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# Pharmacokinetics of ketoprofen enantiomers after different doses of the racemate

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The pharmacokinetics of the enantiomers of ketoprofen after oral administration of 12.5 mg, 25 mg and 50 mg and i.v. administration of 50 mg racemic ketoprofen to 24 healthy subjects were investigated. The AUC values of R- ($r^2$ = 0.929) and S-ketoprofen ($r^2$ = 0.930) were proportional to dose. The absolute bioavailability of the 50 mg oral dose was 84.5 (s.d. 20.6) % and 81.4 (18.0) % for R-ketoprofen and S-ketoprofen, respectively. With the exception of AUC values no dose dependent differences in pharmacokinetic parameters were observed. However, the R-enantiomer had higher AUC, lower clearance data and higher $C_{max}$ values than the S-form after oral administration. The results suggest that stereochemical and pharmacokinetic considerations cannot explain the lack of dose response observed with ketoprofen doses below 50 mg.

**Keywords** ketoprofen pharmacokinetics enantiomers stereoselectivity

## Introduction

Ketoprofen (KT), a congener of the 2-arylpropionic acid class of non-steroidal anti-inflammatory drugs is used clinically in its racemic form in doses ranging from 50 to 200 mg [1]. Although an intravenous formulation of racemic KT is available the absolute bioavailability of KT and its enantiomers from oral preparations has not been determined [1]. Furthermore no data on the dose-AUC relationship at doses below 50 mg are available although there are clinical studies showing analgesic activity below 50 mg of the racemate [2–4]. However, in this dose range there was no evidence of a ketoprofen dose response [2–4]. In the present study we have determined the absolute bioavailability of KT and its enantiomers from an oral formulation of racemic KT (50 mg) as well as pharmacokinetic parameters following oral administration of 12.5, 25 and 50 mg racemic KT to show whether or not stereochemical pharmacokinetic aspects have to be considered for the explanation of the lack of dose response.

## Methods

### *Reference compounds*

(R)- and (S)-ketoprofen and the racemic compound with chemical and optical purities greater than 98.5% were supplied by Bayer AG (Wuppertal, Germany). Tablets containing 25 mg (lot: D180989-004R), and 12.5 mg (lot: D150989-009R) of racemic ketoprofen and the intravenous preparation (lot: N9009N9823) were also from this source.

### *Protocol*

Twelve female (age 29.1 ± 5.1 years; on oral contraceptives) and twelve male volunteers (age 27.0 ± 3.6 years) participated in the study after giving written informed consent. Their mean (± s.d.) weights were 74.9 ± 10.8 kg (males) and 57.6 ± 4.3 kg (females). The study protocol was approved by the Medical Ethics Review Committee of the University of Erlangen. According to a four-way randomized cross-over

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design the subjects took either 12.5 mg, 25 mg or 50 mg (2 × 25 mg tablets) of racemic ketoprofen with 200 ml of water or were injected intravenously with 50 mg of the racemic compound over 5 min after an overnight fast. Food and fluid were withheld for a further 4 h after dosage. The wash-out period between each dose was at least 1 week. Venous blood samples were collected into heparinized tubes prior to dosing and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 12 h after oral administration and at 5, 10, 15, 20, 30 and 45 min and 1, 1.5, 2, 3, 4, 6, 8 and 10 h after i.v. administration. Plasma samples were frozen immediately and stored at –25° C.

*Drug assay*

Plasma (R)- and (S)-ketoprofen concentrations were assayed by h.p.l.c. using a chiral $\alpha_1$-acid glycoprotein column (AGP, Grom, Herrenberg, Germany) as described previously [5]. The limit of quantification (the lowest concentration that could be determined with either precision or accuracy of less than or equal to 15%) was 0.03 μg $ml^{-1}$ for both enantiomers. The coefficient of variation over the calibration range of 0.03 to 10 μg $ml^{-1}$ was less than 10%. Absolute recovery from spiked plasma samples was 96%.

*Data analysis*

Non-compartmental pharmacokinetic analysis was carried out using the TOPFIT® software package [6]. AUC values were calculated using the linear trapezoidal rule with extrapolation to infinity using $C_{last}/\lambda_z$. The extrapolated area was less than 5% of the total. Absolute bioavailability was determined by comparing the AUC after intravenous and oral administration of the 50 mg dose. The terminal elimination rate constant $\lambda_z$ was estimated by unweighted linear least-squares regression analysis of the linear segment of the log plasma drug concentration-time data. The terminal elimination half-life ($t_{1/2,z}$) was calculated from $0.693/\lambda_z$. Total clearance was calculated from dose/AUC. $C_{max}$ and $t_{max}$ values were noted directly from the data. The statistical analysis was carried out using two tailed Student's *t*-test, paired or unpaired as appropriate. $P < 0.05$ was considered to be statistically significant.

## Results

The pharmacokinetic parameters are summarized in Table 1. In the dose range investigated the AUC values of both enantiomers were linearly related to dose $kg^{-1}$ body weight (R: $r^2 = 0.929$, S: $r^2 = 0.930$). Absolute bioavailabilities from the 50 mg tablet dose were 84.5 ± 20.6 (s.d.) % and 81.4 ± 18.0 % for R- and S-KT, respectively. Assuming dose linearity of AUC the absolute bioavailabilities from the 25 mg and 12.5 mg tablets were 89.1 ± 34.3 and 82.9 ± 26.8 % for R-KT, and 79.8 ± 26.6 and 71.6 ± 24.1 % for S-KT, respectively. The differences in bioavailability between both enantiomers were statistically significant

**Table 1** Mean ± s.d. pharmacokinetic parameters of R- and S-ketoprofen following intravenous administration of 50 mg and oral administration of 12.5, 25 and 50 mg of racemic ketoprofen to 24 volunteers, [the 95% confidence intervals for differences are given in square brackets]

| | *50 mg KT i.v.* | | | *50 mg KT p.o.* | | | *25 mg KT p.o.* | | | *12.5 mg KT p.o.* | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *R-KT* | *S-KT* | * | *R-KT* | *S-KT* | * | *R-KT* | *S-KT* | * | *R-KT* | *S-KT* | * |
| $t_{max}$† (h) | — | — | — | 0.75 (0.25–4) | 0.75 (0.25–2.5) | $P = 0.614$ | 0.75 (0.25–2) | 0.75 (0.25–2) | $P = 0.054$ | 0.5 (0.25–2.5) | 0.5 (0.25–2.5) | $P = 0.327$ |
| $C_{max}$ (μg $ml^{-1}$) | — | — | — | 2.3 ± 0.6 | 2.2 ± 0.5 | $P < 0.001$ [0.05; 0.17] | 1.3 ± 0.4 | 1.2 ± 0.3 | $P < 0.05$ [0.00; 0.21] | 0.60 ± 0.18 | 0.56 ± 0.17 | $P < 0.001$ [0.03; 0.06] |
| AUC (μg $ml^{-1}$ h) | 6.3 ± 1.4 | 6.0 ± 1.3 | $P < 0.02$ [0.04; 0.42] | 5.1 ± 1.9 | 4.8 ± 0.8 | $P < 0.01$ [0.12; 0.59] | 2.6 ± 0.8 | 2.3 ± 0.6 | $P < 0.001$ [0.17; 0.47] | 1.2 ± 0.4 | 1.1 ± 0.4 | $P < 0.001$ [0.10; 0.28] |
| $t_{1/2,z}$ (h) | 1.5 ± 0.7 | 1.4 ± 0.5 | $P = 0.452$ [–0.21; 0.39] | 1.3 ± 0.3 | 1.4 ± 0.5 | $P = 0.274$ [–2.47; 0.04] | 1.3 ± 0.3 | 1.1 ± 0.3 | $P < 0.01$ [0.56; 0.27] | 1.3 ± 0.6 | 1.2 ± 0.5 | $P = 0.275$ [–0.11; 0.36] |
| CL (ml $min^{-1}$) | 69.9 ± 15.5 | 72.3 ± 15.1 | $P < 0.02$ [–4.35; –0.47] | — | — | — | — | — | — | — | — | — |

*Comparison of parameters between R- and S-ketoprofen.
†median values, range is given in parentheses.

for the 12.5 and 25 mg dose ($P < 0.01$) but not for the 50 mg dose ($P = 0.108$). Elimination half-lives and clearances were not dose-dependent. However, R- and S-KT differed significantly with respect to AUC following i.v. and p.o. administration, with the R-enantiomer predominating in plasma. Elimination half-lives of the enantiomers differed significantly only after oral administration of 25 mg KT. No differences in pharmacokinetics were observed between male and female subjects.

## Discussion

The absolute oral bioavailability of KT was found to be lower than that estimated indirectly by Jamali & Brocks [1] from separate i.v. and oral studies (92%). However, our results extend their findings of a linear dose-AUC relationship for R- and S-KT in the range 50 to 200 mg (KT racemate) to lower doses. In line with previous findings [7, 8] plasma concentrations of R-KT exceeded those of the S-enantiomer following both i.v. and oral administration. However, in other studies with elderly or arthritic patients the pharmacokinetic parameters of R- and S-KT were either similar or not statistically significantly different [8–10]. Dose dependent plasma protein binding, reported for S-KT [9], does not appear to affect the pharmacokinetics based on total (unbound + bound fraction) plasma concentrations in the dose range investigated.

In conclusion, the observed statistically significant differences between the two enantiomers in $C_{max}$, AUC and clearances are relatively small and seem to be of negligible clinical relevance. The lack of a ketoprofen dose response in the dose range below 50 mg [2–4] cannot be explained by stereochemical and/or pharmacokinetic aspects.

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