Stereoselective pharmacokinetics of ketoprofen and ketoprofen glucuronide in end-stage renal disease: evidence for a 'futile cycle' of elimination

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Aims To assess if futile cycling of ketoprofen occurs in patients with decreased renal function.

Methods Ketoprofen was administered to six haemodialysis-dependent patients with end-stage renal disease as single (50 mg) or multiple doses (50 mg three times daily, for 7 days). Plasma and dialysate concentrations of the unconjugated and glucuronidated R- and S-enantiomers of ketoprofen were determined using h.p.l.c. following the single and multiple dosing.

Results The oral clearance was decreased and terminal elimination half-lives of R- and S-ketoprofen and the corresponding acyl glucuronides were increased in functionally anephric patients compared with healthy subjects. In contrast with the R-isomers, S-ketoprofen and S-ketoprofen glucuronide exhibited an unexpected accumulation (2.7–3.8 fold) after repeated dosing achieving S:R ratios of 3.3 ± 1.7 and 11.2 ± 5.3 , respectively. The plasma dialysis clearances for R- and S-ketoprofen glucuronides were 49.4 ± 19.8 and 39.0 ± 15.9 ml min⁻¹, respectively, and 10.8 ± 17.6 and 13.3 ± 23.5 ml min⁻¹ for unconjugated R- and S-ketoprofen.

Conclusions The selective accumulation of S-ketoprofen and its acyl glucuronide are consistent with amplification of chiral inversion subsequent to futile cycling between R-ketoprofen and R-ketoprofen glucuronide. Severe renal insufficiency, and possibly more modest decrements, results in a disproportionate increase in systemic exposure to the S-enantiomer which inhibits both pathologic and homeostatic prostaglandin synthesis.

Keywords: acyl glucuronide, enantiomers, futile cycle, haemodialysis, ketoprofen

Introduction

Ketoprofen, [(R,S)-2-(3'-benzoylphenyl)propionic acid] is a member of the 2-arylpropionic acid or 'profen' class of nonsteroidal anti-inflammatory drugs (NSAIDs) and is widely employed therapeutically as a racemic mixture. NSAIDs are an important and ever growing class of drugs which share at least one mechanism of action, inhibition of cyclooxygenase, but vary considerably in their disposition [1]. Defining the pharmacokinetic changes which occur with ageing and in disease states is important in predicting efficacy and avoiding toxicity of individual NSAIDs. By virtue of their ability to inhibit prostaglandin synthesis, NSAIDs may induce decrements in renal

function, such as glomerular filtration rate, in certain risk groups. In particular, patients with pre-existing renal insufficiency constitute a high risk group because renal synthesis of prostaglandins acts to support renal perfusion in such patients [2, 3]. However, the relative contribution of increased sensitivity and altered pharmacokinetics to the increased risk in such patients groups is unknown.

Along with other 2-arylpropionic acids, ketoprofen undergoes a unidirectional chiral inversion from the R- to the S-enantiomer and the latter isomer is primarily responsible for the inhibition of cyclooxygenase activity [4, 5]. In healthy, human volunteers the extent of inversion is 10–15% of an oral dose [6, 7]. The major pathway of R- and S-ketoprofen elimination in healthy humans is the formation of ester (or acyl) glucuronides which are predominantly excreted in the urine and account for approximately 80% of an oral dose [8, 9]. The acyl glucuronides of ketoprofen undergo hydrolysis

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Received 4 September 1998, accepted 24 June 1999.

in the presence of plasma proteins to regenerate ketoprofen and it has been hypothesized that, under conditions of renal insufficiency, significant 'futile cycling' of the drug and acyl glucuronide occurs [10, 11]. This futile cycle may allow a greater proportion of R-ketoprofen to undergo chiral inversion to S-ketoprofen leading to an accumulation of the active S-isomer. This process of 'futile cycling' and subsequent amplification of chiral inversion has been demonstrated in a rabbit model of uraemia [12, 13]. The increased half-life and/or decreased apparent clearance of ketoprofen in elderly volunteers and patients with mild to moderate renal impairment is consistent with this hypothesis [11, 14, 15]. Thus by increasing the exposure to the S-enantiomer, futile cycling may elevate the risk of reductions in renal function in patients who are already predisposed to these effects.

The objective of our study was to assess whether futile cycling of ketoprofen occurs in patients with decreased renal function. To maximize the possibility of finding evidence for the futile cycling of ketoprofen in humans, we used multiple dosing of patients who were functionally anephric. In addition we examined the impact of haemodialysis on the clearance of ketoprofen and glucuronide.

Methods

Materials

Racemic ketoprofen, was obtained from Wyckoff Chemical Co. (South Haven, MI). R-(–)-ketoprofen and S-(+)-ketoprofen were obtained from Sepracor (Marlborough, MA). R-(–)-naproxen was obtained from Syntex (Palo Alto, CA).

Study participants

Six adult patients (two male and four female, mean age 45 years, range 34–58 years) with end-stage renal disease undergoing chronic haemodialysis therapy participated in the study (Table 1). The Institutional Review Board of Indiana University approved the study and written informed consent was obtained from each patient. Prior to enrolment, a medical history, physical examination, electrocardiogram, and routine laboratory tests were obtained. All patients received thrice weekly (Tuesday, Thursday and Saturday: patients 1, 2 and 3 and Monday, Wednesday and Friday: patients 4, 5 and 6) haemodialysis using hollow fibre cellulose acetate dialysers for 3.5–4.5 h. Patients with a history of peptic ulcer disease, allergy to aspirin or NSAIDs, receiving glucocorticoids or mineralocorticoids, or with significant liver disease were excluded from the study. Patients use of aspirin and over the counter NSAIDs (aspirin, ibuprofen and paracetamol)

was discontinued at least 2 weeks prior to entering the study.

Study design

Patients underwent two pharmacokinetic studies. The first evaluated the kinetics of a single 50 mg dose of ketoprofen (Orudis®, Wyeth-Ayerst). Patients were admitted to the General Clinical Research Center (GCRC) the day following a dialysis treatment and received 50 mg ketoprofen. Patients fasted from midnight until 4 h post dose and routine medications were withheld during this time. Blood samples (7 ml) were obtained from an antecubital vein at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 h after drug administration and added to heparin containing tubes (Vacutainer, Becton Dickinson Ltd. Rutherford, NJ, USA). The blood samples were immediately centrifuged ($3000 \text{ rev min}^{-1}$ 10 min) and 1 ml aliquots of the plasma were placed in plastic vials containing 50 µl 2 M sulphuric acid and immediately frozen at -20°C to minimize hydrolysis and intramolecular rearrangement of any acyl glucuronides [16].

After completing the single dose study, patients were discharged from the GCRC and dosing commenced with ketoprofen 50 mg (Orudis®) three times a day with meals for 8 days. On a scheduled dialysis day patients received their scheduled ketoprofen dose 1 h prior to dialysis. Dialysate samples (50 ml) were obtained at the onset and at 1 and 2 h post onset of dialysis during the dialysis session following initiation of ketoprofen administration. Blood samples were obtained from the afferent and efferent limbs of the dialyser. Following 8 days of ketoprofen administration, patients were readmitted to the GCRC and underwent a pharmacokinetic study identical to the first.

Sample analysis

Unconjugated R- and S-ketoprofen concentrations in plasma and dialysate were quantified using an h.p.l.c. method previously described [16]. Briefly, 1 ml aliquots of plasma or dialysate were diluted 1:1 with 10 mM trifluoroacetic acid. One ml was used for the analysis of unconjugated R- and S-ketoprofen and the remainder (1 ml) for the analysis of R- and S-ketoprofen glucuronide. For unconjugated ketoprofen analysis, samples were spiked with internal standard, acidified to pH 2.0 with 100 µl 2 M H_2SO_4 and extracted into 2 ml of iso-octane:isopropyl alcohol (95:5 v/v). The organic layer was removed, evaporated and quantified using a chiral S,S-Whelk column (Regis Technologies Inc., Morton Grove, IL). Ketoprofen glucuronide was quantified after precipitation of plasma protein with acetonitrile which was reduced to dryness, reconstituted in mobile phase and

Table 1 Patient characteristics.

Patient	Age (years)	Sex	Renal disease	Significant medication
1	34	Female	Lupus	Triphasil, nifedipine
2	58	Male	Diabetes type II Hypertension	Glyburide, nifedipine, cimetidine
3	35	Female	Diabetes type I	Clonidine, bethanechol, bromocriptine, amitriptyline, insulin, metoclopramide, cimetidine
4	59	Female	Polycystic kidney disease	Nifedipine, aspirin, cimetidine
5	38	Female	Hypertension	Enalapril
6	45	Male	Hypertension	Nifedipine, aspirin, cimetidine metoprolol, amitriptyline, isosorbide

ketoprofen glucuronide isolated using reversed phase h.p.l.c. The glucuronide was hydrolysed with alkali and the resultant unconjugated ketoprofen analysed using the above chiral h.p.l.c. method.

Data analysis

Pharmacokinetic parameters were calculated using standard methods. The terminal rate constant (k) was calculated by log-linear regression of the terminal phase of the concentration *vs* time profiles. All patients displayed a good log-linear relationship that relied on at least four data points in the terminal phase. Half-lives were calculated by dividing 0.693 by k . The area under the plasma concentration-time curve to infinity (AUC) was calculated by a combination of the linear and log-trapezoidal rules with extrapolation to infinity using the last measurable plasma concentration and the terminal disposition rate constant (WINONLIN, Statistical Consultants Inc., Chapel Hill, NC); percentage of the total area extrapolated beyond the last sample was 6% or less for both enantiomers. For the chronic dose, the AUC(0,8h) was calculated for the interval between the time of administration of the final dose and 8 h later which corresponds to the dosing interval. Oral clearance was calculated from dose/AUC for the first dose and dose/AUC(0,8h) for the final dose which assumes that steady-state had been achieved.

Dialysis clearance values (CL_D) were calculated from the pre and postfilter plasma concentrations using the equation:

$$CL_D = (Q_{in} \cdot C_{in} - Q_{out} \cdot C_{out}) / C_{in} \quad (1)$$

where Q_{in} and Q_{out} are the plasma flows and C_{in} and C_{out} are the plasma concentrations entering and leaving the dialyser.

Data are expressed as mean $\pm$ s.d. and statistical comparisons were made using the Student's paired *t*-test at a significance level of $P \leq 0.05$. The distribution of AUC measurements was skewed and therefore statistical com-

parisons ($P \leq 0.05$) were made using log transformed data and are summarized as the logarithmic mean and 95% confidence interval (PROC MIXED, SAS for Windows version 7, SAS Institute Inc., Cary, NC, USA).

Results

All six patients completed the study but three patients complained of myalgias following approximately 3 days of therapy. These symptoms were relieved with dialysis. Plasma concentration-time profiles of ketoprofen and ketoprofen glucuronide enantiomers following single and multiple dose studies are depicted in Figure 1 and 2, respectively. The glucuronide metabolites were readily detectable up to 16 h post dose and displayed significant stereoselectivity in favour of the S-isomer. The corresponding pharmacokinetic parameters after single and multiple dosing are presented in Table 2. The accumulation factor, which is the ratio of the AUC(0, ∞) after chronic administration to the AUC(0, ∞) after single dose administration was significantly greater than unity for both enantiomers of ketoprofen and ketoprofen glucuronide. Accumulation was particularly marked for S-ketoprofen and its glucuronide compared with R-ketoprofen and its glucuronide (Table 2). The half-lives after acute and chronic administration were not significantly different except for R-ketoprofen (Table 2). There was no significant difference in the apparent oral clearance for R-ketoprofen between the first dose value of 67.5 ± 25.9 ml min⁻¹ and the final dose value of 74.8 ± 31.1 ml min⁻¹ as expected for a linear system and the corresponding accumulation factor was 1.3 (Table 2). However the oral clearance of S-ketoprofen was significantly lower for multiple dosing relative to single dose administration (68.9 ± 34.1 *vs* 54.8 ± 30.7 ml min⁻¹; $P < 0.05$) which indicates a deviation from linear pharmacokinetics and there is a correspondingly greater accumulation of 2.7-fold for this isomer following chronic dosing. Significant stereoselectivity for oral clearance in favour of the S-enantiomer was apparent only after

Figure 1 Plasma concentration-time profiles of R-ketoprofen (○), S-ketoprofen (●), R-ketoprofen glucuronide (□) and S-ketoprofen glucuronide after (■). Panel a, single 50 mg oral dose of ketoprofen ($n=6$). Panel b, 50 mg ketoprofen oral dose following 8 days of dosing with 50 mg three times daily ($n=6$).

multiple dosing ($P<0.05$). The S:R-ketoprofen and S:R-ketoprofen glucuronide AUC ratios were significantly greater for chronic administration relative to acute administration indicating an accumulation of S-ketoprofen and S-ketoprofen glucuronide relative to R-ketoprofen and its glucuronide after chronic administration (Table 2).

Blood flow into and out of the dialyser was 375 ± 48 and 354 ± 44 ml min⁻¹, respectively. Haematocrit increased from $30.6 \pm 2.6\%$ before dialysis to $32.4 \pm 2.9\%$ postdialysis. Both R- and S-ketoprofen and R- and S-ketoprofen glucuronide were detected in the pre and postdialyser plasma. Dialysis clearance was 10.8 ± 17.6 and 13.3 ± 23.5 ml min⁻¹ for R- and S-ketoprofen, respectively (equation 1). For the glucuronides dialysis clearance was 49.4 ± 19.8 and 39.0 ± 15.9 ml min⁻¹ for the R- and S-isomers, respectively. However, only conjugated S-ketoprofen was detectable in the dialysate

resulting in a dialysate clearance of 46.3 ± 23.5 ml min⁻¹ when dialyser extraction was based on appearance in dialysate rather than loss from plasma.

Discussion

NSAIDs are commonly used in the elderly and with patients with rheumatologic conditions in whom renal function is often reduced [17–19]. While being very efficacious, NSAIDs also have adverse effects on renal function, which are related to their mechanism of action, namely the inhibition of prostaglandin synthesis [2, 20, 21]. The severity of these adverse effects is thought to be in part determined by the degree and duration of prostaglandin inhibition [3]. Accumulation of NSAIDs, especially of the active S-enantiomers may confound this problem. It is therefore essential to characterize alterations in NSAID pharmacokinetics in patients with renal dysfunction in order to optimize the therapeutic effects and minimize toxicity.

Ketoprofen is a commonly prescribed NSAID and is currently available in an over the counter preparation. While there is no significant alteration in pharmacokinetics of the similar 'profen' NSAIDs, ibuprofen [22] and flubiprofen [23] in patients with renal dysfunction, ketoprofen's elimination appears to be inversely related to renal function [11, 14, 15]. Our data confirm the effect of renal dysfunction and indicate that oral clearance is substantially lower at 68 ml min⁻¹ for R- and S-ketoprofen in anephric patients compared with 107 ml min⁻¹ in healthy young volunteers [6, 14, 15]. There is a corresponding increase in half-life from 3.8 and 2.5 h for R- and S-ketoprofen in healthy volunteers to 5.9 and 8.2 h, respectively, in our patient group [9]. Other studies of the disposition of ketoprofen in renally compromised patients, and animal models of renal failure, show a similar reduced clearance of the parent drug, even though ketoprofen itself undergoes negligible renal excretion. This finding may seem paradoxical in that the majority of ketoprofen is eliminated via hepatic conjugation.

Stafanger *et al.* [14] showed that ketoprofen plasma clearance was reduced with decreasing creatinine clearance in elderly subjects. Adventier *et al.* [15] proposed this reduced elimination, at least in the elderly, was due to reduced glucuronidation but Verbeeck [24] suggested that futile cycling of ketoprofen glucuronide, as proposed by Meffin *et al.* [25] for clofibric acid, caused reduced clearance of ketoprofen in the elderly. In this futile cycle the acyl (or ester) glucuronides are readily hydrolysed in biological fluids at physiological pH [26]. Thus under conditions of renal insufficiency, clearance of the glucuronides is reduced and the resulting higher plasma concentrations of the glucuronide favour hydrolysis back

	<i>R</i> -ketoprofen	<i>S</i> -ketoprofen	<i>R</i> -glucuronide	<i>S</i> -glucuronide
AUC(0,∞) acute ¹ (nmol ml ⁻¹ min)	1547 (1152–2077)	1657 (989–2776)	174* (144–210)	1058* (746–1502)
AUC(0,8h) chronic ² (nmol ml ⁻¹ min)	1417 (999–2012)	2063* (1255–3393)	134 (108–168)	1323* (967–1810)
AUC(0,∞) chronic ³ (nmol ml ⁻¹ min)	1950 (1374–2767)	4010* (2036–8257)	238* (180–313)	3441* (2470–4794)
<i>t</i> _{1/2} , acute (h)	2.9 ± 1.7*	8.3 ± 4.6	9.6 ± 9.7	13.0 ± 6.2
<i>t</i> _{1/2} , chronic (h)	5.9 ± 2.2*	8.2 ± 2.2	7.9 ± 3.6	16.3 ± 10.7
Accumulation factor	1.3 ± 0.3*	2.7 ± 0.9*	1.5 ± 0.4*	3.8 ± 1.5*
S:R(AUC(0,∞)) acute	1.1 ± 0.5*	6.9 ± 2.9*		
S:R(AUC(0,8h)) chronic	1.6 ± 0.7*	10.1 ± 3.4*		
S:R(AUC(0,∞)) chronic	2.6 ± 1.7*	17.9 ± 10.7*		

* $P \leq 0.05$, acute *vs* chronic.

¹AUC(0,∞)acute, AUC from zero to infinity for first dose presented as logarithmic mean (95% confidence interval).

²AUC(0,8h)chronic, AUC for the 8 h dosing interval following the final dose presented as logarithmic mean (95% confidence interval).

³AUC(0,∞)chronic, AUC from time of administration of final dose extrapolated to infinity presented as logarithmic mean (95% confidence interval).

to the parent drug. Similarly, coadministration of probenecid reduced ketoprofen clearance by 40–70% [27, 28]. Other compounds, such as benoxaprofen [29], diflunisal [30], naproxen [31], ximoprofen [32], for which acyl glucuronide formation is a major route of elimination also have reduced clearance of the parent compound in renal insufficiency and probenecid coadministration impairs the clearance of carprofen [33]. This 'futile cycle' may play an important role in the accumulation of active drug and toxicity in patients with decreased renal function.

An additional pharmacokinetic property which needs to be considered in the metabolism of the 2-arylpropionic acid NSAIDs is metabolism by inversion which results in conversion of the *R*-enantiomer, which does not inhibit cyclooxygenase activity, to the active *S*-enantiomer. This process varies considerably among 2-arylpropionic acids resulting in approximately 90% and 65% inversion of the *R*-enantiomers of fenoprofen [34] and ibuprofen [35], respectively, but is absent for *R*-flubiprofen [36] in humans. In healthy volunteers chiral inversion accounts for approximately 15% of the dose of *R*-ketoprofen [6, 7].

In our functionally anephric patient population the oral clearance of *R*-ketoprofen was lower than that in healthy individuals [9] but there was no unexpected accumulation of this enantiomer on multiple dosing as reflected in the constancy of oral clearance. Plasma concentrations of *R*-ketoprofen glucuronide were approximately 10% of the aglycone (Table 2) but undetectable in healthy controls [9]. In contrast, the glucuronide of *S*-ketoprofen represented about 50% of parent drug concentration and there was a disproportion-

ate accumulation of *S*-ketoprofen and glucuronide upon multiple dosing (Table 2). Neither the accumulation of drug on multiple dosing nor the stereoselectivity in glucuronide plasma concentrations has been observed in healthy individuals [9]. In a study restricted to single doses, similar relationships between the enantiomers of ketoprofen and their glucuronides have been noted in patients with severe renal dysfunction [37]. Why then is there a selective accumulation of *S*-ketoprofen and its glucuronide in these functionally anephric patients? We propose that chiral inversion of *R*-ketoprofen provides an outlet for this enantiomer that is not available to its antipode. Futile cycling of *R*-ketoprofen and its glucuronide acts to increase the proportion of the dose that is available for inversion. In contrast the *S*-enantiomer cannot undergo chiral inversion and therefore accumulates along with its glucuronide. Interestingly, the rate of hydrolysis of *R*-ketoprofen glucuronide by human serum was twice as great as the rate for the *S*-isomer [10]. Thus the 'futile cycle' of elimination of ketoprofen leads to preferential accumulation of *S*-ketoprofen and its glucuronide via amplification of the chiral inversion process. However, without direct administration of the individual enantiomers or extensive recovery of metabolites in urine we cannot directly estimate the percentage inversion of *R*-to *S*-ketoprofen in our patient group.

An alternative explanation for the accumulation of *S*-ketoprofen in our anephric patients could be a stereoselective and time-dependent decline in clearance of this isomer between first and final doses. However this is unlikely because *S*-ketoprofen glucuronide, the product of the major elimination pathway, accumulated to a

Table 2 Mean ($\pm$ s.d.) pharmacokinetic parameters for patients with ESRD after acute (50 mg orally) or chronic (50 mg, orally three times daily for 8 days) administration of ketoprofen ($n=6$).

greater degree than its precursor and the conjugation pathway does not exhibit significant stereoselectivity *in vivo* or *in vitro* [9, 37, 38].

Usually the major route of elimination for ketoprofen is the renal excretion of glucuronides but the mechanism of clearance in functionally anephric subjects has not been defined. Increased biliary elimination of ketoprofen does not appear to be the answer because probenecid administration did not enhance the excretion of the glucuronides in cholecystectomy patients [27]. However the biliary excretion of oxidative metabolites, which usually plays only a minor role in the elimination of ketoprofen, has not been examined. Decreased protein binding due to decreased albumin and displacement from protein binding sites in uraemia may enhance these processes [39]. The clearance of both ketoprofen and glucuronide due to dialysis was low and not stereoselective as would be expected for molecules highly bound to plasma albumin in a nonstereoselective manner [11, 39]; only a small fraction of the body load would be removed by this route. Another possible pathway could involve the covalent binding of the acyl glucuronide metabolites to proteins in plasma and possibly other sites [40]. This may be particularly relevant to the glucuronide of S-ketoprofen which covalently binds to albumin to a greater extent than the R-isomer in a concentration dependent manner and which is present in plasma at higher concentrations in our patients than in healthy individuals. The chiral inversion of propionic acid NSAIDs proceeds via the formation coenzyme A thioesters and therefore provides the opportunity for the formation of hybrid triglycerides and other lipids which may be incorporated into tissues [41]. This has been demonstrated for ketoprofen *in vivo* and *in vitro* using a rat model [42] and may also constitute an elimination route in our patients.

Several of our patients developed fatigue and severe myalgias after several days of administration of ketoprofen. There is a probable causal relationship between ketoprofen use and myalgias listed in the Physicians' Desk Reference [43]. Could this adverse effect reported by 3 of 6 of our subjects be related to accumulation of ketoprofen or its metabolites? Of note these symptoms were relieved during the course of haemodialysis. Our dialysis clearance estimates suggest that ketoprofen glucuronides are removed by haemodialysis more efficiently than the parent compounds. We postulate that the myalgias, which were relieved by haemodialysis, could be related to the unusual accumulation of acyl glucuronide metabolites in these patients.

In conclusion, our data in dialysis patients support the occurrence of 'futile cycling' of glucuronide conjugates via hydrolysis back to the parent compounds with subsequent amplification of the unidirectional chiral

inversion process of R-to S-ketoprofen leading to accumulation of the active S-enantiomer. The accumulation of S-ketoprofen following repetitive dosing in anephric patients may have important therapeutic and toxicological effects which may be extrapolated to patients with lesser degrees of renal dysfunction. The toxic effects of prostaglandin inhibition on the gastrointestinal and renal systems are thought to related to the S-enantiomer and we would expect greater toxicity to occur with greater exposure to S-enantiomer.

This research was supported by a USA Public Health Service Grant DK37994 and GCRC Grant M01 RR00750. A Faculty Development Award in Clinical Pharmacology from the PRMAF supported DWR.

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