Fleroxacin Pharmacokinetics in Patients with Liver Cirrhosis

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In this open-label study, the disposition of fleroxacin in liver disease in 12 healthy male volunteers, 6 male cirrhotics without ascites (group A), and 6 male cirrhotics with ascites (group B) was evaluated. Fleroxacin (400 mg) was administered orally and intravenously to each subject in a random crossover fashion. Fleroxacin was completely absorbed and achieved similar peak concentrations in plasma in all three study groups (P > 0.05). The volume of distribution exceeded 1 liter/kg in healthy controls and was not affected by liver impairment (P > 0.05). Only group B demonstrated differences in the pharmacokinetic parameters evaluated: the systemic and renal clearances of fleroxacin and the renal clearances and clearances of the two major metabolites of fleroxacin formed, N-demethyl fleroxacin and fleroxacin N-oxide, were significantly lower and the half-lives of the parent drug and its metabolites were significantly longer in group B than in healthy controls and group A (P < 0.05). The elimination of the two metabolites appeared to be formation rate limited in all three study groups. It was concluded from this study that a 50% reduction in the fleroxacin maintenance dose in patients with liver disease appears justified only in patients with ascites. However, no change in the fleroxacin loading dose is needed in patients with compromised liver function.

Fleroxacin [6,8-difluoro-1-(2-fluoroethyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-quinoline-3-carboxylic acid; AM-833; Ro 23-6240] is a new fluoroquinolone derivative. It possesses a broad antibacterial spectrum and potent activity in vitro against gram-positive and gram-negative bacteria (MIC for 90% of isolates, ≤0.05 to 2 mg/liter), including Pseudomonas aeruginosa, methicillin-resistant staphylococci (MIC for 90% of isolates, ≤0.5 to 4.0 mg/liter), and β-lactamase-producing bacteria resistant to broad-spectrum cephalosporins (16). The overall activity of fleroxacin is roughly comparable to those of norfloxacin, enoxacin, lomefloxacin, ofloxacin, and pefloxacin (1, 3, 5).

Fleroxacin is rapidly and completely absorbed from the gastrointestinal tract (19, 20). After one single oral dose of 400 mg, fleroxacin reaches peak concentrations in plasma (Cmax) of 4.2 to 6.1 mg/liter within 1 to 2 h (25, 29). Fleroxacin is well distributed into interstitial fluid and various tissues (20, 21, 26, 30). Fleroxacin is primarily renally eliminated, with 50 to 60% of the drug being excreted unchanged. It has an extended half-life (t1/2) (10.8 h; range, 7 to 14 h), which allows for once-a-day dosing (7, 15, 25). The protein binding of fleroxacin in human serum is low (23 to 32%) (12, 14, 15, 25) and is comparable to those of other fluoroquinolones.

Fleroxacin is metabolized in humans by the liver to a small extent via oxidation, demethylation, and glucuronidation (11, 22, 28). The active N-demethyl fleroxacin and the inactive fleroxacin N-oxide were identified as the major metabolites in plasma and urine. Only 4 to 6% of the fleroxacin dose has been found to be excreted as the N-demethyl and N-oxide metabolites (22).

Because metabolism by the liver appears to represent only a minor pathway for fleroxacin elimination, the use of this drug seems justified in patients afflicted by liver impairment. However, at this point it is unknown whether the hepatic elimination of fleroxacin is modified in the setting of liver disease. Such a modification could potentially cause the accumulation of the parent drug, an active metabolite, or both. Hence, the focus of this study was to determine any alterations in the disposition of fleroxacin in patients with liver cirrhosis of increasing severity, as characterized by the absence or presence of ascites.

MATERIALS AND METHODS

Study design. This was an open-label, random crossover study involving 12 healthy male volunteers and 12 male patients with the diagnosis of stable liver cirrhosis (6 without ascites [group A] and 6 with ascites [group B]). All subjects were 30 to 68 years of age and within 20% of their ideal body weight. Diagnosis of liver cirrhosis was confirmed by medical history, clinical signs, biochemical parameters, an abnormal liver function test, and/or biopsy. Only subjects who were clinically stable, i.e., who had no significant changes in their clinical or laboratory profile during a 4-week period prior to the initiation of the study, were included. Immediately prior to investigation, 11 subjects were categorized as Child-Turcotte group A and 1 subject was categorized as Child-Turcotte group B (6). Healthy subjects were diagnosed as free of disease by medical history, physical examination, and laboratory evaluation. Table 1 summarizes the exclusion criteria for both groups.

The use of any medication was prohibited in the healthy volunteer group. The only concurrent drugs allowed in the cirrhotic group were those used in the treatment of chronic liver cirrhosis (e.g., diuretics and vitamin supplements). Subjects were instructed to discontinue the use of other drugs at least 5 days prior to treatment.

The study subjects entered the research unit on the evening before each drug treatment and remained there until 48 h after each drug treatment. They were treated as outpatients for 48 to 96 h after drug treatment. Shortly before dosing, an indwelling catheter was inserted into the antecu-

* Corresponding author.
TABLE 1. Summary of exclusion criteria used in this study

<table>
<thead>
<tr>
<th>Group</th>
<th>Exclusion criteria</th>
</tr>
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<tbody>
<tr>
<td>Normal healthy controls</td>
<td>Active infectious process within 2 weeks of study start; history of significant allergies; cardiovascular, endocrine, gastrointestinal, hematological, hepatic, or renal disease; or use of over-the-counter medications within 3 days of study start</td>
</tr>
<tr>
<td>Liver cirrhosis subjects</td>
<td>Recent history of gastrointestinal bleeding (within 1 month of study start); moderate to severe encephalopathy; current treatment for cardiovascular, endocrine, gastrointestinal, hematological, or renal disease; a creatinine clearance of &lt;50 ml/min; active infectious process within 2 weeks of study start; or use of concurrent medication, with the exception of medications used in the treatment of chronic liver cirrhosis</td>
</tr>
<tr>
<td>All subjects</td>
<td>History of psychiatric illness; history of concomitant diagnosis of drug abuse (except alcohol); alcohol consumption within 72 h of study start; or known hypersensitivity to quinolones</td>
</tr>
</tbody>
</table>

...bital vein for serial blood sampling. Prior to drug administration, predose samples and blank urine samples were collected. Both population groups received a single oral dose of 500 mg of antipyrine on day 1 of the study to evaluate liver microsomal enzyme activity. On study days 8 and 15, they received a single 400-mg dose of fleroxacin orally or intravenously (i.v.) (60-min infusion) in a random crossover fashion. Fleroxacin was administered after an 8-h fast. All subjects were required to remain in a sitting position for 2 h following fleroxacin administration. Laboratory tests for the evaluation of safety were performed at baseline, on study days 1 and 8, and at follow-up. The study protocol was approved by the Institutional Review Board of the University of Kentucky, and subjects' written consent was obtained prior to enrollment in the study.

Sampling. (i) Antipyrine liver function study. Immediately before and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, and 72 h after antipyrine administration, a 5-ml venous blood sample was collected.

(ii) Fleroxacin study. (a) Blood. Serial blood samples were taken immediately before and at 10, 20, 30, and 45 min and 1, 2, 3, 4, 6, 9, 12, 24, 36, 48, 60, 72, and 96 h after fleroxacin administration. During the i.v. infusion, additional samples were taken 30 min after the start and exactly at the end of the 60-min infusion.

(b) Urine. Complete urine samples were collected at the following time intervals: predose and 0 to 6, 6 to 12, 12 to 24, 24 to 36, 36 to 48, 48 to 72, and 72 to 96 h after drug administration. Fleroxacin is light sensitive, so appropriate precautions (brown glassware, aluminum foil) were taken.

Laboratory data. Laboratory data were collected during the screening, at baseline, on study days 1 and 8, and at follow-up. Hematological and urine analyses were performed at baseline and at follow-up.

(i) Blood chemistry. Tests were performed for total protein, albumin, uric acid, creatinine, urea, electrolytes, iron, P₄, cholesterol, triglycerides, total bilirubin, glucose, and liver function.

(ii) Hematological analysis. Analyses were done for hemoglobin, hematocrit, erythrocytes, differential leukocytes, prothrombin time, and platelets.

(iii) Urine analysis. Analyses were done for protein, glucose, erythrocytes, leukocytes, and casts.

Analytical methods. Plasma and urine samples were analyzed at F. Hoffmann-La Roche Ltd., Basel, Switzerland, for unchanged drug and the two main metabolites of fleroxacin, N-demethyl fleroxacin and fleroxacin N-oxide, by use of a modified ion-pair high-pressure liquid chromatography (HPLC) assay (8). AM-735, a quinolone compound provided by F. Hoffmann-La Roche, was used as the internal standard for plasma and urine samples. A plasma aliquot was mixed with trichloroacetic acid, and the precipitated protein was subsequently removed by centrifugation. An aliquot of the supernatant was diluted with the mobile phase (see below) and chromatographed. Urine samples, to which pipemic acid was added, were diluted with the mobile phase (see below) and chromatographed. The HPLC system consisted of the following components: Toyo Soda ODS-120T column (5-μm particle size; 250 by 4.6 mm); Kontron 414LC pump (flow rate, 0.8 ml/min); Merck/Hitachi FI1000 fluorescence spectrometer (excitation, 290 nm; emission, 450 nm); Perkin-Elmer ISF 100 Kontron autoinjector; and Spectra Physics 4200 computing integrator. The mobile phase was a mixture of 5 mM tetrabutylammonium hydrogen sulfate (aqueous solution) and methanol (72:28 [vol/vol]). In each analytical run, a number of quality control samples (spiked plasma or urine samples) covering the complete range of quantification were analyzed to ensure precision and reproducibility. The bias for unchanged fleroxacin ranged from −3.6 to +6.9% for the plasma samples and from −4.3 to +2.2% for the urine samples. The bias was defined as [(found concentration − spiked concentration)/spiked concentration] × 100. The inter- and intraday coefficients of variation for fleroxacin and metabolites over the concentration range studied were less than 6% (27).

Antipyrine was analyzed at the College of Pharmacy, University of Kentucky, Lexington, by use of an established HPLC assay (4, 25). A stock solution of phenacetin (0.5 μg/ml) was prepared in 100% HPLC-grade methanol to be used as the internal standard. One hundred microliters of the internal standard was pipetted into a glass test tube and dried under nitrogen gas. One hundred microliters of sample plasma was added to the test tube, and then 100 μl of 5 N NaOH and 1.0 ml of methylene chloride were added. After being vortexed for approximately 10 s, the tube was centrifuged (Beckman TJ6R) at 4,000 rpm for 5 min. The top (aqueous) plasma layer was vacuumed off. The bottom (methylene chloride) layer was poured into a clean glass test tube and dried under nitrogen gas. The samples were reconstituted with 100 μl of the mobile phase (see below), and 30 μl was injected into the HPLC. The HPLC system consisted of the following components: Shimadzu SPD-6A V UV-VIS spectrometer detector; Shimadzu LC-6A pump (flow rate, 1.0 ml/min); Shimadzu SCL-6B system controller; Shimadzu CF601 Chromatopac recorder/integrator; and Beckman Al-tex-UltraspHERE ODS column (C-18) (5-μm particle size; 4.6 mm by 25 cm). The mobile phase was a mixture of 45% methanol and 55% water containing 0.01 M triethylamine...
(pH, approximately 4.7) (adjusted with HPLC-grade phosphoric acid). A reproducibility study demonstrated intra- and interday coefficients of variation of 5.3 to 7.9% and 5.6 to 8.6%, respectively.

Formulations. Fleroxacin was supplied by F. Hoffmann-La Roche as 200-mg tablets for oral administration (Ro 23-6240/619; catalog no. 149627-006) and as a sterile solution of 400 mg of fleroxacin per 20 ml of sterile water for injection (Ro 23-6240/626; catalog no. 150487-001) for i.v. administration. Antipyrine was purchased from Eastman Kodak Co., Rochester, N.Y.

Safety parameters. Adverse events were defined as signs and symptoms that emerged during the study, i.e., events that were not present at baseline. All adverse events were recorded and graded as mild, moderate, or severe (27).

Pharmacokinetic evaluation. Antipyrine and fleroxacin data were analyzed by noncompartmental pharmacokinetic methods. The fleroxacin concentration-time data for each volunteer were also fitted individually to a two-compartment, open model. The terminal phase rate constant was obtained by extended least-squares regression analysis (PC-NONLIN). A weighting factor of the reciprocal of the measured concentration (1/y²) was chosen for curve fitting. The plasma fleroxacin concentrations were best described by equations chosen on the basis of the minimum Akaike Information Criterion estimation. The t₁/₂ was calculated with the equation t₁/₂ = 0.693/B, where B is the terminal elimination rate constant. Cₘₐₓ and the time of their occurrence (Tₘₐₓ) were read directly from the observed data. The area under the plasma concentration-time curve (AUC) was obtained by the trapezoidal rule up to the last datum point and then extrapolated to infinity with the following formula: CₘₐₓB, where Cₘₐₓ is the last measured concentration-time point. The total systemic clearance (CLR) was calculated as CLR = dose/\(AUC_{\text{total}}\). The apparent volume of distribution at steady state (V₅₀) was calculated as \(V₅₀ = \frac{[dose \times (AUMC/AUC)^2]}{[dose \times (T/2) \times AUC]}\), where AUMC is the area under the movement curve and T is the duration of the infusion. Absolute bioavailability (F) was calculated as \(F = \frac{\text{AUC}}{\text{AUC}_\text{O}} \times \frac{\text{dose}_\text{O}}{\text{dose}_\text{i}}\), where \(\text{AUC}_\text{O}\) and \(\text{AUC}_\text{I}\) are oral and iv in trafficking. The proportion of unchanged fleroxacin and metabolites excreted in the urine was calculated as follows: % excreted = \(\frac{A_i \times 100}{A_d}\), where \(A_d\) is the total amount of unchanged drug or metabolite excreted in the urine. It was assumed that the amount of drug and/or metabolites eliminated after the 96-h collection period was negligible, i.e., \(X_{u,96} = X_u\), where \(X_u\) is the total amount of fleroxacin excreted in urine. The renal clearance (CLR) was computed as \(\text{CLR} = \frac{X_{u,96}}{\text{AUC}_{\text{O,u,96}}}\). The clearances of the metabolites formed (CLR of metabolites) were obtained with the equation \(\text{CLR} = \frac{X_u}{\text{AUC}_{\text{O,u,96}}}\), where \(X_u\) represents the total amount of metabolite excreted in the urine. It was assumed that all of the metabolite formed was excreted in the urine.

Statistical analysis. Demographic data and baseline characteristics were analyzed by a one-way analysis of variance. A two-way analysis of variance with repeated measures for random study design (Statistical Analysis System) was used to determine the statistical significance of pharmacokinetic parameter differences between and within groups (i.e., healthy subjects versus subjects with cirrhosis and no ascites and versus subjects with cirrhosis and ascites) and treatments (i.e., oral versus i.v. administration). A P value of <0.05 was considered statistically significant (2). Geometric regression was used to correlate the CLR of the metabolites with antipyrine clearances from the same subjects (17).

### Table 2. Summary of demographic data and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy subjects (n = 12)</th>
<th>Without ascites (group A) (n = 6)</th>
<th>With ascites (group B) (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52 ± 10</td>
<td>54 ± 9</td>
<td>58 ± 8</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>86 ± 13</td>
<td>78 ± 7</td>
<td>77 ± 9</td>
</tr>
<tr>
<td>Ht (cm)</td>
<td>179 ± 11</td>
<td>176 ± 4</td>
<td>177 ± 5</td>
</tr>
<tr>
<td>Antipyrine clearance (liters/h)</td>
<td>3.4 ± 1.1</td>
<td>3.0 ± 1.1</td>
<td>1.0 ± 0.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Creatinine clearance (liters/h)</td>
<td>6.0 ± 1.3</td>
<td>6.1 ± 1.3</td>
<td>4.3 ± 1.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Serum creatinine (μmol/liter)</td>
<td>97 ± 13</td>
<td>82 ± 17</td>
<td>91 ± 18</td>
</tr>
<tr>
<td>Albumin (g/liter)</td>
<td>46 ± 3</td>
<td>43 ± 3</td>
<td>33 ± 7&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bilirubin (μmol/liter)</td>
<td>10 ± 3</td>
<td>13 ± 6</td>
<td>30 ± 22&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>SGOT (U/liter)</td>
<td>23 ± 9</td>
<td>23 ± 9</td>
<td>50 ± 9&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>12 ± 1</td>
<td>13 ± 1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14 ± 2&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> P < 0.01 versus healthy subjects.  
<sup>b</sup> P < 0.05 versus healthy subjects.  
<sup>c</sup> P < 0.001 versus healthy subjects.

### RESULTS

All of the 24 enrolled subjects completed the study. One subject in cirrhotic group B received only 320 mg of the fleroxacin infusion owing to displacement of the venous catheter. Six of the 12 cirrhotic subjects (three each in groups A and B) suffered from alcohol-related liver cirrhosis, and 10 were taking concomitant medications, the most common being diuretics, laxatives, and vitamins. None of the subjects was actively drinking during the study. Three of the cirrhotic subjects had a diagnosis of liver cirrhosis confirmed by biopsy. In the other subjects, diagnosis was made on the basis of medical history, physical examination, and laboratory evaluation.

Table 2 summarizes the demographic data and baseline characteristics of the subjects. Subjects were well matched for age, height, and weight (P > 0.05). The subjects in cirrhotic group A (ascites absent) had baseline characteristics similar to those of the subjects in the healthy volunteer group, except for a statistically significant increase in the prothrombin time (P < 0.05). The subjects in cirrhotic group B (ascites present) had baseline characteristics similar to those of the subjects in the healthy volunteer group, except for a statistically significant increase in the prothrombin time (P < 0.05). The subjects in cirrhotic group B (ascites present) had significantly lower antipyrine clearance (P < 0.01), creatinine clearance (P < 0.05), and serum albumin (P < 0.0001) and significantly higher serum bilirubin (P < 0.05), serum glutamic oxalacetic transaminase (SGOT) (P < 0.0001), and prothrombin time (P < 0.01) than did the subjects in the healthy volunteer group and in the subjects in cirrhotic group A, respectively.

One subject from each study group experienced a moderate to severe headache after the oral administration of fleroxacin; this effect was possibly related to the fleroxacin. One subject in cirrhotic group B developed mild pruritus at the injection site after receiving i.v. fleroxacin; this effect was probably related to the drug treatment. None of these adverse events resulted in discontinuance or dose adjustment.
TABLE 3. Summary of pharmacokinetic parameters of fleroxacin and its two major metabolites

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy volunteers (n = 12)</th>
<th>Cirrhotic subjects</th>
<th>Data (mean ± SD) for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
<td>i.v.</td>
<td>Group A (n = 6)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/liter)</td>
<td>5.4 ± 2.0</td>
<td>4.2 ± 0.8</td>
<td>6.1 ± 1.6</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2.2 ± 3.2</td>
<td>1.8 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fleroxacin</td>
<td>15.0 ± 1.9</td>
<td>14.1 ± 1.8</td>
<td>15.3 ± 2.4</td>
</tr>
<tr>
<td>N-Demethyl fleroxacin</td>
<td>13.6 ± 2.7</td>
<td>13.7 ± 3.4</td>
<td>13.4 ± 3.3</td>
</tr>
<tr>
<td>Fleroxacin N-oxide</td>
<td>11.6 ± 3.4</td>
<td>11.3 ± 2.4</td>
<td>14.6 ± 3.1</td>
</tr>
<tr>
<td>F (%)</td>
<td>0.13 ± 11</td>
<td>0.10 ± 7</td>
<td>0.05 ± 3.8</td>
</tr>
<tr>
<td>V&lt;sub&gt;ss&lt;/sub&gt; (liters)</td>
<td>41.2 ± 9.2</td>
<td>36.2 ± 7.2</td>
<td>39.7 ± 10.9</td>
</tr>
<tr>
<td>Urinary excretion (0 to 96 h) (%)</td>
<td></td>
<td>5.9 ± 1.7</td>
<td>5.0 ± 1.3</td>
</tr>
<tr>
<td>CL&lt;sub&gt;F&lt;/sub&gt; (liters/h)</td>
<td>3.5 ± 0.9</td>
<td>3.2 ± 0.9</td>
<td>3.9 ± 1.6</td>
</tr>
<tr>
<td>Fleroxacin</td>
<td>2.7 ± 0.8</td>
<td>2.9 ± 0.8</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>N-Demethyl fleroxacin</td>
<td>11.8 ± 3.6</td>
<td>13.0 ± 3.8</td>
<td>13.8 ± 5.4</td>
</tr>
<tr>
<td>Fleroxacin N-oxide</td>
<td>10.7 ± 4.1</td>
<td>11.2 ± 3.4</td>
<td>12.1 ± 3.3</td>
</tr>
<tr>
<td>CL&lt;sub&gt;ex&lt;/sub&gt; (liters/h)</td>
<td>0.26 ± 0.11</td>
<td>0.27 ± 0.07</td>
<td>0.33 ± 0.12</td>
</tr>
<tr>
<td>Fleroxacin N-oxide</td>
<td>0.23 ± 0.08</td>
<td>0.22 ± 0.07</td>
<td>0.21 ± 0.07</td>
</tr>
<tr>
<td>Fleroxacin N-oxide</td>
<td></td>
<td></td>
<td>0.14 ± 0.08c</td>
</tr>
</tbody>
</table>

<sup>a</sup> P < 0.001 versus healthy subjects.
<sup>b</sup> Five subjects were included because of incomplete i.v. administration of fleroxacin to one subject.
<sup>c</sup> P < 0.01 versus healthy subjects.
<sup>d</sup> P < 0.05 versus healthy subjects.

The key pharmacokinetic parameters, expressed as means ± standard deviations, are shown in Table 3.

(i) Parent drug. There was no statistically significant difference between treatment groups, i.e., the route of administration did not significantly alter the pharmacokinetic parameters of the parent drug within the same patient group. Also, the influence of treatment (i.v. versus oral) or the sequence of drug administration on the parameters did not vary with the choice of patient groups. In all three groups, fleroxacin was completely absorbed and similar C<sub>max</sub> were achieved approximately 2 h after oral administration (for F, C<sub>max</sub> and t<sub>max</sub>, P > 0.05). The V<sub>ss</sub> values were almost identical in all three study groups (P > 0.05). The t<sub>1/2</sub> values did not differ between the healthy volunteer group and cirrhotic group A (P > 0.05). The t<sub>1/2</sub>, which was significantly lower in cirrhotic group B than in healthy subjects (P < 0.001) and cirrhotic group A (P < 0.001). The CL<sub>F</sub> was only moderately lower in cirrhotic group A than in healthy volunteers (P > 0.05). However, the CL<sub>F</sub> was significantly lower in cirrhotic group B than in healthy volunteers (P < 0.001) and cirrhotic group A (P < 0.01). The average percentage of unchanged fleroxacin excreted in the urine ranged from 32.1 to 41.2% in all three groups (P > 0.05). The CL<sub>F</sub>, which was lower in all liver cirrhosis patients; however, only in the presence of ascites was this reduction significant (P < 0.001).

(ii) N-Demethyl fleroxacin. The t<sub>1/2</sub> of N-demethyl fleroxacin was significantly longer in cirrhotic group B than in healthy controls and cirrhotic group A (P < 0.001). The average percentage of N-demethyl fleroxacin excreted in the urine ranged from 4.0 to 5.9% in all three groups (P > 0.05). The CL<sub>F</sub> of this metabolite was significantly lower in cirrhotic group B than in healthy subjects (P < 0.01) and cirrhotic group A (P < 0.05). Also, the CL<sub>F</sub> was significantly lower in cirrhotic group B than in healthy volunteers and cirrhotic group A (P < 0.01). Figure 1 shows that the CL<sub>F</sub> of N-demethyl fleroxacin correlated well with the antipyrine clearance from the same subjects (r = 0.718; P < 0.001).

(iii) Fleroxacin N-oxide. The t<sub>1/2</sub> of fleroxacin N-oxide in cirrhotic group B was significantly lower than those in healthy volunteers (P < 0.001) and cirrhotic group A (P < 0.01). The average percentage of fleroxacin N-oxide excreted in the urine ranged from 3.1 to 4.3% in all three groups (P > 0.05). The CL<sub>F</sub> of this metabolite was lower in cirrhotic group B than in healthy subjects (P < 0.05) and cirrhotic group A (P > 0.05). The CL<sub>F</sub> was significantly lower in cirrhotic group B than in healthy subjects (P < 0.001) and cirrhotic group A (P < 0.01). Figure 1 shows that the CL<sub>F</sub> of N-demethyl fleroxacin correlated well with the antipyrine clearance from the same subjects (r = 0.718; P < 0.001).
cirrhotic group B than in healthy controls ($P < 0.01$). The $CL_F$ of fleroxacin N-oxide did not correlate well with the antipyrine clearance from the same subjects ($r = 0.295; P > 0.05$) (Fig. 2).

**DISCUSSION**

This study was undertaken to examine the pharmacokinetic changes of fleroxacin, a fluoroquinolone characterized by a long $t_{1/2}$ and a high bioavailability, in cirrhotic patients with and without ascites.

As shown previously (24), the route of administration (i.v. versus oral) did not significantly influence fleroxacin disposition in any of the three study groups. The pharmacokinetic parameters determined in this study for healthy controls were in good agreement with previously published data (7, 11, 21, 26). The percentage of unchanged fleroxacin excreted in the urine in this study appeared to be consistently lower than that reported by Weidekamm et al. (24, 25). Other investigators have reported lower or higher values for the percentage of unchanged fleroxacin excreted (7, 11, 22). The lower urinary recovery of fleroxacin in our investigation is unexplained at this point. However, the $CL_R$ determined in this study was consistent with previously published results (19).

Overall, cirrhotics without ascites (cirrhotic group A) had baseline characteristics and pharmacokinetic parameters similar to those of healthy controls. Group A cirrhotics had only a significantly higher prothrombin time. However, we would expect a reduced production of proteins, including several clotting factors, in liver disease.

Cirrhotics with ascites (cirrhotic group B) showed signs of more advanced liver disease with less hepatic reserve, illustrated by significantly less hepatic microsomal enzyme activity (i.e., significantly lower antipyrine clearance), significantly lower renal function (i.e., significantly lower creatinine clearance) and albumin levels, significantly prolonged prothrombin time, and significantly higher serum bilirubin and SGOT levels than in the healthy population. These disease-related differences in hepatic metabolic activity and renal function caused significant changes in the pharmacokinetic parameters in cirrhotic group B compared with healthy controls and cirrhotic group A.

The $CL_S$ of fleroxacin was decreased by more than 50% and resulted in approximately a twofold prolongation of the fleroxacin $t_{1/2}$ in cirrhotic group B compared with healthy controls and cirrhotic group A. This reduction in the $CL_S$ can be attributed principally to the substantially lower $CL_R$ in cirrhotic group B than in healthy controls. Renal excretion in patients with ascites reflected the normal quantitative metabolite pattern: 4.6 to 5.0% of the administered fleroxacin dose was excreted as the N-demethyl metabolite, and 3.9 to 4.3% was excreted as the N-oxide metabolite. However, the $CL_R$ and the $CL_F$ values of both metabolites were significantly lower in cirrhotic group B than in healthy controls because of compromised renal and hepatic function. Primary biliary cirrhosis in the early stages involves predominantly the periportal region and results in a relative sparing of the oxidative system. However, more advanced stages of cirrhosis, as present in our group B patients, are associated with an impairment of oxidative pathways. A 30 to 50% decrease in cytochrome P-450 levels is seen in active liver cirrhosis (9). Consequently, the $t_{1/2}$ values of both metabolites were two times longer in cirrhotic group B than in healthy controls. This change in the $t_{1/2}$ values of the metabolites occurred in parallel with the change in the $t_{1/2}$ of fleroxacin. Therefore, the elimination of the two main metabolites appeared to be formation rate limited in all three study groups (Fig. 3A to C).

It has been hypothesized that two different enzyme systems are involved in the metabolism of fleroxacin (21). Demethylation is predominantly caused by cytochrome P-450, whereas N oxidation of xenobiotics containing nucleophilic nitrogen atoms, as found in fleroxacin, is dependent on flavoproteins. It is possible that flavoprotein activity is influenced to a lesser degree by liver cirrhosis than is the P-450 mixed-function oxidase system of the liver (9, 13). Our study reflects the involvement of two different mechanisms of metabolism of fleroxacin, as shown by the presence and absence of a relationship between metabolite $CL_F$ and antipyrine clearance from the same subjects (Fig. 1 and 2). The $CL_F$ of N-demethyl fleroxacin correlated significantly with the antipyrine clearance ($r = 0.718; P < 0.001$), suggesting the involvement of the cytochrome P-450 enzyme system. However, there was no relationship between the $CL_F$ of fleroxacin N-oxide and the antipyrine clearance ($r = 0.295; P > 0.05$), implying that N-oxide formation may not be due to P-450 metabolism. When patients with ascites were considered alone in the regression analysis, they showed a better relationship between the antipyrine clearance and the $CL_F$ of fleroxacin N-oxide. All patients with ascites had an antipyrine clearance of less than 2 liters/h and were compromised in their ability to form the N-oxide metabolite as well as the N-demethyl metabolite. Therefore, our results propose that the metabolic pathway of the N-oxide metabolite may be affected by severe liver disease.

In all three study groups, $CL_R$ accounted for approximately 40% and $CL_F$ accounted for 7 to 10% of the $CL_S$ of fleroxacin, leaving approximately 50% of fleroxacin clearance being unaccounted for. This observation is consistent with those of other studies (7, 22, 24, 26). Since the calculation of $CL_F$ is done under the assumption of complete recovery of the metabolite and, in the case of fleroxacin, only 50% of the $CL_F$ is accounted for, one should be cautious when interpreting $CL_F$.

In summary, fleroxacin was eliminated to a large extent unchanged via renal excretion, and only a negligible amount of parent drug was metabolized by the liver to N-demethyl fleroxacin and fleroxacin N-oxide. No major changes in the

![Graph](https://example.com/graph.png)
pharmacokinetic parameters of fleroxacin occurred in cirrhosis without ascites. The CL\textsubscript{R} of fleroxacin was significantly lower in cirrhosis with ascites than in healthy controls and cirrhotics without ascites, partly because of significantly lower CL\textsubscript{R} and CL\textsubscript{F} in this patient population. Our study results indicate that no dosage changes are necessary in cirrhotics without ascites. In cirrhotics with ascites, the loading dose does not require adjustment; however, a reduced daily maintenance dose, i.e., 200 mg once daily instead of 400 mg once daily, is recommended.

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REFERENCES