term alleviation of postoperative pain in surgical patients (Buckley & Brogden 1990; Forbes et al. 1990; Resman-Targoff 1990; Stanski et al. 1990). Because ketorolac is an NSAID, however, it does share many of the same side effects as other NSAIDs (Buckley & Brogden 1990; Litvak & McEvoy 1990; Resman-Targoff 1990). In this article we review the clinical pharmacokinetics of ketorolac. The pharmacokinetics of the enantiomers in a healthy volunteer are also reported for the first time.

1. Analytical Methods

Very few assay procedures have been published for the quantitative analysis of ketorolac in biological specimens (Jamali et al. 1989b; Wu et al. 1986). The manufacturer, Syntex, has developed an assay for its quantification, although it has only been published as an abstract (Wu et al. 1986). Mroszczak et al. (1987) briefly describe another method, but details were not included. All of the available methods involve initial acidification of the sample, followed by extraction into an organic solvent. Ultraviolet absorbance is used for detection by all methods, either at 280 or 313nm. Radiolabelled ketorolac has also been used to follow the time course of the drug and its metabolites in biological samples (Ling & Combs 1987; Mroszczak et al. 1987). The assay of Wu et al. (1986) is also capable of measuring an inactive metabolite, $p$-hydroxy-ketorolac, in human plasma (Jung et al. 1989).

To date there is only 1 assay procedure, re-