The pharmacokinetics of ketorolac enantiomers following intramuscular administration of the racemate

P. J. HAYBALL[1], J. WROBEL[2], J. G. TAMBLYN[1] & R. L. NATION[3]
[1]Pharmacy Department and [2]Intensive Care Unit, Repatriation General Hospital, Daw Park, Adelaide, South Australia, 5041, and [3]School of Pharmacy, University of South Australia, Adelaide, South Australia, 5000

A single dose of racemic ketorolac (30 mg of the tromethamine salt, Toradol®) was administered by bolus intramuscular injection to four young, healthy volunteers. The concentrations of total (bound plus unbound) (R)- and (S)-ketorolac were measured in plasma for 9 h after dosing. The mean ± s.d. clearance of (S)-ketorolac (45.9 ± 10.1 ml h^{-1} kg^{-1}) exceeded ($P = 0.0032$) that of the (R)-enantiomer (19.0 ± 5.0 ml h^{-1} kg^{-1}). The mean ± s.d. AUC ratio for (S)-ketorolac:(R)-ketorolac (0.442 ± 0.043) was signifcantly different from unity ($P = 0.0001$). The steady-state volume of distribution of (S)-ketorolac (0.135 ± 0.022 l kg^{-1}) was significantly different ($P = 0.0013$) from that of its optical antipode (0.075 ± 0.014 l kg^{-1}) and the half-lives of (S)- and (R)-ketorolac (2.35 ± 0.23 h and 3.62 ± 0.79 h, respectively) were also significantly different ($P = 0.026$). These data indicate that the disposition of ketorolac in man is subject to marked enantioselectivity and, because of possible differences in biological activity of (S)- and (R)-ketorolac, emphasize the need to monitor separate stereoisomer concentrations of the drug if pharmacological data are to be interpreted correctly.

Keywords ketorolac enantiomers (R)-ketorolac (S)-ketorolac pharmacokinetics enantioselectivity

Introduction

Ketorolac ((rac)-5-benzoyl-1,2-3*H*-pyrrolo[1,2*a*]pyrrole-1-carboxylic acid) has a chiral carbon atom located within the pyrrolidine ring, and is marketed for clinical use as a racemate [1]. It is used as a non-narcotic analgesic and is believed to exert this effect by inhibition of prostaglandin synthesis peripheral to the central nervous system. Animal studies have shown that ketorolac-induced inhibition of prostanoid synthesis is highly stereoselective with predominant activity residing with the (S)-enantiomer [2]. While no concentration-effect data exist for the separate enantiomers of ketorolac in humans, based on *in vitro* pharmacodynamic data for structurally and pharmacologically related 2-aryl-propionic acid nonsteroidal anti-inflammatory drug enantiomers [3], high eudismic ratios for the prostaglandin-dependent actions of ketorolac are likely to exist in humans.

With the exception of an abstract [4], there have been no reports of pharmacokinetic data for ketorolac enantiomers in humans. Extensive data generated for the various formulations of ketorolac [5–7] have relied upon nonstereoselective analytical methods and,

consequently, have limited value given likely enantioselective pharmacological effects. This report describes the kinetics of ketorolac enantiomers following intramuscular (i.m.) administration of a single therapeutic dose of rac-ketorolac to young, healthy volunteers.

Methods

Subjects

Following approval of the Research and Ethics Committee at the Repatriation General Hospital four healthy subjects (two males and two females of mean age 30 years and range 22–40 years, none of whom was taking any medication) gave informed consent to participate in the study. The subjects fasted from midnight preceding the study and for 4 h after dosing. On study days, fluid intake (caffeine-free) was restricted to 300 ml until 4 h after dosage, after which time food and drink were permitted *ad libitum*.

Correspondence: Dr Peter J. Hayball, Pharmacy Department, Repatriation General Hospital, Daw Park, Adelaide, South Australia, 5041, Australia

Ketorolac administration and blood sampling

Rac-ketorolac (30 mg as the tromethamine salt, Toradol®, Syntex, Sydney, Australia) was administered in a 1 ml volume by bolus intramuscular injection into the deltoid muscle. Venous blood samples (10 ml) were collected into heparinized glass tubes prior to drug administration then at 15 min intervals for the first hour after dosing then half-hourly for the next 2 h and finally every hour to give a total 9 h post-dose sampling period for each subject.

Immediately upon collection, blood samples were placed on ice then centrifuged (2000 g, 10 min, 2° C) within 30 min of collection. Plasma aliquots (1.0 ml) were adjusted to pH 3 by the addition of 50 μl of 2.0 M sulphuric acid to quench possible metabolite deconjugation [8]. Tubes were stored at −20° C prior to analysis. Preliminary experiments confirmed that frozen storage of pH-stabilized *ex vivo* plasma aliquots for up to 1 month did not lead to a detectable change in the concentration of ketorolac enantiomers compared with samples assayed on the day of collection.

Enantioselective ketorolac analysis

The concentrations of (S)-ketorolac in *ex vivo* plasma samples (expressed in terms of the enantiomeric free acids) were measured by h.p.l.c. as described elsewhere [9].

Attempts were made in this study to measure the urinary excretion of the acyl-linked glucuronide metabolites of ketorolac. Nonenantioselective analytical methods have shown signficant urinary recovery of these biotransformation products (*circa* 80% in normal volunteers [5]). When an indirect approach for measuring acyl-glucuronides involving cleavage to the respective enantiomeric aglycone was employed, it was not possible to effect complete glucuronide cleavage whilst simultaneously maintaining aglycone stereochemical integrity. β-Glucuronidase-mediated hydrolysis of ketorolac urinary metabolites was incomplete, presumably because of rearrangement of the biosynthetic 1-*O*-acyl-glucuronide to β-glucuronidase-resistant regioisomers [8]. Mild alkaline hydrolysis (0.5 M sodium hydroxide) or acid hydrolysis (pH<1) conditions, while effecting complete cleavage of the acyl-linked metabolites, led to racemization of the aglycone (data not shown). Attempts to measure the metabolites by a direct analytical approach were unsuccessful.

Pharmacokinetic and statistical methods

For each subject, total (bound plus unbound) clearance (CL) values for each ketorolac enantiomer were calculated by dividing the i.m. enantiomeric dose by the respective AUC value (linear kinetics [6] and complete i.m. bioavailability [10] were assumed). The AUC of each enantiomer was calculated by the linear trapezoidal rule with extrapolation to infinity.

The extrapolated area was determined by dividing the final plasma concentration (interpolated from log-linear regression analysis) by the terminal rate constant, and in all cases this area was less than 15% of AUC. Values of V_{SS} were derived for each enantiomer according to the method of Benet & Galaezzi [11]. The terminal slope, determined by log-linear regression of at least the final eight data points, was used to calculate the half-life $(t_{1/2})$ for each enantiomer. The selection of the terminal data points for estimation of the terminal slope was based on visual examination of the semi-logarithmic plotted data.

Pharmacokinetic parameters for (S)- and (R)-ketorolac were compared by the paired t-test with differences considered significant at $P < 0.05$. In addition, the 95% confidence interval for the difference between mean enantiomeric values was calculated.

Results and discussion

Plasma concentrations of (S)- and (R)-ketorolac are shown for each subject in Figure 1. Highly significant enantiomeric differences were observed for CL and V_{SS} (Table 1). The time-averaged plasma concentration of the pharmacologically active (S)-enantiomer was approximately half that of its optical antipode based on a mean ± s.d. (S)/(R) AUC ratio of 0.442 ± 0.043 (different from unity, $P = 0.0001$). The mean elimination half-life of (S)-ketorolac was shorter that that of (R)-ketorolac (Table 1).

The ketorolac (S)/(R) AUC ratio in this study was similar to the mean value reported previously (0.37 [4]). Earlier estimates of unresolved drug CL following i.m. administration to healthy subjects (mean values of 18–26 ml h^{-1} kg^{-1} [5–7] compared with a mean 27 ml h^{-1} kg^{-1} calculated for unresolved drug in our subjects) clearly underestimate the CL of pharmacologically active (S)-ketorolac. Similarly, both the distribution

Table 1 Pharmacokinetic parameters (mean ± s.d.) of (S)- and (R)-ketorolac following i.m. administration of 30 mg (rac)-ketorolac tromethamine to four young, healthy volunteers

Parameter	(S)-Ketorolac	(R)-Ketorolac	Probability*	95% confidence interval‡
CL (ml h^{-1} kg^{-1})	45.9 ± 10.1	19.0 ± 5.0	$P = 0.0032$	17.1–36.7
V_{SS} (l kg^{-1})	0.135 ± 0.022	0.075 ± 0.014	$P = 0.0013$	0.044–0.075
$t_{1/2}$ (h)	2.35 ± 0.23	3.62 ± 0.79	$P = 0.026$	0.29–2.24

*Paired t-test probability value of the difference between (S)-ketorolac and (R)-ketorolac.
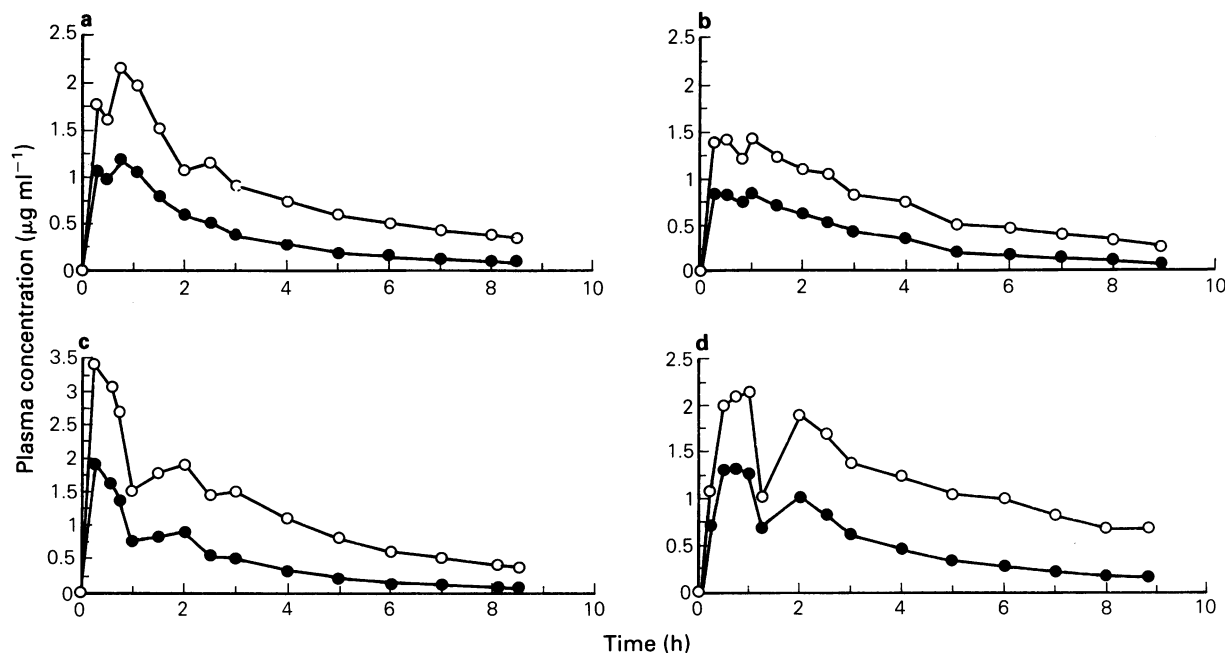‡95% confidence interval for the difference between the mean enantiomeric values.

Figure 1 Plasma concentrations of (S)-ketorolac (●) and (R)-ketorolac (○) in each subject following a single i.m. injection of 30 mg (rac)-ketorolac tromethamine.

volume and elimination half-life of the separate enantiomers are misrepresented when nonstereoselective analytical methods are used (see Table 1 and [5–7, 11]).

Like most NSAIDs, ketorolac is a drug of low hepatic extraction and thus the total clearance of its enantiomers will be dependent on their unbound fraction in plasma [12]. In the absence of plasma protein binding data for the individual enantiomers of ketorolac, assigning mechanisms for the observed enantioselective disposition is speculative. However, based on the higher volume of distribution for (S)-ketorolac, it is possible that the unbound fraction of this enantiomer exceeds that of its optical antipode and this may contribute to the significantly higher total plasma clearance of the (S)-enantiomer.

The derivation of clearance and volume of distribution terms for the (S)-enantiomer (Table 1), assumes no (R) to (S) metabolic chiral inversion. While this process cannot be excluded, it would appear unlikely. Generally held conceptions of parent drug-metabolite kinetics

imply that it would not be feasible for such unidirectional inversion of configuration to take place while simultaneously maintaining a shorter $t_{1/2}$ for the (S)-isomer (the metabolite in this case). In contrast to the 2-arylpropionate homologues for which chiral inversion has been documented [3], ketorolac has a chiral carbon atom as part of a heterocyclic ring and there are no reports of such structures undergoing metabolic inversion of configuration.

In summary, this study, although conducted in only four subjects, indicates that the disposition of ketorolac is markedly enantioselective. Given the probable involvement of highly enantioselective prostaglandin-dependent processes for both the activity and toxicity of this drug, plasma concentrations should be expressed for the individual enantiomers.

References

1 Rook WH, Tomolonis AJ, Maloney PJ, Wallach MB, Schuler ME. The analgesic and anti-inflammatory profile of (±)-5-benzoyl-1,2-dihydro-3H-pyrrolo[1,2a]pyrrole-1-carboxylic acid (RS-37619). *Agents Actions* 1982; **12**: 684–690.

2 Guzman A, Yuste F, Toscano RA, Young JM, Van Horn AR, Muchowski JM. Absolute configuration of (−)-5-benzoyl-1,2-dihydro-3*H*-pyrrolo[1,2*a*]pyrrole-1-carboxylic acid. *J med Chem* 1986; **29**: 589–591.

3 Evans AM. Enantioselective pharmacodynamics and pharmacokinetics of chiral non-steroidal anti-inflammatory drugs. *Eur J clin Pharmac* 1992; **42**: 237–256.

4 Mroszczak E, Combs D, Tsina I, Tam Y, Massey I, Chaplin M, Yee J. Pharmacokinetics of (−)S and (+)R enantiomers of ketorolac (K) in humans following administration of

racemic ketorolac tromethamine (KT). *Clin Pharmac Ther* 1991; **49**: 126 (Abstract PI-13).

5 Mroszczak E, Lee FW, Combs D, Sarnquist FH, Huang · B-L, Wu AT, Tokes LG, Maddox ML, Cho DK. Ketorolac tromethamine absorption, distribution, metabolism, excretion, and pharmacokinetics in animals and humans. *Drug Metab Dispos* 1987; **15**: 618–626.

6 Jung D, Mroszczak EJ, Wu A, Ling TL, Sevelius H, Bynum L. Pharmacokinetics of ketorolac and p-hydroxyketorolac following oral and intramuscular administration of ketorolac tromethamine. *Pharm Res* 1989; **6**: 62–65.

7 Jallad NS, Garg DC, Martinez JJ, Mroszczak EJ, Weidler DJ. Pharmacokinetics of single-dose oral and intramuscular ketorolac in the young and elderly. *J clin Pharmac* 1990; **30**: 76–81.

8 Spahn-Langguth H, Benet LZ. Acyl glucuronides revisited: Is the glucuronidation process a toxification as well as a detoxification mechanism? *Drug Metab Rev* 1992; **24**: 5–48.

9 Hayball PJ, Tamblyn JG, Holden Y, Wrobel J. Stereoselective analysis of ketorolac in human plasma by high-performance liquid chromatography. *Chirality* 1993; **5**: 31–35.

10 Jung D, Mroszcak E, Bynum L. Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intramuscular and oral administration. *Eur J clin Pharmac* 1988; **35**: 423–425.

11 Benet LZ, Galaezzi RL. Noncompartmental determination of the steady-state volume of distribution. *J pharm Sci* 1979; **68**: 1071–1074.

12 Wilkinson GR, Shand DC. A physiological approach to hepatic drug clearance. *Clin Pharmac Ther* 1975; **18**: 377–390.