Pharmacokinetic Comparison of Flurbiprofen in End-Stage Renal Disease Subjects and Subjects with Normal Renal Function

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This study compared the pharmacokinetics of flurbiprofen (F) and three major metabolites in patients with end-stage renal disease (ESRD) undergoing continuous ambulatory peritoneal dialysis (CAPD) with the pharmacokinetics of F in normal subjects. A single 100-mg dose of F was administered to each of nine normal subjects and eight ESRD subjects. Blood and urine samples were collected in both groups; serial and end of dwell dialysate samples were obtained from the ESRD subjects. Plasma was analyzed for both the R and S optical isomers of F and its major metabolite, 4'-hydroxy-flurbiprofen (HF). Urine and dialysate were analyzed for F and three known metabolites. Plasma concentrations of F in the ESRD subjects were approximately 50% of the values obtained from the normal subjects (P < .05). Flurbiprofen half-life and Tmax were not different. Elimination of HF was reduced in ESRD subjects. Urinary data suggest HF was the major metabolite excreted (36% of the dose) in normal subjects whereas 3', 4'-dihydroxy-flurbiprofen was the major metabolite (9% of the dose) excreted in the ESRD group. Mean urinary recovery of the dose was 73% in the normal subjects, but only 16% in ESRD subjects. Neither F nor its metabolites were detected in dialysate. Small enantiomer differences were seen. This study suggests that ESRD subjects have lower plasma levels of F than normal subjects when administered equal size doses. Accumulation of metabolites may occur in ESRD subjects upon multiple dosing. Enantiomer differences are not clinically significant.

Flurbiprofen (DL-2-(2-fluoro-4-biphenylyl) propionic acid), F, is an orally active nonsteroidal anti-inflammatory drug administered as the racemate of R and S optical isomers. It is indicated for conditions associated with mild-to-moderate pain such as arthritis, postepisiotomy pain, and dysmenorrhea. After oral administration to healthy volunteers, it is well absorbed with greater than 70% of the dose appearing in the urine as F, 4-hydroxyflurbiprofen (HF), 3,4-dihydroxyflurbiprofen (DHF), 3'-hydroxy-4-methoxyflurbiprofen (HMF), and their conjugates.1-3 Chemical structures of F, HF, DHF, and HMF are shown in Figure 1. The metabolites have minimal anti-inflammatory activity.4 Flurbiprofen is bound extensively (>90%) to plasma proteins.1,3,5-6

Studies suggest that the absorption, distribution, clearance, and plasma-protein binding of non-steroidal anti-inflammatory drugs may be altered in patients with compromised renal function.7-14 Since ESRD patients may be administered F, this study compared the pharmacokinetics of F in ESRD patients and subjects with normal renal function (NRF). Since stereoselective pharmacokinetic processes have been identified for F6,15 and other

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FLURBIPROFEN PHARMACOKINETICS

**Figure 1.** Chemical structures of flurbiprofen (F), 4'-hydroxy-flurbiprofen (HF), 3'4'-dihydroxy-flurbiprofen (DHF), 3'-hydroxy-4'-methoxy-flurbiprofen (HMF). *Chiral center.*

NSAIDS, 16–18 pharmacokinetic analyses of R and S isomers were included in this study.

**MATERIALS AND METHODS**

**Subjects**

Nine healthy subjects (5 men, 4 women) between the ages of 23–42 years (mean: 33 ± 7.3 yr) and weighing 50–115.9 kg (mean: 71.9 ± 20.8 kg) were enrolled into the NRF group and completed the study. The ESRD group consisted of 8 subjects (5 men, 3 women) between the ages of 21–56 years (mean: 43.1 ± 12.6 yr), weighing 45.5–85.5 kg (mean: 65.4 ± 15.9 kg) and with creatinine clearances of less than 3.5 mL/min undergoing continuous ambulatory peritoneal dialysis (CAPD). All ESRD subjects had been undergoing CAPD for greater than 1 year and had not experienced peritonitis in the past 6 months.

Before enrollment, all normal volunteers were determined to be in good health through medical history, physical examination, electrocardiogram and laboratory tests (hematology, blood chemistry, and urinalysis). The study was approved by the University Investigational Review Board, and each volunteer provided a written informed consent before entering the study. ESRD subjects were allowed to take only necessary medicines. NRF subjects received no other drugs except for 30 mL of aluminum hydroxide gel after each meal to simulate antacid use in the ESRD group. All volunteers were confined to the study area throughout the study. They all fasted for at least 8 hours before dosing and continued fasting for 3 hours after dosing. Each volunteer was administered a single 100 mg tablet followed by 120 mL of tap water. Meals and meal schedules were similar in the two groups.

Serial 5 mL blood samples were obtained in collection tubes containing EDTA. These samples were obtained just before the dose and at 0.33, 0.66, 1, 1.33, 1.66, 2, 2.66, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 27, 30, 33, 36, 39, and 48 hours after the dose in the ESRD group. Serial blood samples were obtained from the NRF group just before the dose and at 0.5,
0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 9, 11, 13, 15, 18, 21, 24, 27, 30, 33, 36, 40, 44, and 48 hours after dosing. All blood samples were centrifuged immediately. The plasma was harvested and frozen at −20°C until assayed.

Total urine collections were made over 0–6, 6–12, 12–16, 16–24, 24–30, 30–36, 36–40, and 40–48 hours in the NRF group. Urine collections for ESRD patients were made at 0–8, 8–12, 12–16, 16–24, 24–32, 32–36, 36–40, 40–48, 48–72, and 72–96 hours, as urine was available. Peritoneal dialysate samples were obtained during and at the end of each dwell throughout the study. Twenty mL aliquots of urine and dialysate were frozen at −20°C until assayed.

**Analytical Assay**

All assays were conducted at Hazelton-Raltech Laboratories, Madison, Wisconsin. Concentrations of F and 4'-hydroxy-flurbiprofen (HF) were determined by a stereospecific, sensitive and reproducible high-performance liquid chromatographic (HPLC) method. In this method, diastereomeric amides of F and HF are formed enabling determination of R and S enantiomer concentrations. The relative standard deviations of this assay are less than 10% for both optical isomers of F and HF. The lower level of quantitation for these species is 0.1 mg/L. Dialysate and urine samples were assayed for the free species and conjugates of F, HF, 3', 4'-dihydroxy-flurbiprofen (DHF) and 3'-hydroxy-4'-methoxy-flurbiprofen (HMF) by a specific, sensitive and reproducible HPLC method developed by Szpunar. The relative standard deviations for this assay are 8–16% at 1 mg/L and less than 10% for concentrations of 2–100 mg/L.

**Pharmacokinetic Analysis**

Linear regression was used to determine the slope (β) of the terminal phase of the F concentration–time data. Estimates for β were not obtained for HF because the terminal concentrations were at the lower level of quantitation in the NRF group and too erratic in the ESRD group. Area under the curve to the last observable concentration–time point (AUCt), was calculated by the trapezoidal rule. For the flurbiprofen enantiomers, this area was extrapolated to infinity using the equation $\text{AUC}_{\infty} = \text{AUC}_t + \text{Cpt}/\beta$ where Cpt is the plasma concentration at the final measurable sampling time, t. The pharmacokinetic parameters were compared for subject as well as enantiomer differences.

**RESULTS**

The mean plasma F and HF concentration–time data are illustrated in Figures 2 and 3. The pharmacokinetic parameters are listed in Tables I and II. Amounts of F, HF, DHF, and HMF recovered in the urine as percent of dose are found in Table III. Neither flurbiprofen nor any of the metabolites were detected in the dialysis fluid.

F was absorbed rapidly in both the NRF and ESRD groups. The mean maximum plasma F isomer concentrations (Cmax) for the NRF group occurred between 0.5 and 3.5 hours (mean: 1.7 ± 0.9 hr). The maximum plasma F concentration for the ESRD group occurred between 0.67 and 4.0 hours (mean: 2.3 ± 1.2 hr). The mean time to peak plasma concentration (Tmax) was not statistically different between the two groups by t test. The mean Tmax val-
values for the F enantiomers within each study group were the same. Mean F isomer Cmax values for the NRF group (7.3 ± 2.3 mg/L for R and 7.3 ± 2.2 mg/L for S) were significantly greater than those of the ESRD group (4.6 ± 1.5 mg/L for R and 4.8 ± 1.6 mg/L for S) at P < .05. The F isomer mean AUC∞ values for the NRF group (36.4 ± 11.1 mg·hr/L for R and 41.9 ± 12.8 mg·hr/L for S) are also significantly greater than those for the ESRD group (22.1 ± 11.0 mg·hr/L for R and 21.9 ± 10.9 mg·hr/L for S) by t test. In the NRF group, the mean AUC∞ value for the S enantiomer was significantly greater than that of the R enantiomer. This difference was not seen in the ESRD group. The F plasma concentrations declined in a biexponential fashion in both groups. Only mean β estimates for the S enantiomer showed significant differences between the NRF and ESRD groups (0.13 ± 0.04 and 0.21 ± 0.09 hr⁻¹, respectively). The β value for the flurbiprofen R isomer in the NRF group was significantly greater than that of the S isomer in the NRF group.

Mean isomer Cmax values of HF for the ESRD group (approximately 0.8 mg/L) were significantly greater (P < .05) than those of the NRF group (approximately 0.4 mg/L). Since estimates of β were not determined for HF, AUCt values are compared instead of AUC∞. The HF isomer AUCt values for the ESRD group (18.6 ± 10.1 mg·hr/L for R and 7.2 ± 6.3 mg·hr/L for S) were significantly greater than those of the NRF group. The AUCt value for the R isomer in the ESRD group was significantly greater than that of the S isomer in the same subjects.

The major compounds excreted in the urine by the NRF group were F (20 ± 4% of the dose) and HF (36 ± 3% of the dose). Approximately 73% of the dose

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**TABLE I**

Mean Pharmacokinetic Parameters of Flurbiprofen in NRF Subjects (N = 9) and ESRD Subjects (N = 8) After a 100 mg Dose of Flurbiprofen

<table>
<thead>
<tr>
<th>Parameter Mean</th>
<th>Cmax (mg/L)</th>
<th>Tmax (hr)</th>
<th>β (hr⁻¹)</th>
<th>AUC∞ (mg·hr/L)</th>
<th>t¹⁄₂β (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>S</td>
<td>R</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>NRF</td>
<td>7.3</td>
<td>7.3</td>
<td>1.7</td>
<td>1.7</td>
<td>0.18†</td>
</tr>
<tr>
<td>SD</td>
<td>2.3</td>
<td>2.2</td>
<td>0.9</td>
<td>0.9</td>
<td>0.04</td>
</tr>
<tr>
<td>ESRD</td>
<td>4.6</td>
<td>4.8</td>
<td>2.3</td>
<td>2.3</td>
<td>0.23</td>
</tr>
<tr>
<td>SD</td>
<td>1.5</td>
<td>1.6</td>
<td>1.2</td>
<td>1.2</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* Significantly different between groups (P < .05).
† Significantly different between isomers within the group (P < .05).
‡ Harmonic mean.
was recovered in the urine after 48 hours. In the ESRD group, DHF was the major compound excreted in the urine (9 ± 4% of the dose). Only 16 ± 11% of the dose was accounted for in the urine after 96 hours.

All pre-study and post-study physical examinations, laboratory tests, and electrocardiograms were acceptable. No adverse reactions were reported.

Discussion

The mean Tmax and 1/2 parameters of F obtained for the NRF group are consistent with previous reports. A more thorough comparison of these studies with the present data is not possible, since separate analysis of the F enantiomers was not conducted in the other studies. The urine recovery data in the NRF group (73% of the dose recovered) is consistent with the urine data from normal healthy subjects published by Szpunar et al. (77% of the dose recovered). Although these investigators sampled urine for 48 hours longer than in our NRF group, this only accounted for 4% more of the dose. Therefore, in NRF subjects, most of the dose is excreted in 48 hours. Szpunar et al. determined that the extent of absorption for a 100-mg tablet is 96% relative to a solution of F in normal healthy volunteers. Since we both report similar urine recoveries, the extent of absorption in our NRF group is probably similar.

Tmax values of F for the NRF and ESRD groups were similar suggesting similar rates of absorption in the two groups. Conclusions about the absolute bioavailability of F in ESRD cannot be made due to the absence of radiolabelled or intravenous F data. Statistically smaller mean Cmax and AUC∞ values of F in the ESRD subjects suggest a proportionately smaller extent of absorption in this group. The administration of antacids to the ESRD group probably did not lower their absorption of F in this study. We attempted to balance the effect of antacids used in the ESRD group by administering aluminum hydroxide gel on a similar schedule as that used in the NRF group. Furthermore, Caillé et al. found that an aluminum and magnesium hydroxide antacid suspension did not affect the absorption of F in normal healthy volunteers.

Altered protein binding could also possibly explain the lower AUC∞ values observed for F in the ESRD group. Knadler et al. conducted F binding studies which showed that subjects with renal insufficiency had 36% more unbound F than subjects with normal renal function. Such modification in protein binding is not uncommon in renal insufficiency. If present in this case, a higher fraction of unbound F could translate into greater clearance, a large volume of distribution and lower plasma F concentrations.

Mean values of Cmax and AUCt for HF were significantly greater in the ESRD group. Although these differences could be due to diminished ability for ESRD patients to eliminate this more polar metabolite, an increased metabolism of F to HF due to an increased unbound fraction of F is just as likely. A

### TABLE II

Mean Pharmacokinetic Parameters of 4'-Hydroxy-Flurbiprofen in NRF Subjects (N = 9) and ESRD Subjects (N = 8) After a 100 mg Dose of Flurbiprofen

<table>
<thead>
<tr>
<th>Parameter Mean</th>
<th>NRF</th>
<th>SD</th>
<th>ESRD</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>θ (mg/L)</td>
<td>0.4</td>
<td>0.2</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>5.7</td>
<td>9.2</td>
<td>6.7</td>
<td>5.7</td>
</tr>
<tr>
<td>AUCt (mg·hr/L)</td>
<td>3.1</td>
<td>1.0</td>
<td>18.6</td>
<td>10.1</td>
</tr>
</tbody>
</table>

* Significantly different between groups (P < .05).
† Significantly different between isomers within group (P < .05).

### TABLE III

Mean Urinary Excretion Data (SD)

<table>
<thead>
<tr>
<th>Species</th>
<th>NRF Group (N = 9)</th>
<th>ESRD Group (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>20 (4)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>HF</td>
<td>36 (3)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>DHF</td>
<td>11 (10)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>HMF</td>
<td>6 (2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Total</td>
<td>73 (11)</td>
<td>16 (8)</td>
</tr>
</tbody>
</table>

* Significantly different between groups (P < 0.05).
† mmolar basis where 100 mg dose = 0.405 mmoles.
F = flurbiprofen; HF = 4-hydroxy-flurbiprofen; DHF = 3,4-dihydroxy-flurbiprofen; HMF = 3-hydroxy-4-methoxy-flurbiprofen.
trend towards larger values of β for F in the ESRD group was evident in our study, further corroborating an increased clearance hypothesis. Unfortunately, protein binding experiments were not conducted in this study.

Enantiomer differences were demonstrated in this study. In the NRF group, β was statistically larger and AUC∞ was statistically smaller for the R isomer of F. Jamali et al. also observed significantly smaller AUC∞ values for this isomer. Unidirectional R to S inversion has been documented for ibuprofen, fenoprofen and benoxaprofen, but based on the results of administering the R isomer of F to one subject, Jamali et al. have suggested that R to S conversion does not occur in humans. Assuming this to be true, the lower AUC∞ for the R isomer could be attributed to a larger volume of distribution and greater clearance since this enantiomer displays slightly lower protein binding than the S enantiomer (6% less). Interestingly, β for the R isomer was larger than for the S isomer, further agreeing with the concept of increased clearance for the R isomer.

Enantiomer differences in F pharmacokinetics were not evident in the ESRD group. Absence of enantiomer differences could be due to the inability to detect these differences at the plasma concentrations seen in the ESRD group. The only enantiomer difference suggested in the ESRD group was a greater, though not significantly greater, AUCt value for the R isomer of HF. A similar trend for AUCt of HF was demonstrated in the NRF group, but did not reach statistical significance. If the R isomer of HF has a greater clearance than the S isomer, it would be expected that the AUC values of the R isomers of the metabolites would be greater than those of the S isomers.

This study suggests that ESRD patients have 40–50% lower plasma F concentrations than subjects with normal renal function. The lower F concentrations could be due to a combination of poor extent of absorption, greater volume of distribution, and/or increased clearance resulting from decreased protein binding. Since a positive correlation between plasma ibuprofen concentrations and analgesia exists, the difference in F concentrations could translate into lower than expected pain relief in ESRD. Although some differences were observed between the isomers of F and HF, their small relative magnitudes are of academic interest only. Comparison of the pharmacokinetic parameters of HF for the two groups suggests that this metabolite could accumulate after multiple dosing to a greater extent in ESRD than in NRF patients. HF has minimum anti-inflammatory activity, therefore accumulation of this and/or other metabolites would only be clinically significant if this metabolite proved toxic.

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REFERENCES


