Effect of buffering on pharmacokinetics of ketoprofen enantiomers in man

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Aims Concomitant administration of magnesium hydroxide may affect the rate or extent of absorption of non-steroidal anti-inflammatory drugs. In order to find out whether or not buffering modifies the pharmacokinetics of ketoprofen, plasma concentration–time courses resulting from oral administration of unbuffered formulations were compared with those of buffered formulations.

Methods Two groups of 12 healthy and young male subjects were included in two randomized cross-over studies and received single oral doses of ketoprofen 12.5 or 25 mg, respectively, given as tablets which were either unbuffered or buffered with magnesium hydroxide/citrate. Ketoprofen enantiomers in plasma were determined by h.p.l.c. up to 24 h post-dose.

Results Maximum plasma concentrations ($C_{\max}$) of both the (R)- and (S)-enantiomer, observed after administration of the buffered formulations (12.5 and 25 mg), were higher compared with the unbuffered tablets by about 50–80%. The area under concentration–time data (AUC) was unaffected, and, hence, $C_{\max}$ /AUC was increased by buffering. Time to $C_{\max}$ ($t_{\max}$) and mean residence time (MRT) tended to be or was shortened by buffering.

Conclusions It is concluded that buffering of two ketoprofen formulations with magnesium hydroxide/citrate enhanced the concentration maximum by increasing the rate of absorption and leaving AUC unaffected.

Keywords: pharmacokinetics, humans, magnesium hydroxide/citrate buffer, ketoprofen enantiomers, non-steroidal anti-inflammatory drugs

Introduction

Ketoprofen (2-(3-benzoylphenyl)propionic acid) is a congener of the 2-arylpropionic acid class of non-steroidal anti-inflammatory drugs. It is an effective inhibitor of cyclo-oxygenases and inhibits synthesis of prostaglandins [1]. Ketoprofen is clinically used in its racemic form in doses from 50–200 mg to treat rheumatic disorders and various non-rheumatic musculoskeletal joint diseases, and in lower doses from 12.5–25 mg, for mild to moderate pain and fever. Upon administration of *rac*-ketoprofen, equal amounts of (R)- and (S)-ketoprofen appear in the plasma, and show essentially similar pharmacokinetics [2–3] (see also [1]). The (S)-enantiomer is considered to be the biologically active enantiomer [1].

The absorption characteristics of some congeners of propionic acid such as ibuprofen and naproxen and other non-steroidal anti-inflammatory drugs e.g. tolfenamic and mefenamic acid may be notably affected by co-administration of magnesium hydroxide or sodium bicarbonate [4]. It was suggested that increasing the gastric pH by alkaline, buffering agents may increase the solubility and absorption of weakly acidic drugs that are non-ionized at gastric pH but are sparingly water soluble [4]. Thus the rate of absorption and maximum plasma concentration of ibuprofen [5] or mefenamic acid was increased by magnesium hydroxide, and of naproxen by sodium bicarbonate in man [4].

Interestingly in humans magnesium hydroxide had no significant effect on the pharmacokinetics of ketoprofen determined in the plasma as racemate [5]. Since it is difficult to understand why buffering would leave the pharmacokinetics of ketoprofen unaffected, it was decided to investigate in more detail whether or not the plasma concentration–time courses of ketoprofen are influenced by addition of a magnesium hydroxide/citrate buffer (resulting in an acid neutralization capacity (ANC) of 5 mEq). An enhanced rate of absorption of ketoprofen may be accompanied by a faster onset of pharmacodynamic action. A fast analgesic effect may be needed for the treatment of headaches or other pain. In the present study, the analysis of the pharmacokinetic characteristics was based on the determination of the enantiomers in the plasma. A preliminary account of the work was presented at the Meeting of the American Society for Clinical Pharmacology and Therapeutics 1997 (San Diego, USA) [6].

Methods

Subjects

Two groups of 12 healthy male subjects each (group I: age between 23 and 42 years, mean age 34 years; body weight 61–82 kg, 73 kg; height 162–187 cm, 179 cm; group II: 23–42 years, 31 years; body weight 70–92 kg, 80 kg; height 171–188 cm, 180 cm) were included in, and completed the studies. Before enrollment and at the end of the study, all

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subjects were checked medically by physical examination, vital sign parameters, ECG, and clinical laboratory tests including haematology and clinical chemistry. All subjects received detailed written information on the trial medication and study procedures. In addition, they were informed verbally about aim and possible risks of the studies by a physician in the presence of a witness. After having given written informed consent they were confined to the medical ward until the end of the study. The investigation was carried out in accordance with the German Drug Law, GCP Guidelines, the Declaration of Helsinki and the US FDA regulations. The protocols were approved by IRB and the Ethics Committee of the responsible Medical Board (Landesärztekammer Rheinland/Pfalz).

Study design

Both studies followed a randomized Latin square cross-over design with repeated measurements. The studies were not blinded. In different periods, subjects received a single oral dose of unbuffered or buffered tablets containing ketoprofen (12.5 mg, group I; 25 mg, group II) in fasting state at 08.00 h. The wash-out time was 48 h. The unbuffered tablets (12.5 mg, batch number 533212E; 25 mg, 533350D) and the buffered tablets (12.5 mg, 521185S; 25 mg, 531881E) were provided by Bayer AG, Leverkusen. Buffered formulations contained a mixture of magnesium hydroxide and citrate combined in a tablet of a weight lower than 250 mg and had an ANC 5 mEq. The tablets were taken together with 100 ml of tap water. Subjects refrained from taking in liquids until 2 h, and food until 4 h post-dose. Laboratory safety tests were carried out before and 24 h after the last dosing. All adverse events observed and reported by volunteers were recorded. Blood samples were taken immediately before administration and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14 and 24 h post-dose. (R)(-)- and (S)(+)-enantiomers of ketoprofen were simultaneously determined in plasma by reversed-phase high-performance liquid chromatography with a chiral stationary phase coupled to a u.v. detector [7]. The lower limit of quantitation was $40 \mu\text{g l}^{-1}$. The coefficient of variation was between 4 and 8% for both enantiomers at various concentrations tested. Quality control samples showed an inaccuracy of less than 2.6%.

Pharmacokinetic calculations and statistical analysis

Pharmacokinetic characteristics of both ketoprofen enantiomers were determined by non-compartmental analysis. The maximum concentration in plasma (C_{max}) and the time to reach maximum concentration (t_{max}) were calculated from the observed concentrations. For t_{max} a frequency table was drawn up. The plasma concentrations during the elimination phase were analysed by exponential regression to obtain the elimination half-life. The area under the plasma concentration-time data (AUC) was calculated according to the log linear trapezoidal rule and extrapolated to infinity using the obtained time constant of the elimination phase. As a measure for the rate of absorption, the ratio $C_{\text{max}}/\text{AUC}$ was determined. The mean residence time

(MRT) was calculated as the ratio: area under the first moment curve/AUC.

With regard to intra-subject coefficient of variations of about 6–8% in previous studies, sample size estimations were carried out to reach a power of 90% and a significance level of 5% for the ratio of AUCs (buffered/unbuffered) to be within the range of 0.8–1.25. All data were subject to analysis of variance after log-transformation taking into account treatment, period and within subject variation. The buffered/unbuffered ratios of the pharmacokinetic characteristics of ketoprofen enantiomers and geometric means with 95% confidence limits were calculated after logarithmic transformation. Presented are means and standard deviations (s.d.) of raw values. Statistical significance of differences between pharmacokinetic characteristics of unbuffered *vs* buffered formulations was determined by Bonferroni's modified *t*-test. Differences were considered to be significant at $P < 0.05$.

Results

Concentration-time courses of (R)-ketoprofen were similar to those of (S)-ketoprofen under all study conditions

Figure 1 Concentration-time courses of ketoprofen enantiomers in plasma of 12 healthy young subjects. Means and s.d. of (R)- (upper panel, a) and (S)-ketoprofen (lower panel, b). Open symbols, unbuffered formulations; filled symbols, buffered formulations. Circles and squares, 12.5 mg; triangles, ketoprofen 25 mg. Symbols and s.d. overlap in part. At blood sampling times beyond 5 h after dosing, plasma concentrations of ketoprofen enantiomers were lower than limit of quantification.

(Figure 1). In agreement with a previous report [3], the elimination half-life of the (R)-enantiomer was 1.0–1.3 h, and of the (S)-enantiomer 1.1–1.5 h independent of the 12.5 or 25 mg dose (not documented). In agreement with dose linearity reported previously [3], AUC calculated from the data obtained after the 25 mg dose was about twofold that seen after the 12.5 mg dose in case of both enantiomers (Table 1). $C_{\max}$ also increased with dose (see Figure 1 and Table 1). Administration of buffered ketoprofen formulations resulted in marked and statistically significant increases in $C_{\max}$ of both enantiomers (Figure 1, Table 1) compared to unbuffered tablets. This was true for the 12.5 and for the 25 mg dose. The extent of increase (by about 50–80%, Table 1) was similar for both enantiomers.

Independent of the ketoprofen dose, AUC of both enantiomers was not significantly affected by buffering (Table 1). Correspondingly, the ratio $C_{\max}$ /AUC was significantly higher with the buffered, compared with the unbuffered doses (12.5 and 25 mg) with regard to both enantiomers (Table 1). MRT was significantly reduced ((S)-ketoprofen, 12.5 mg), or tended to be shorter upon administration of the buffered formulation in comparison with the unbuffered tablet (Table 1). When buffered formulations were given, $t_{\max}$ of (R)- and (S)-ketoprofen appeared to be more frequently short than with unbuffered ketoprofen (Figure 2).

All formulations were well tolerated and no abnormalities in laboratory tests were noted. Three adverse events were reported (headache, abdominal discomfort and tiredness). They were assessed as mild and possibly or remotely drug related.

Discussion

The results of the two studies clearly show that the rate of absorption of ketoprofen enantiomers was increased by buffering of the presently used oral ketoprofen formulations with the tested magnesium hydroxide/citrate buffer resulting in a faster increase in plasma drug concentrations within

Figure 2 Frequency distribution of time of $C_{\max}$ ($t_{\max}$). Given are numbers of subjects with $C_{\max}$ of ketoprofen enantiomers observed at a given blood sampling time (time corresponding to $t_{\max}$, in h) after dosing. Upper panel (a), (R)-enantiomer, lower panel (b), (S)-enantiomer of ketoprofen. Black column correspond to data from subjects dosed 25 mg, cross-hatched, 12.5 mg of the buffered formulation each, open column to those of 25 mg, and hatched of 12.5 mg of the unbuffered formulation.

Table 1 Pharmacokinetic characteristics of ketoprofen enantiomers. Given are means $\pm$ s.d. ($n=12$) of AUC, the geometric mean ratio of AUC buffered/unbuffered formulation with 95% confidence limits (AUC ratio expressed as a percentage of the unbuffered AUC), $C_{\max}$, the ratio of $C_{\max}$ buffered/unbuffered formulation as geometric mean with 95% confidence limits, the ratio of $C_{\max}$ /AUC as a measure for rate of absorption, and mean residence time (MRT). Asterisks indicate significant differences between pharmacokinetic parameters of the buffered formulation in comparison with the respective value of the unbuffered formulation.

Formulation	Enantiomer	AUC ($\text{mg l}^{-1} \text{h}$)	AUC ratio [%] (95% CI)	$C_{\max}$ (mg l^{-1})	$C_{\max}$ ratio (%) (95% CI)	$C_{\max}$ /AUC (lh^{-1})	MRT (h)
KN	(R)-KN	0.98 ± 0.19	100	0.51 ± 0.16	100	0.52 ± 0.16	2.13 ± 0.57
12.5 mg	(S)-KN	0.91 ± 0.25	100	0.49 ± 0.17	100	0.56 ± 0.21	2.24 ± 1.06
KN-MgHC	(R)-KN	0.91 ± 0.14	92 (86–101)	$0.81 \pm 0.15^{***}$	164 (139–192)	$0.90 \pm 0.18^{***}$	1.45 ± 0.26
12.5 mg	(S)-KN	0.84 ± 0.18	94 (80–110)	$0.80 \pm 0.18^{***}$	169 (141–203)	$0.95 \pm 0.14^{***}$	$1.48 \pm 0.25^*$
KN	(R)-KN	1.97 ± 0.43	100	1.18 ± 0.29	100	0.62 ± 0.19	1.91 ± 0.56
25 mg	(S)-KN	1.89 ± 0.40	100	1.16 ± 0.32	100	0.63 ± 0.19	2.02 ± 0.45
KN-MgHC	(R)-KN	2.09 ± 0.49	106 (100–111)	$1.72 \pm 0.21^{***}$	149 (128–173)	$0.86 \pm 0.20^*$	1.52 ± 0.29
25 mg	(S)-KN	1.98 ± 0.43	105 (98–113)	$1.70 \pm 0.21^{***}$	151 (128–178)	$0.90 \pm 0.23^*$	1.66 ± 0.41

*** $P < 0.001$; * $P < 0.05$; Bonferroni's modified t -test.

30 min after administration. This was demonstrated for two rather low doses of ketoprofen and the effect was similar for both enantiomers indicating lack of stereoselectivity. Other explanations for modification of the absorption characteristics such as circadian differences in pharmacokinetics [8] or effect of food [9–10] are excluded, since both influences were prevented as confounding factors by the design of the study. The time course of plasma concentrations immediately after ketoprofen intake indicate that the first few blood samplings should have taken place even earlier than done to describe more completely the ascending part of the concentration-time course and, hence, the full extent of $C_{\max}$ increase by buffering.

The results are partly in contrast with previous work in which no influence of magnesium hydroxide on ketoprofen pharmacokinetics was found (in six subjects) when co-administered in the form of an aqueous suspension [5]. However, the influence of buffering may depend on the type of formulation of a drug. Thus, magnesium hydroxide had only little influence on AUC and $C_{\max}$ of glibenclamide given as a micronised formulation, but enhanced AUC and $C_{\max}$ three-fold each when administered as a non-micronised preparation [11].

The increase in $C_{\max}$ was marked and about twice as large as that described, for instance, for the influence of magnesium hydroxide on $C_{\max}$ of ibuprofen [5]. Furthermore, the frequency distribution of $t_{\max}$ demonstrates that in the majority of subjects $C_{\max}$ occurs between 15 and 30 min after dosing with the buffered formulations, but clearly later with the unbuffered tablets. The increase in $C_{\max}$ and rate of absorption appears large enough to have pharmacodynamic consequences. It may be speculated that the onset of an analgesic effect could thus be shortened, but this remains to be verified in pharmacodynamic studies.

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