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Stereoselective disposition of flurbiprofen in healthy subjects following administration of the single enantiomers

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Plasma concentrations of the enantiomers of flurbiprofen were measured following oral administration of (S)-flurbiprofen 50 mg and (R)-flurbiprofen 50 mg and 100 mg to sixteen healthy subjects. Chiral inversion did not occur to a measurable exent. Significantly higher values of AUC (55.2 ± 17.0 *vs* 44.6 ± 11.2 μg ml^{-1} h) elimination half-life (5.6 ± 1.4 *vs* 4.0 ± 1.0 h) and mean residence time (7.5 ± 1.6 *vs* 5.7 ± 1.2 h) were observed after 50 mg (S)-flurbiprofen as compared with 50 mg (R)-flurbiprofen. With the exception of C_{max} and AUC values pharmacokinetic data for the 50 mg and the 100 mg dose of (R)-flurbiprofen did not differ significantly. The data are of clinical relevance if (R)-flurbiprofen also has analgesic activity in humans and is to be developed as an analgesic.

Keywords flurbiprofen enantiomers stereoselective pharmacokinetics

Introduction

Flurbiprofen [(±)-2-fluoro-α-methyl-4-biphenylacetic acid], a chiral 2-arylpropionic acid derivative, is an anti-inflammatory and analgesic drug. The anti-inflammatory activity is mediated by inhibition of prostaglandin synthesis, which is exerted mainly by the (S)-enantiomer, whereas analgesic effects may be exerted by both flurbiprofen enantiomers [1]. Previous studies indicated a stereoselective disposition of flurbiprofen in both healthy subjects and patients following administration of the racemate [2–4]. With the exception of data from a single subject given (R)-flurbiprofen [5] pharmacokinetic data following administration of the single enantiomers are lacking.

The aim of this study was to characterize the disposition of the enantiomers of flurbiprofen following their oral administration to healthy subjects and to determine the effect of dose (50 mg and 100 mg) on the disposition of (R)-flurbiprofen. These pharmacokinetic data are of relevance to studies in progress to investigate whether (R)-flurbiprofen also has analgesic activity in humans.

Methods

Reference compounds

(R)- and (S)-flurbiprofen were kindly supplied by PAZ Arzneimittelentwicklungsgesellschaft mbH (Frankfurt/Main, Germany) with chemical and optical purities of greater than 98.5%. (R)-flurbiprofen (lot 1151-A-5-R) and (S)-flurbiprofen (lot 1151-A-5-S) were administered in gelatine capsules of the same size containing either 50 mg (S)-flurbiprofen and 50 mg or 100 mg (R)-flurbiprofen.

Protocol

Sixteen healthy females (taking an oral contraceptive), between 23 and 36 years of age, participated in the study. All subjects were within 20% of their ideal body weight which was 58.9 ± 3.5 kg. The protocol was approved by the University of Erlangen Medical Ethics Review Committee, and subjects took part after giving written informed consent. According to a randomized 4-way crossover design, the subjects took either placebo, 50 mg (S)-flurbiprofen, 50 mg (R)-flurbiprofen or 100 mg (R)-flurbiprofen with 200 ml water following an overnight fast, after which food and fluid were withheld for a further 4 h. The wash-out interval between each dose was at least 1 week. Venous blood samples were collected into heparinized tubes prior to flurbiprofen dosing and at 0.25, 0.5 0.75, 1.25, 1.5, 1.75, 2.25, 4.0, 6.0, 8.0, 10.0 and 24.0 h. Plasma samples were frozen immediately and stored at −25° C with quality control samples pending analysis.

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Analysis of flurbiprofen

(R)- and (S)-flurbiprofen concentrations were measured by stereoselective h.p.l.c. as described previously [6]. The limit of quantification (lowest concentration that could be determined with either precision or accuracy of less than or equal to 10%) was 50 ng ml^{-1} for both enantiomers. The coefficient of variation over the calibration range of 0.05–25 μg ml^{-1} of each enantiomer was less than 7%. Absolute recovery from spiked plasma samples was 99%.

Analysis of data

Non-compartmental pharmacokinetic analysis was carried out using the TOPFIT® software package [7]. The terminal elimination rate constant (λ_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 $0.693/\lambda_z$. Values of AUC were estimated using the linear and log-linear trapezoidal rules with extrapolation to infinity using $C_{(last)}/\lambda_z$. The extrapolated area was less than 6% of the total AUC. Oral clearance (CL_o) was calculated by dividing the dose of enantiomer by the AUC. Mean residence times (MRT) were calculated from the area under the first moment curve (AUMC) divided by the AUC. C_{max} and t_{max} were noted directly from the data. Statistical analysis was by analysis of variance and Student's unpaired two-tailed *t*-test. $P < 0.05$ was considered to be statistically significant.

Results

Neither (R)- nor (S)-flurbiprofen was inverted to its optical antipode to a measurable extent. However, between 0.5 and 4 h after dosing in a few subjects (four, five and eight subjects in the 50 mg (R)-, 50 mg (S)- and 100 mg (R)-flurbiprofen groups, respectively) chromatograms indicated small amounts of the optical antipode (0.02–0.07 μg ml^{-1}). Mean plasma drug concentrations after oral administration of 50 mg (S)-flurbiprofen were higher than those after 50 mg (R)-flurbiprofen as indicated by higher AUC values (55.2 ± 17.0 *vs* 44.6 ± 11.2 μg ml^{-1} h). In addition, values of the elimination half-life (5.6 ± 1.4 *vs* 4.0 ± 1.0 h) and mean residence time (7.5 ± 1.6 *vs* 5.7 ± 1.2 h) were significantly greater for the (S)-enantiomer (Table 1). Pharmacokinetic parameters were similar for the two doses of (R)-flurbiprofen, except for C_{max} (8.2 ± 1.3 *vs* 16.4 ± 2.6 μg ml^{-1}) and AUC (44.6 ± 11.2 *vs* 92.5 ± 25.7 μg ml^{-1} h; Table 1).

Discussion

The detection of very low plasma concentrations of the opposite enantiomer may be due to impurity of the administered flurbiprofen enantiomer rather than inversion. The present findings are consistent with those of Jamali *et al.* [5] who found no measurable inversion from (R)- to (S)-flurbiprofen, and with the inability of flurbiprofen to form a coenzyme A thioester *in vitro* [8–9].

Significant differences in AUC, $t_{1/2,z}$ and MRT values between the enantiomers may be explained by stereoselective plasma protein binding ((S)-flurbiprofen > (R)-flurbiprofen) and stereoselective metabolite formation, as shown by Knadler *et al.* [3]. Unlike in rats [5, 10–11], kinetic interactions between the isomers of flurbiprofen do not appear to occur to a significant extent in humans as the enantioselective differences following racemate administration [2–4] were of the same magnitude as those found in the present study after administration of single enantiomers. In conclusion, flurbiprofen does not undergo

Table 1 Mean ± (s.d.) pharmacokinetic parameters describing the fate of the individual enantiomers of flurbiprofen following oral administration of 50 mg (S)-flurbiprofen and 50 mg and 100 mg (R)-flurbiprofen to 16 healthy females (median value; range, given in parentheses). [The 95% confidence intervals for differences are given in square brackets]

	50 mg (S)-flurbiprofen	*Significance**	*50 mg (R)-flurbiprofen*	*Significance†*	*100 mg (R)-flurbiprofen*
t_{max} (h)	(1.3; 3.3)		(1.3; 3.5)		(1.3; 3.3)
C_{max} (μg ml^{-1})	9.3 ± 1.9 (9.5; 7.7)	$P = 0.074$ [−0.1 to −2.1]	8.2 ± 1.3 (8.2; 4.9)	$P = 0.0001$ [−9.4 to −7.0]	16.4 ± 2.6 (16.8; 9.9)
AUC (μg ml^{-1} h)	55.2 ± 17.0 (53.7; 39.8)	$P = 0.049$ [6.8 to 17.8]	44.6 ± 11.2 (39.3; 39.8]	$P = 0.0001$ [−57.2 to −38.7]	92.5 ± 25.7 (83.3; 99.3)
$t_{1/2,z}$ (h)	5.6 ± 1.4 (5.7; 5.4)	$P = 0.001$ [1.0 to 2.5]	4.0 ± 1.0 (4.0; 3.8)	$P = 0.162$ [−0.9 to 0.0]	4.5 ± 0.7 (4.3; 3.4)
MRT (h)	7.5 ± 1.6 (7.7; 5.8)	$P = 0.001$ [1.2 to 2.8]	5.7 ± 1.2 (5.6; 4.4)	$P = 0.366$ [−1.2 to 0.3]	6.2 ± 1.5 (5.6; 4.7)
CL_o (ml min^{-1})	16.4 ± 4.9 (15.5; 18.9)	$P = 0.057$ [−5.8 to −2.1]	19.6 ± 4.1 (21.2; 13.8)	$P = 0.650$ [−0.8 to 2.2]	19.0 ± 3.8 (20.0; 13.9)

*Comparison of parameters between 50 mg (S)- and 50 mg (R)-flurbiprofen groups.
†Comparison of parameters between 50 mg (R)- and 100 mg (R)-flurbiprofen groups.

chiral inversion to a significant extent in healthy female subjects. The data indicate that studies of the potential analgesic action of (R)-flurbiprofen in humans may be conducted without the difficulty of interpretation imposed by chiral inversion. A major advantage for developing (R)-flurbiprofen as an analgesic may be that it may lack the gastrointestinal toxicity associated with the (S)-enantiomer, as demonstrated in rats [1].

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