Stereoselective disposition of flurbiprofen in uraemic patients

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- 1 Both single and multiple oral doses of 50 mg racemic flurbiprofen were given to eight patients with mild to moderate renal impairment. The plasma and urine concentrations of the R- and S-enantiomers of flurbiprofen and its major metabolites were measured by a stereoselective h.p.l.c. assay.
- 2 For R-flurbiprofen the oral clearance (mean $\pm$ s.d.: 38.3 ± 12.8 vs 30.8 ± 11.5 ml min^{-1}) and volume of distribution (V_z ; 17.6 ± 3.9 vs 14.6 ± 2.5 l) were significantly greater ($P < 0.05$) than for the S-enantiomer. A significantly greater ($P < 0.05$) percent of the dose was excreted in the urine in the R-configuration (16.4 ± 6.0 vs $10.9 \pm 4.2\%$).
- 3 Plasma protein binding of the enantiomers of flurbiprofen was determined by ultrafiltration. The unbound clearance and unbound V_z were not different between enantiomers consistent with the (not significantly) greater percent unbound of R-flurbiprofen ($0.079 \pm 0.014\%$) vs S-flurbiprofen ($0.064 \pm 0.015\%$).
- 4 Relative to normal volunteers, the uraemic subjects exhibited a significantly greater ($P < 0.05$) oral clearance, V_z and percent unbound for both enantiomers; unbound clearance and unbound V_z did not differ from healthy controls.
- 5 The disposition of flurbiprofen enantiomers was not changed upon multiple dosing and no evidence of futile cycling was found. Adjustment of flurbiprofen dosing rate in uraemic subjects is not indicated on the basis of pharmacokinetics.

Keywords flurbiprofen enantiomers stereoselective uraemia
pharmacokinetics protein binding

Introduction

Flurbiprofen is an arylpropionic acid which is administered for its anti-inflammatory and analgesic actions as a racemic mixture. Like other arylpropionic acids, the major mode of elimination is metabolism to either glucuronide conjugates or to oxidized forms which also undergo glucuronidation (Drew & Knights, 1985; Risdall *et al.*, 1978). Traditionally, elimination of such drugs was considered to be insensitive to changes in renal function (Fabre & Balant, 1976) but more recently a number of exceptions to this expectation have been documented. For example, clearance of ketoprofen (Stafanger *et al.*, 1981), benoxaprofen (Aronoff *et al.*, 1982), and naproxen (Anttila *et al.*, 1980), all of which are arylpropionic acids eliminated primarily by metabolism, is reduced in patients with renal impairment.

In addition to any alteration in drug metabolism and protein binding that may occur due to the accumulation of endogenous organic anions, uraemia may also be associated with a 'futile cycle' which lowers drug clearance. Meffin and co-workers have shown that in rabbits

with renal dysfunction, excretion of the acylglucuronides of 2-phenylpropionic acid (Meffin *et al.*, 1986) and diphenylacetic acid (Sallustio *et al.*, 1989) is impaired, and that hydrolysis occurs *in vivo* to regenerate parent drug. This so-called 'futile cycle' results in a lowered plasma clearance of parent drug and may explain the changes noted above for ketoprofen, benoxaprofen, and naproxen, for which acylglucuronide formation is a major route of elimination. Although not specifically tested, this phenomenon may be accentuated during chronic drug administration (Upton *et al.*, 1984).

Previous studies have not examined the effect of renal impairment on the disposition of flurbiprofen, and studies of the pharmacokinetics of arylpropionic acids in general have not investigated the possibility that any disease associated alterations in the disposition of these compounds are enantioselective. This is particularly important because only the S-enantiomer is active (Hutt & Caldwell, 1984). Thus, we studied the disposition of R- and S-flurbiprofen and its metabolites in patients

with mild to moderate renal impairment after both acute and chronic administration of racemic flurbiprofen.

Methods

Drug administration

Eight patients with mild to moderate renal insufficiency participated in this study. Table 1 lists the demographic details of each participant. Written informed consent was obtained from all patients and the study was approved by the Indiana University School of Medicine Institutional Review Board. The volunteers received oral doses of racemic flurbiprofen (Ansaïd, Upjohn Co., Kalamazoo, MI) in the form of a 50 mg tablet four times daily with meals except on study days (Day 1, and Days 8 and 27 after the first study day) when a single 50 mg dose was administered. Patients entered the hospital for 5 days before and until day 8 of dosing (Murray *et al.*, 1992). As inpatients, they ingested a metabolic diet which contained 150 mEq of sodium and 60–80 mEq of potassium. On study days, the volunteers did not take breakfast but were allowed lunch. Other medications received by the patients during the study are listed in Table 1. These represented continuation of chronic therapy.

Plasma and urine collection

Venous blood samples were collected into heparinized tubes at 0, 1.2, 2.2, 3.2, 5, 8, 12, 16, and 22 h after flurbiprofen administration on each of the 3 study days. Plasma was obtained after centrifugation at 800 g for 10 min and was frozen at -20°C until analysis.

Urine was collected in intervals for 24 h after drug administration. For the first 4–5 h, urine was collected every 20 min, then hourly to 8 h, and then at 10, 12, and 24 h post dosing. For each collection period, the urine volume was measured and a 20 ml aliquot was combined with 100 μl glacial acetic acid to adjust the pH of the urine to below 4 in order to prevent spontaneous

degradation of acyl-glucuronides. Samples were stored at -20°C . The amounts of drug and metabolite were determined for all collection periods and summed when necessary to give the cumulative excretion.

Plasma and urine analyses

Plasma and urine were assayed for R- and S-flurbiprofen and the R- and S-enantiomers of the metabolites of flurbiprofen as described previously (Knadler & Hall, 1989). Briefly, the compounds were extracted into hexane or dichloromethane after acidification of the plasma or urine then derivatized with S-(α)-methylbenzylamine to form diastereomeric amide derivatives which were separated on a Beckman Ultrasphere ODS column (Beckman, San Ramon, CA). Ultraviolet detection at 245 nm was used for monitoring flurbiprofen in plasma, but fluorescence detection was used for urine analyses and metabolite analyses. The composition of the mobile phase which consisted of acetonitrile/ H_2O or acetonitrile/0.05 M acetic acid/tetrahydrofuran was adjusted depending on the biological fluid and whether parent or metabolites were being measured. The amounts of R- and S-flurbiprofen and enantiomers of the metabolites in plasma and urine were determined before and after hydrolysis in 3 M HCl in a 90°C water bath for 30 min. Limited sample volumes precluded complete analyses on all plasma samples.

Protein binding

The protein binding of both R- and S-flurbiprofen was determined by ultrafiltration as described previously (Knadler *et al.*, 1989). Briefly, an Amicon Micropartition Ultrafiltration System (MPS-I) with YMT membranes (Amicon, Danvers, MA) was used to evaluate the *ex vivo* binding of R- and S-flurbiprofen to protein in plasma at 37°C . [^{14}C]-labelled R- or S-flurbiprofen was added to plasma, and the radioactivity before ultrafiltration and in the ultrafiltrate was measured by liquid scintillation spectroscopy.

To determine if the binding was concentration-dependent or if the presence of metabolites affected the

Table 1 Demographics of study patients

Patient	Sex	Age (years)	Weight (kg)	Height (in)	Plasma albumin (g dl^{-1})	Inulin clearance (ml min^{-1})	Medications during study
1	M	49	87.2	71.5	3.78	12.7	Metoprolol, frusemide, enalapril
2	M	66	62.6	68.0	3.90	10.5	Enalapril, clonidine
3	M	59	85.6	69.5	4.27	21.0	Frusemide, isosorbide dinitrate, nifedipine, captopril, quinidine, nitroglycerine
4	M	59	55.3	67.5	3.75	24.8	Propoxyphene, albuterol, theophylline, reserpine, hydrochlorothiazide
5	M	55	71.5	68.5	3.97	25.5	Nifedipine, isosorbide dinitrate, clonidine, nitroglycerine
6	F	68	73.5	65.0	3.50	42.8	Frusemide, verapamil, enalapril, minoxidil, ferrous sulphate
7	M	51	68.0	66.5	3.88	17.3	Diltiazem, frusemide, prazosin, quinine
8	M	65	90.6	66.0	3.76	34.1	Nifedipine, frusemide, insulin, enalapril

protein binding of racemic flurbiprofen, the percent unbound was determined at three time points; initially when no metabolites would be present, at $C_{\max}$ when flurbiprofen and metabolite concentrations would be high, and at 12 h post dose when metabolite concentrations are significant and in pseudo-equilibrium with parent drug.

Pharmacokinetic analyses

The pharmacokinetics of R- and S-flurbiprofen were determined using conventional noncompartmental linear analyses. The elimination rate constant, λ_z , was obtained by log-linear regression of the terminal phase of the plasma concentration vs time curve. The area under the plasma concentration vs time curve was determined by the linear trapezoidal rule on the ascending part of the curve and the log-linear trapezoidal rule on the descending portion up to the last data point. The areas were extrapolated to infinite time (AUC) by dividing the last data point by λ_z . The terminal elimination half-life, ($t_{1/2,z}$), was calculated as $0.693/\lambda_z$, the oral clearance (CL) as dose/AUC, and the renal clearance (CL_R) as the total amount excreted in urine/AUC. The volume of distribution associated with the terminal elimination phase (V_z) was calculated as CL/λ_z . These calculations assumed complete bioavailability. This is reasonable, since previous reports have shown that greater than 95% of oral 50 mg doses were excreted in urine (Risdaal *et al.*, 1978) and the bioavailability of 100, 200, or 300 mg tablets relative to a solution was 94% (Spzunar *et al.*, 1987).

The accumulation factor after multiple dose administration was calculated as the ratio AUC last dose/AUC first dose as proposed by Wagner (1988). Since the amount of drug in the body after administration of the last dose was superimposed on that which remained from the previous dose, the 'corrected' AUC^c from the last dose alone was calculated by subtracting the extrapolated AUC due to the previous dose from the total AUC for the last dose. The subtracted area was calculated from $C(0)/\lambda_z$ where $C(0)$ is the concentration immediately before the last dose. Values for all parameters were determined after single dose administration, but not after multiple dose administration since the dosing interval was not uniform.

Statistical analysis

Values for R-flurbiprofen were compared with those for the S-enantiomer with a paired *t*-test. Percent unbound values were compared with a nonparametric Wilcoxon Rank Sum test. Values for the single dose and the two multiple dose study periods were compared with a one-way ANOVA.

Results

Pharmacokinetics of R- and S-flurbiprofen

Mean plasma concentrations of the isomers in the eight patients following single or multiple doses of racemic

Figure 1 Mean ($\pm$ s.d.) plasma concentrations of R-($\square$) and S-flurbiprofen ($\bullet$) after administration of racemic flurbiprofen on study day 1 (a), day 8 (b) and day 27 (c).

flurbiprofen are shown in Figure 1. The corresponding pharmacokinetic parameters are listed in Tables 2 and 3. Peak plasma concentrations were achieved simultaneously for the two enantiomers following both single and multiple dosing (Table 2 and 3). Plasma concentrations of S-flurbiprofen were consistently higher than those of R-flurbiprofen in all patients such that the area under the curve and $C_{\max}$ of the S-enantiomer were significantly greater ($P < 0.05$) than for the R-enantiomer. Statistically significant differences ($P < 0.05$) between R- and S-flurbiprofen were found for oral clearance, renal clearance and volume of distribution following a single dose of the racemate (Table 2). Thus, the R-enantiomer was cleared faster than the S-enantiomer and had a larger volume of distribution. In this patient group, both R- and S-flurbiprofen were cleared primarily by metabolism with renal clearance accounting for less than 1% of the total clearance. Since the clearance and volume of distribution of the R-enantiomer were proportionately

Table 2 Mean ($\pm$ s.d.) pharmacokinetic parameters for R- and S-flurbiprofen in uraemic patients after single dose administration of the racemate

	R	S
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	2.4 ± 0.7	$2.7^* \pm 0.8$
$t_{\max}$ (h)	2.7 ± 1.2	2.4 ± 0.8
$t_{1/2,z}$ (h)	5.7 ± 1.6	5.9 ± 1.7
AUC ($\mu\text{g ml}^{-1} \text{ h}$)	12.2 ± 4.8	$15.3^* \pm 6.7$
CL (ml min^{-1})	38.3 ± 12.8	$30.8^* \pm 11.5$
CL _R (ml min^{-1})	0.08 ± 0.04	$0.04^* \pm 0.03$
V_z (l)	17.6 ± 3.9	$14.6^* \pm 2.5$

*R is significantly different from S at $P \leq 0.05$

increased, the half-life for the two enantiomers was not different following single or multiple doses (Tables 2 and 3). Although the magnitude of the differences varied among patients, all eight showed similar stereoselectivity in the disposition of R- and S-flurbiprofen.

As expected, plasma concentrations of R- and S-flurbiprofen had reached steady state by Day 8 as indicated by the similar area under the curve values on Days 8 and 27 (Table 3). The mean ($\pm$ s.d.) value for the accumulation factor associated with the first and last doses was $1.6 (\pm 0.4)$ for R-flurbiprofen and $1.5 (\pm 0.4)$ for S-flurbiprofen, indicating the accumulation was not enantioselective. The corrected area under the curve following the final dose of racemic flurbiprofen was not significantly different from the AUC following the first dose for either enantiomer. The mean ratio ($\pm$ s.d.) of AUC^c/AUC was $0.94 (\pm 0.11)$ for R-flurbiprofen and $0.98 (\pm 0.10)$ for the S-enantiomer. A comparison of the terminal half-lives following single and multiple dosing did not reveal any significant differences (Tables 2 and 3). Therefore, the disposition of the enantiomers of flurbiprofen does not appear to change upon multiple dosing.

Protein binding of R- and S-flurbiprofen

The percent unbound for racemic flurbiprofen was not significantly different for plasma samples obtained pre-dose, at $C_{\max}$ and 12 h post-dose; mean ($\pm$ s.d.) values were $0.067 (\pm 0.013)$, $0.069 (\pm 0.010)$ and $0.067 (\pm 0.013)$, respectively. Thus, within the ranges examined the percent flurbiprofen unbound was independent of the presence of metabolites and the plasma concentrations of the enantiomers as noted previously (Knadler *et al.*, 1990). Although the mean percent unbound of R-flurbiprofen (0.079 ± 0.014) was not significantly different from that for the S-enantiomer (0.064 ± 0.015), the

enantiomeric binding ratio (percent unbound R:S) varied from 0.85 to 1.82 with a mean ($\pm$ s.d.) of 1.29 ± 0.34 .

Pharmacokinetic parameters based on unbound concentrations following the first dose of racemic flurbiprofen are presented in Table 4. With the exception of the renal clearance, there were no significant differences between the parameters for R- and S-flurbiprofen. These data indicate that the enantioselectivity observed in the disposition of flurbiprofen based on total drug concentrations in the uraemic patients was at least in part due to enantioselective plasma protein binding. The enantioselectivity in unbound renal clearance is unlikely to contribute to the overall enantioselective disposition of flurbiprofen in view of the minor fraction of the dose excreted by the kidney.

Metabolite disposition

The plasma concentrations of conjugated flurbiprofen were determined in seven patients after both the first and last doses. The majority of circulating flurbiprofen was not conjugated. The AUC for conjugated flurbiprofen represented $14 \pm 2\%$ and $13 \pm 2\%$ of the total AUC (conjugated plus unconjugated) for R- and S-flurbiprofen, respectively. Upon multiple dosing these percentages increased slightly to $23 \pm 2\%$ and $18 \pm 2\%$, respectively, indicating that as for flurbiprofen *per se* the conjugates of flurbiprofen show only a modest degree of accumulation.

Peak plasma concentrations of the unconjugated enantiomers of 4'-hydroxyflurbiprofen were low and did not exceed 10% of the corresponding parent drug. 3'-hydroxy, 4'-methoxyflurbiprofen was not detectable in plasma following single or multiple doses. In two subjects, plasma concentrations of the conjugates of 4'-hydroxyflurbiprofen and 3'-hydroxy, 4'-methoxyflurbiprofen

Table 4 Mean ($\pm$ s.d.) pharmacokinetic parameters for R- and S-flurbiprofen based on unbound plasma concentrations in uraemic patients following single dose administration of racemate flurbiprofen

	R	S
$C_{u\max}$ ($\mu\text{g ml}^{-1}$)	1.9 ± 0.7	1.8 ± 0.7
$t_{\max}$ (h)	2.7 ± 1.2	2.4 ± 0.8
$t_{1/2,z}$ (h)	5.6 ± 1.7	5.8 ± 1.8
AUC _u ($\text{ng ml}^{-1} \text{ h}$)	9.8 ± 4.7	9.7 ± 4.2
CL _u (l min^{-1})	50.3 ± 19.3	50.0 ± 19.0
CL _{uR} (l min^{-1})	0.11 ± 0.06	$0.07^* \pm 0.04$
V_{uz} ($\text{l} \times 10^4$)	2.3 ± 0.8	2.3 ± 0.6

*R is significantly different from S, $P \leq 0.05$

Table 3 Mean ($\pm$ s.d.) pharmacokinetic parameters for R- and S-flurbiprofen following multiple dose administration

	Day 8		Day 27	
	R	S	R	S
$C_{\max}$ ($\mu\text{g ml}^{-1}$)	3.0 ± 0.7	$3.5 \pm 0.9^*$	2.8 ± 1.2	$3.2 \pm 1.4^*$
$t_{\max}$ (h)	1.9 ± 0.8	1.9 ± 0.8	2.3 ± 1.0	2.3 ± 1.0
$t_{1/2,z}$ (h)	6.4 ± 1.1	6.8 ± 2.0	6.7 ± 1.46	6.9 ± 2.5
AUC ($\text{mg ml}^{-1} \text{ h}$)	19.3 ± 8.7	$24.6 \pm 13.6^*$	20.7 ± 11.8	$26.9 \pm 19.1^+$

*R is significantly different from S at $P \leq 0.05$

$^{+}0.05 < P < 0.10$

Figure 2 Mean ($\pm$ s.d.) urinary recoveries of flurbiprofen and its metabolites after administration of a single dose of racemic flurbiprofen on study day 1. Data are expressed as molar percent of dose. ■ S, □ R.

were determined following the first and last dose of racemic flurbiprofen. Following the first dose average peak plasma concentrations of R- and S-4'-hydroxy-flurbiprofen conjugates were 270 ng ml^{-1} and 136 ng ml^{-1} , respectively, rising to 980 ng ml^{-1} and 416 ng ml^{-1} , respectively, following multiple dosing. Similarly, for R- and S-3'-hydroxy, 4'-methoxyflurbiprofen conjugates the average peak concentrations were 155 ng ml^{-1} and 181 ng ml^{-1} after the first dose and 806 ng ml^{-1} and 1254 ng ml^{-1} following the last dose. Therefore, the accumulation of the oxidative metabolite conjugates appears to be greater than that noted for the enantiomers of flurbiprofen and their conjugates.

The mean urinary excretion of R- and S-flurbiprofen and the R- and S-enantiomers of the metabolites after the first dose of racemic flurbiprofen are shown in Figure 2. A significantly larger percentage of the dose was excreted as the R-enantiomer of unconjugated flurbiprofen, total flurbiprofen, 4'-hydroxyflurbiprofen, and as total percent of the dose. Similar amounts of R-3'-hydroxy, 4'-methoxyflurbiprofen and the corresponding S-enantiomer were excreted during the collection interval. Overall, the patients excreted a significantly ($P < 0.05$) larger percentage of the dose as metabolites derived from the R-enantiomer than the S-enantiomer (16.4 ± 6.0 vs $10.9 \pm 4.2\%$), while plasma concentrations of S-flurbiprofen were higher than those of R-flurbiprofen.

Discussion

Flurbiprofen, and most of the 2-arylpropionic acid non-steroidal anti-inflammatory drugs are characterized by a low systemic clearance and a small volume of distribution, and therefore their disposition is sensitive to changes in plasma protein binding which is usually extensive (Lin *et al.*, 1987; Risdall *et al.*, 1978). The uraemic patients of this study exhibited a modest but significant degree of enantioselectivity in both oral clearance and volume of distribution which disappeared

when unbound drug concentrations were considered (Tables 2 and 4). It therefore appears that plasma protein binding makes a major contribution to the enantioselective disposition of flurbiprofen in this patient group. The modest enantioselectivity in disposition noted in this study is consistent with that observed in subjects with normal renal function (Jamali *et al.*, 1988; Knadler *et al.*, 1992; Young *et al.*, 1991). In general, the 2-arylpropionic acids exhibit little enantioselectivity in their pharmacokinetics in humans with the exception of those undergoing significant chiral inversion. Flurbiprofen, however, does not form a coenzyme A thioester *in vitro* (Knadler & Hall, 1990; Knihinicki *et al.*, 1989), a prerequisite for chiral inversion, and individual enantiomer administration to humans does not result in formation of its antipode (Jamali *et al.*, 1988), indicating that chiral inversion does not occur to a significant extent.

Previously, we reported the disposition of R- and S-flurbiprofen in a group of normal volunteers (Knadler *et al.*, 1992). When compared with normal subjects the uraemic patients exhibit significantly greater ($P < 0.05$) values of oral clearance (R: 38.3 ± 12.8 vs 20.4 ± 4.7 ; S: 30.8 ± 11.5 vs $16.1 \pm 3.6 \text{ ml min}^{-1}$) and volume of distribution (R: 17.6 ± 3.9 vs 9.1 ± 1.8 ; S: 14.6 ± 2.5 vs 8.5 ± 1.3). These differences between study populations are less and not statistically significant when unbound clearance and unbound volume of distribution are compared. Plasma protein binding therefore appears to make a major contribution to the increased clearance and volume of distribution in uraemic relative to normal subjects which is consistent with the significantly greater percent unbound of R- (0.079 ± 0.014 vs 0.055 ± 0.008 ; $P < 0.05$) and S-flurbiprofen (0.064 ± 0.015 vs 0.049 ± 0.009 ; $0.05 < P < 0.1$) in the uraemic subjects. Reduced plasma protein binding of acidic drugs in uraemic subjects is expected primarily due to the accumulation of endogenous anions (Lindup *et al.*, 1991). However, in the patients of this study a significantly lower ($P < 0.05$) plasma albumin concentration, relative to normal subjects (3.85 ± 0.22 vs $4.53 \pm 0.24 \text{ g dl}^{-1}$), may have contributed to the elevated percent unbound. The degree of enantioselectivity in flurbiprofen clearance in this study group was similar to that in normal subjects consistent with the similarity in enantioselective ratio for percent unbound. A striking difference between uraemic and normal subjects was observed in the urinary recovery of metabolites. The lower percent of the dose recovered in uraemic patients (27.3 ± 10.2 vs $62.4 \pm 8.1\%$) does not appear to reflect an insufficient urinary collection period because plasma metabolite concentrations declined in parallel to parent drug. The basis of this difference is therefore unknown, but Foster *et al.* (1989) noted that when renal excretion of organic acids was attenuated by probenecid there was an enhanced elimination of ketoprofen glucuronide via biliary excretion. A similar diversion of flurbiprofen metabolites may therefore contribute to the reduced recovery of flurbiprofen metabolites in the present study.

Meffin and coworkers proposed that an acyl-glucuronide futile cycle was responsible for the decreased clearance of the predominantly metabolized compounds R- and S-2-phenylpropionic acid (Meffin *et al.*, 1986) and diphenylacetic acid (Sallustio *et al.*, 1989) in uraemic

rabbits. In such a cycle the renal excretion of the acyl-glucuronides, which are major metabolites of the latter compounds, is decreased leading to increased plasma concentrations of conjugated drug which is then hydrolyzed to regenerate the parent compound. The futile cycle may therefore explain the decreased clearance of benoxaprofen (Aronoff *et al.*, 1982), ketoprofen (Stafanger *et al.*, 1981), and naproxen (Anttila *et al.*, 1980), in patients with renal impairment. For the latter drugs, acyl-glucuronide formation constitutes a major pathway of elimination (Aronoff *et al.*, 1982; Delbarre *et al.*, 1976; Upton *et al.*, 1984). In this study the clearance of R- and S-flurbiprofen following a single oral dose increased rather than decreased relative to normal subjects (*vide infra*) and therefore the futile cycle does not appear to be of significance. This occurs despite measurable plasma acyl-glucuronide concentrations and ready hydrolysis of these glucuronides in the systemic circulation (Knadler & Hall, 1991). In renal failure where renal excretion of an acyl-glucuronide is reduced, there is the opportunity for substantial accumulation of the conjugate to occur upon multiple dosing, thus amplifying any potential futile cycle. However, our data indicate that despite accumulation of the conjugates of 4'-hydroxyflurbiprofen and 3'-hydroxy, 4'-methoxy-

flurbiprofen there was little accumulation of R- and S-flurbiprofen glucuronide and no change in the clearance of the parent enantiomers following repetitive dosing. As noted by Sallustio *et al.* (1991), the relatively low quantitative importance of acyl-glucuronide formation and possible elimination of the conjugate by non-renal pathways, e.g. biliary, may both limit the significance of futile cycling for R- and S-flurbiprofen in uraemic patients. From a mechanistic standpoint, it would be prudent to measure unbound drug concentrations in future studies of acyl-glucuronide futile cycling so that changes in fraction drug unbound between study groups, as occurs for R- and S-flurbiprofen, do not confound the data analysis.

In conclusion, the stereoselective disposition of flurbiprofen was not dramatically influenced by the presence of renal failure, thus dosage adjustments are not necessary in this patient group unless elevated plasma metabolite concentrations are associated with toxicity. A futile cycle of flurbiprofen elimination was not detected in uraemic subjects.

This work was supported in part by NIH grants DK37994, AG07631 and a grant from the Upjohn Company.

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(Received 16 July 1991,
accepted 1 November 1991)