Pharmacokinetics of Rufloxacin in Patients with Impaired Renal Function

GREG PERRY, TIM G. K. MANT, PAUL J. MORRISON, STEVEN SACKS, JOCELYN WOODCOOK, RICHARD WISE, AND BRUNO P. IMBIMBO

The Renal Unit, Guy’s Hospital, London, and Department of Medical Microbiology, Dudley Road Hospital, Birmingham, United Kingdom, and Mediolanum Farmaceutici, Milan, Italy

Received 8 May 1992/Accepted 25 January 1993

The pharmacokinetics of rufloxacin were investigated in normal subjects and in patients with various degrees of renal failure after the administration of a single oral 400-mg dose. Twenty-four subjects were classified by glomerular filtration rate (GFR) normalized for body surface area. Group 1 subjects had GFRs of >80 ml/min, group 2 subjects had GFRs of 30 to 80 ml/min, group 3 subjects had GFRs from 8 to 29 ml/min, and group 4 subjects had GFRs of <8 ml/min. The patients in group 4 were on continuous peritoneal dialysis or underwent hemodialysis 48 h after dosing. Plasma and urinary rufloxacin concentrations were determined by high-performance liquid chromatography. A two-compartment model was used to calculate rufloxacin pharmacokinetic parameters. Apparent total body clearance of the drug was linearly related to GFR (r = 0.696; P < 0.01). The elimination half-life increased proportionally with the severity of renal impairment, with values of 30 ± 3, 36 ± 5, and 44 ± 3 h in groups 1, 2, and 3, respectively. In patients undergoing dialysis (group 4), the elimination half-life (27 ± 4 h) was not significantly different from that of controls, probably because of the clearance effect of dialysis. The renal clearances of rufloxacin decreased linearly with the decrease in GFR (r = 0.842; P < 0.01). The 0- to 96-h cumulative urinary recoveries of rufloxacin were 33 ± 3, 27 ± 3, 14 ± 2, and 1 ± 1% of the administered dose in groups 1, 2, 3, and 4, respectively. In patients with moderate renal failure, dosage adjustment of rufloxacin is not needed. The rufloxacin dose interval should be prolonged to 48 h as the GFR falls below 30 ml/min/1.73 m².

Rufloxacin is a new oral fluoroquinolone characterized by a broad spectrum of activity against gram-negative and gram-positive aerobic bacteria (4). The antibacterial activity of rufloxacin is roughly comparable to that of norfloxacin in vitro (17, 24) and that of ciprofloxacin in vivo (21). Pharmacokinetic studies in both healthy subjects (11, 13, 15, 25) and patients with lower respiratory tract infections (7, 22) showed that rufloxacin is eliminated slowly, with a plasma half-life (t1/2) of about 30 h. The drug penetrates well into most tissues (2, 14, 16, 25), and because of its long t1/2, it can be used for once-a-day treatment of urinary (18) and respiratory (8) tract infections.

The aim of the present study was to determine the pharmacokinetics of rufloxacin following a single 400-mg oral dose in patients with various degrees of renal failure. (Part of this work was presented at the 28th Annual Scientific Meeting of the Australian and New Zealand Society of Nephrology, Melbourne, 26 to 28, February 1992 [abstr. 59].)

MATERIALS AND METHODS

Subjects. Twenty-four subjects (12 males and 12 females) with renal function ranging from normal to end-stage renal failure participated in the study, after informed written consent was obtained. They were divided into four groups according to their glomerular filtration rate (GFR) normalized for body surface area: group 1 subjects (n = 6) had GFRs of >80 ml/min, group 2 subjects (n = 6) had GFRs of 30 to 80 ml/min, group 3 subjects (n = 8) had GFRs of 8 to 29 ml/min, and group 4 subjects (n = 4) had GFRs of <8 ml/min. GFR was measured by determining 51Cr-EDTA clearance (5). GFR estimations were not performed in patients in group 4 because they had progressed to end-stage renal failure and were on maintenance dialysis. Two were on hemodialysis (HD) and two were on continuous ambulatory peritoneal dialysis (CAPD). Three of them were anuric. The patients on HD were not dialyzed until 48 h following dosing, while the patients on CAPD continued their usual exchanges during the study without interruption. Initial creatinine clearance (CLCR) values were estimated by the equation of Cockcroft and Gault (6). Minor alterations in patients’ usual medications were made in the study. Beta-blockers were withheld for 24 h prior to dosing and during the study period because of their potential effect on hepatic blood flow. Calcium carbonate, prescribed as a phosphate-binding agent, was also withheld in case it prevented the absorption of the test drug.

Procedure. The protocol of the study was approved by the Ethics Committee of Guy’s Hospital. All subjects were confined to the Drug Research Unit of Guy’s Hospital and were under continuous supervision from 12 h before drug administration until 96 h after the dose. Before entering into the study, volunteers underwent a complete screening visit including physical examination and medical history, hematology, plasma chemistry, urinalysis, blood and urine drug screening, and electrocardiogram. Blood and urine tests as well as electrocardiograms were performed predose and at 24 and 96 h postdose. Body temperature was obtained predose and at 96 h postdose. Standing and supine blood pressure and heart rate were measured predose and at 2, 4, 8, 24, 48, 72, and 96 h postdose. All subjects fasted overnight before the study and for 4 h after rufloxacin administration. They were given a single oral dose of 400 mg of rufloxacin. Four hours after administration, all subjects had breakfast; thereafter, food and drink were allowed ad libitum. Blood
specimens were collected predose and then at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 h postdose. Plasma, which was separated by centrifugation, was frozen at −20°C until it was analyzed. Urine was collected predose (−2 to 0 h) and over the intervals of 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, and 72 to 96 h postdose. Sample aliquots of the urine collections were frozen at −20°C until they were analyzed. Subjects were monitored for adverse events and used diaries to record any subjective effects.

**Assays.** Plasma and urine samples were analyzed by high-performance liquid chromatography (HPLC). The HPLC method used for assaying the serum samples employed a Hamilton 10-μL PRP1 column (150 by 4.1 mm; Anachem Ltd.). Detection was by fluorescence detection with excitation at 294 nm and with a 475-nm bandpass filter. The lower limit of sensitivity was 0.5 μg/ml. The intrarun (within-run) coefficient of variation was 3.5% for 2.5 μg/ml (n = 6) and 5.9% for 5 μg/ml (n = 5). The interrun (between-run) coefficient of variation was 2.4%. The HPLC method used for assaying the urine samples employed a Supelco 5-μL Supellex pKb-100 column (150 by 4.6 mm; Supelchem U.K. Ltd.), and detection was by a fluorescence detector set to 294 nm and with a 550-nm longpass filter. The lower limit of sensitivity was 0.3 μg/ml. The intraand interrun coefficients of variation were 2.2% and 5.0% for 5 μg/ml, respectively.

**Pharmacokinetic analysis.** Pharmacokinetic parameters were calculated by fitting individual plasma concentration datum points for each subject to a two-compartment open model, with first-order input and elimination, corresponding to the following equation: $C_p(t) = Ae^{-at} + Be^{-bt} + Ce^{-kt}$, in which $C_p(t)$ (in micrograms per milliliter) is the estimated concentration of rufloxacin in plasma at time $t$, $A$ is the zero time intercept of the distribution (α) phase, $B$ is the zero time intercept for the elimination (β) phase, $C$ is equal to $-(A + B)$, and $k_d$ is the absorption rate constant. Data were weighted according to the inverse of the observed value squared. The two-compartment model was selected by using the Imbibo index (12). Standard curve-stripping procedures were used to obtain initial estimates of $A$, $B$, $C$, $\alpha$, $\beta$, and $k_d$, while final estimates of the parameters were obtained by nonlinear least-squares regression analysis. Calculations were performed with the program TOPFIT (10). The absorption $t_{1/2A}$ ($t_{1/2A}$ was calculated as $\ln(2)/k_d$, the distribution $t_{1/2D}$ ($t_{1/2D}$ was calculated as $\ln(2)/\alpha$, and the elimination $t_{1/2E}$ ($t_{1/2E}$ was calculated as $\ln(2)/\beta$). The area under the concentration-time curve from time zero to infinity ($\text{AUC}_{0-\infty}$) was calculated as $A/\alpha + B/\beta - C/k_d$, and the apparent volume of distribution ($\text{V}_{\text{area}}$) was expressed as $\text{dose}/(\text{AUC}_{0-\infty} \cdot \beta)$. The maximum drug concentration ($C_{\text{max}}$) and the time to reach $C_{\text{max}}$ ($T_{\text{max}}$) were obtained from the inspection of individual data. The AUC from time zero to 96 h ($\text{AUC}_{0-96}$) was calculated by the linear trapezoidal rule method. Apparent total body clearance ($\text{CL/F}$) was calculated as dose/$\text{AUC}_{0-\infty}$.

**Renal clearance** ($\text{CLR}$) was calculated by dividing the amount of drug excreted in the urine during the 96 h by AUC$_{0-96}$. Nonrenal clearance (CL$_{\text{NR}}$) was calculated as $\text{CL/F} - \text{CLR}$. The percentage of the drug excreted in urine was calculated by dividing the total amount excreted in urine during the 96 h by the dose.

**Statistics.** The significance of differences between the pharmacokinetic parameters of different groups was examined by analysis of variance. Post hoc tests were conducted with linear contrast. The number of post hoc comparisons was confined to the degrees of freedom for the significant effects. As a result, the nominal risk of a type I error (α) of the separate tests is comparable to that of the overall analysis of variance (1, 3). The rejection of a null hypothesis was set at α = 0.05 (two-sided test). The significance level was $P < 0.05$ (two-sided test). Statistical power ($1 - \beta$, where $\beta$ is the risk of a type II error) to detect a 30% difference between pharmacokinetic parameters of the two groups, defined as clinically significant, was calculated at the $\alpha = 0.05$ level. Calculations were performed with the NWA STATPAK statistical package (20). Results are expressed as means ± standard errors of the mean (SEMs).

## RESULTS

There were no statistically significant differences in mean age, height, weight, or body surface area between the patients in the four renal function groups (Table 1). Patients in renal function groups 1, 2, 3, and 4 had GFRs of 104 ± 6, 54 ± 7, 16 ± 3, and 0 ± 0 ml/min/1.73 m$^2$, respectively. CL$_{\text{CR}}$ was 92 ± 9, 50 ± 4, 17 ± 5, and 8 ± 2 ml/min/1.73 m$^2$ for the subjects in groups 1, 2, 3, and 4, respectively (Table 1). There was a strict linear relationship ($r = 0.972; P < 0.01$) between GFR and CL$_{\text{CR}}$.

**Pharmacokinetics.** Mean plasma rufloxacin concentration-versus-time curves for the four groups are shown in Fig. 1. Mean pharmacokinetic parameters are listed in Table 2. The values of $t_{1/2A}$ and $T_{\text{max}}$ did not change significantly among the four groups, indicating that the rate of absorption of the drug was not affected by renal function. The mean $C_{\text{max}}$ was 4.29 ± 0.43 μg/ml in the control group and increased significantly to 6.76 ± 0.32 μg/ml only in the group of patients on dialysis. The rate of distribution ($t_{1/2D}$) of rufloxacin was not influenced by renal function, with the mean value being about 30 min. $V_{\text{area}}$ was 104 ± 6 liters in controls and did not differ significantly in patients in groups 2 and 3. However, patients in group 4 had significantly lower values (69 ± 10 liters) compared with those for controls. The elimination of the drug was significantly influenced by renal function. CL$_{F}$ decreased linearly ($r = 0.696; P < 0.01$) with the decrease in renal function (Fig. 2). The mean $t_{1/2E}$ was 30 ± 3 h in normal subjects and increased to 36 ± 5 and 44 ± 3 h in subjects in groups 2 and 3, respectively. In group 4 patients, which included patients on dialysis, $t_{1/2E}$ (27 ± 4 h) did not change significantly from those for controls. Both AUC$_{0-96}$ and AUC$_{0-\infty}$ were increased by renal impairment.

### TABLE 1. Main demographic and biological characteristics of the four groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Ht (cm)</th>
<th>Wt (kg)</th>
<th>GFR (ml/min/1.73 m$^2$)</th>
<th>CL$_{\text{CR}}$ (ml/min/1.73 m$^2$)</th>
<th>SCR (mmol/liter)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40 ± 7</td>
<td>172 ± 3</td>
<td>70 ± 4</td>
<td>104 ± 6</td>
<td>92 ± 9</td>
<td>84 ± 7</td>
</tr>
<tr>
<td>2</td>
<td>55 ± 3</td>
<td>166 ± 3</td>
<td>73 ± 7</td>
<td>54 ± 7</td>
<td>50 ± 4</td>
<td>141 ± 15</td>
</tr>
<tr>
<td>3</td>
<td>45 ± 5</td>
<td>170 ± 4</td>
<td>69 ± 3</td>
<td>16 ± 3</td>
<td>17 ± 5</td>
<td>605 ± 99</td>
</tr>
<tr>
<td>4</td>
<td>39 ± 6</td>
<td>164 ± 5</td>
<td>59 ± 8</td>
<td>0 ± 0</td>
<td>8 ± 2</td>
<td>1,012 ± 254</td>
</tr>
</tbody>
</table>

* Values are means ± SEMs.

* SCR, serum creatinine level.
FIG. 2. Regression relationship between GFR and the CL/F of rufloxacin.

The pharmacokinetics of quinolones have been extensively studied in patients with impaired renal function (for reviews, see references 9 and 19). Quinolones that are excreted predominantly by the kidneys (ofloxacin) required dose reduction even in patients with moderate renal impairment (GFR, <50 ml/min). Quinolones cleared by both renal and hepatic mechanisms (norfloxacin, ciprofloxacin, enoxacin, floxacin, lomefloxacin, temafloxacin) need dose adjustment only in patients with severe GFR reductions (<30 ml/min). For quinolones cleared predominantly by the liver (pefloxacin, difloxacin), dose alteration is unnecessary even in patients with severe renal impairment.

The results of the present study indicate that rufloxacin elimination is substantially influenced by the status of renal function. The drug is slowly eliminated from the body. The mean t1/2β in subjects with normal renal function was 30 h. Similar values after administration of a single dose were also observed in other studies with healthy subjects (11, 25). The t1/2β of rufloxacin increased in relation to the degree of renal failure, reaching values about 1.5 times those in normal subjects, in patients with GFRs of less than 30 ml/min/1.73

experience nausea and vomiting, but symptoms were time-
related with the drug administration in only two of them. Other adverse effects were only of mild intensity, with no differences between the four groups. No significant changes in biochemical or hematological variables were observed after rufloxacin treatment. No drug crystals were found in any of the urine samples from the subjects.

DISCUSSION

There was a significant linear relationship (r = 0.842; P < 0.01) between GFR and CLR. CLR passed from 72.7 ± 2.3 ml/min in control subjects to 0.1 ± 0.1 ml/min in patients in group 4. Maximum urinary rufloxacin concentrations decreased from 72.7 ± 8.5 µg/ml in control subjects to 1.9 ± 1.9 µg/ml in group 4 subjects (8- to 12-h interval) (Table 3). The 0- to 96-h cumulative urinary recoveries of rufloxacin were 33% ± 3%, 27% ± 3%, 14% ± 2%, and 1% ± 1% of the administered dose in groups 1, 2, 3, and 4, respectively. CLNR was not affected by the renal status of the patients.

Safety. Rufloxacin was generally well tolerated. The most common complaints during the study were headache and gastrointestinal disturbances. Three patients in group 3

TABLE 2. Pharmacokinetic parameters of rufloxacin for the four groups

<table>
<thead>
<tr>
<th>Group</th>
<th>t1/2α (h)</th>
<th>T_max (h)</th>
<th>Cmax (µg/ml)</th>
<th>t1/2α (h)</th>
<th>t1/2β (h)</th>
<th>Vmean/F (liters)</th>
<th>CL/F (ml/min)</th>
<th>CLR (ml/min)</th>
<th>CLNR (ml/min)</th>
<th>AUC0-t (µg·h/ml)</th>
<th>AUC0-∞ (µg·h/ml)</th>
<th>fα (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.90 ± 0.94</td>
<td>3.2 ± 0.3</td>
<td>4.29 ± 0.43</td>
<td>0.46 ± 0.10</td>
<td>29.8 ± 3.2</td>
<td>104 ± 6</td>
<td>44 ± 3</td>
<td>17.1 ± 2.3</td>
<td>27 ± 1</td>
<td>132 ± 9</td>
<td>154 ± 10</td>
<td>32.5 ± 2.5</td>
</tr>
<tr>
<td>2</td>
<td>1.64 ± 0.98</td>
<td>2.8 ± 0.3</td>
<td>4.66 ± 0.37</td>
<td>0.73 ± 0.37</td>
<td>36.4 ± 4.9</td>
<td>100 ± 12</td>
<td>34 ± 2</td>
<td>11.0 ± 1.1</td>
<td>23 ± 2</td>
<td>165 ± 12</td>
<td>199 ± 13</td>
<td>26.9 ± 2.7</td>
</tr>
<tr>
<td>3</td>
<td>1.60 ± 0.54</td>
<td>3.3 ± 0.5</td>
<td>4.32 ± 0.44</td>
<td>0.46 ± 0.12</td>
<td>43.5 ± 2.9</td>
<td>104 ± 8</td>
<td>30 ± 3</td>
<td>5.1 ± 0.8</td>
<td>25 ± 3</td>
<td>189 ± 18</td>
<td>243 ± 26</td>
<td>13.6 ± 1.6</td>
</tr>
<tr>
<td>4</td>
<td>1.97 ± 0.96</td>
<td>3.0 ± 1.2</td>
<td>6.76 ± 0.32a</td>
<td>0.24 ± 0.11</td>
<td>26.6 ± 3.9</td>
<td>69 ± 10</td>
<td>33 ± 5</td>
<td>0.1 ± 0.1</td>
<td>32 ± 5</td>
<td>202 ± 31</td>
<td>219 ± 34</td>
<td>0.5 ± 0.5</td>
</tr>
</tbody>
</table>

Powera | 0.15 | 0.94 | 0.91 | 0.40 | 0.87 | 0.99 | 0.99 | 0.72 | 0.99 | 0.99 | 0.99 | 0.99 |

a Values are means ± SEs. fα, percentage of drug excreted in urine; the definitions of the other abbreviations are given in the text.

b P < 0.05 versus control group.

c Power to detect a significant difference of 30% compared with the value for the control group.
Also, the low value of the CL/F of rufloxacin (45 ml/min in normal subjects) indicates a slow process of elimination of the drug. This value is calculated by assuming 100% rufloxacin bioavailability after oral administration. The oral bioavailability of rufloxacin in humans is not known. Studies in animals (rat, monkey) indicate that it is about 60 to 70% (23). If it is also true that rufloxacin in humans is not completely absorbed after oral administration, the CL/F of rufloxacin in our study would be even lower. The CL/F decreased with the decrease in renal function up to values of about 30 ml/min in groups of subjects with renal impairment. The decrease in CL/F with decreasing renal function can be attributed primarily to a decrease in CLR since the apparent CLNR remained relatively unchanged. CLR was also very low (17 ml/min in control subjects). The plasma protein binding of rufloxacin is about 60%. This suggests that rufloxacin undergoes some renal tubular reabsorption. The renal recycling of rufloxacin may explain the very stable concentration of rufloxacin in urine over time observed in the present study. In subjects with normal renal function, mean concentrations in urine at 0 to 4 h after the dose were 29 μg/ml. At 12 to 24 h, the levels in urine were even higher (68 μg/ml). Three days after the drug administration, the concentrations of rufloxacin in urine were still about 20 μg/ml.

Rufloxacin absorption seemed to be unaffected by renal impairment. Although the point estimate of ka is not robust, peak concentrations in plasma occurred at about 3 h after drug administration in all groups. Although there were no significant differences in t1/2a's between patients with renal impairment and controls, the very low power value for t1/2a implies that more data are needed to test whether this parameter in controls and in patients with renal impairment is statistically equivalent in the range of a 30% difference at α = 0.05. Conversely, there is a certain degree of confidence in stating that the T_max is for controls and patients with decreased renal function were not significantly different, since the power of detecting a 30% difference in the parameter was greater than 0.90.

The mean percentage of rufloxacin recovered in urine (33%) in subjects with normal renal function was in agreement with the results provided by other investigators (11, 25). Urinary recovery of rufloxacin decreased with decreasing renal function, but concentrations of rufloxacin in urine for subjects in groups 1, 2, and 3 exceeded 10 μg/ml 24 h after drug administration (Table 3). These concentrations are greater than the MICS for susceptible strains of *Escherichia coli*, *Proteus* spp., *Neisseria gonorrhoeae*, *Morganella morganii*, *Klebsiella* spp., and *Serratia marcescens* (17, 24).

Plasma drug levels and pharmacokinetic parameters for patients on CAPD and on HD were very similar. In comparison with controls, these patients had higher levels of rufloxacin in plasma (Cmax, AUC0-96, and AUC0-∞) and decreased CL/F. However, the t1/2β for patients on dialysis (27 ± 4 h) was not significantly different from that for controls. Consequently, their *Varea/F* (69 ± 10 liters) was significantly reduced compared with that for controls (104 ± 6 liters). The normal value of t1/2β could be due to the effect of dialysis procedures. Indeed, patients on CAPD continued their usual exchanges during the study without interruption and patients on HD started dialysis 48 h after rufloxacin administration, when the drug had not yet been eliminated by the body. Since an increase in the absorbed extent of the drug in these patients is unlikely, the increase in the AUC seems to be linked to the decrease in the *Varea/F*. However, the mechanism by which dialysis procedures induced this substantial decrease in *Varea/F* remains unclear.

From the results of our study, certain recommendations about the use of rufloxacin in patients with renal failure can be made. In patients with normal renal function, the usual dosage regimen of rufloxacin is 200 mg every 24 h, preceded by a loading dose of 400 mg (8, 18). To maintain levels of drug in plasma similar to those in individuals with normal renal function, a substantial dosage schedule adjustment is not necessary in patients with moderate impaired renal function (GFR, >30 ml/min/1.73 m²). In patients with severe renal failure (GFR, <30 ml/min/1.73 m²), steady-state levels of rufloxacin in plasma in the same range as those in patients with normal renal function can be maintained by prolonging the dose interval up to 48 h.

In conclusion, rufloxacin clearance is significantly affected by renal function, with renal excretion being the primary route of removal. In patients with normal to moderate renal function, 400 mg of rufloxacin every 24 h provides therapeutic and well-tolerated concentrations in plasma. The frequency of rufloxacin administration should be prolonged to 48 h in patients with GFRs of less than 30 ml/min/1.73 m².

### ACKNOWLEDGMENTS

The drug was supplied and the study was supported by a grant from Mediolanum Farmaceutici, Milan, Italy.

### REFERENCES


### TABLE 3. Urinary rufloxacin concentrations for the four groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Conc (μg/ml) at the following time interval (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>29.4 ± 5.4</td>
</tr>
<tr>
<td>4-8</td>
<td>58.3 ± 8.6</td>
</tr>
<tr>
<td>8-12</td>
<td>72.7 ± 8.5</td>
</tr>
<tr>
<td>12-24</td>
<td>67.7 ± 8.6</td>
</tr>
<tr>
<td>24-48</td>
<td>40.3 ± 3.4</td>
</tr>
<tr>
<td>48-72</td>
<td>21.4 ± 3.7</td>
</tr>
<tr>
<td>72-96</td>
<td>12.6 ± 2.0</td>
</tr>
</tbody>
</table>

* Values are means ± SEMs.
RUFLOXACIN PHARMACOKINETICS IN RENAL FAILURE