Pharmacodynamics, chiral pharmacokinetics and PK–PD modelling of ketoprofen in the goat

ABSTRACT

There have been few studies of the pharmacodynamics of nonsteroidal antiinflammatory drugs (NSAIDs) using PKï PD modelling, yet this approach offers the advantage of defining the whole concentrationï effect relationship, as well as its time course and sensitivity. In this study, ketoprofen (KTP) was administered intravenously to goats as the racemate (3.0 mg/kg total dose) and as the single enantiomers, S(+) KTP and R(ī) KTP (1.5 mg/kg of each). The pharmacokinetics and pharmacodynamics of KTP were investigated using a tissue cage model of acute inflammation. The pharmacokinetics of both KTP enantiomers was characterized by rapid clearance, short mean residence time (MRT) and low volume of distribution. The penetration of R(ī) KTP into inflamed (exudate) and noninflamed (transudate) tissue cage fluids was delayed but area under the curve values were only slightly less than those in plasma, whereas MRT was much longer. The S(+) enantiomer of KTP penetrated less readily into exudate and transudate. Unidirectional inversion of R(ī) to S(+) KTP occurred. Both rac-KTP and the separate enantiomers produced marked inhibition of serum thromboxane B2 (TxB2) synthesis (ex vivo) and moderate inhibition of exudate prostaglandin E2 (PGE2) synthesis (in vivo); pharmacodynamic variables for S(+) KTP were Emax (%) = 94 and 100; IC50 (ε g/mL) = 0.0033 and 0.0030; N = 0.45 and 0.58, respectively, where Emax is the maximal effect, IC50 the plasma drug concentration producing 50% of Emax and N the slope of log concentration/effect relationship. The IC50 ratio, serum TxB2:exudate PGE2 was 1.10. Neither rac-KTP nor the individual enantiomers suppressed skin temperature rise at, or leucocyte infiltration into, the site of acute inflammation. These data illustrate for KTP shallow concentrationï response relationships, probable nonselectivity of KTP for cyclooxygenase (COX)-1 and COX-2 inhibition and lack of measurable effect on components of inflammation.

Keyword: Ketoprofen; Pharmacokinetics; Pharmacodynamics; Goat; Nonsteroidal antiinflammatory drugs