Effect of Renal Impairment on Distribution of Ofloxacin


Department of Pharmacy and Pharmaceutical Technology, University of Salamanca, and Nephrology Service, University Hospital, Salamanca, Spain

Received 18 April 1989/Accepted 30 October 1989

A study was made of the plasma and distribution kinetics of ofloxacin administered at a dosage of 400 mg orally to a group of healthy volunteers and a group of patients with renal impairment. Blood and blister fluid samples were taken at programmed times from all individuals included in the study. The analytical techniques for the determination of ofloxacin in both fluids were a plate diffusion method and a high-performance liquid chromatographic technique. The fitting of the experimental data to the kinetic model used was done with the help of the AUTOTAN 2 and NONLIN 84 computer programs. In the groups of healthy volunteers, the elimination half-life mean values were found to be 5.1 and 5.9 h in plasma and blister fluid, respectively. The maximum concentration reached in plasma (3.9 μg/ml) proved to be slightly higher than that in interstitial tissue fluid (2.8 μg/ml). In the patients with renal impairment, the maximum concentrations in both plasma and blister fluid were significantly increased, in the order of 5 to 8 μg/ml in the former and 3 to 4 μg/ml in interstitial tissue fluid. The parameters seen to undergo an increase as a result of the renal impairment were the area under the curve of the plasma-time levels, the area under the curve of the blister fluid-time levels, and the elimination half-life in plasma and blister fluid. The degree of absorption and the access capacity of the drug to interstitial tissue fluid remained constant.

Ofloxacin is a fluorinated quinolone that shows an excellent degree of absorption when administered orally and has a good spectrum against gram-positive and gram-negative microorganisms (1, 10, 17). Its activity against bacteria that are difficult to treat, such as Pseudomonas aeruginosa, Haemophilus influenzae, Neisseria gonorrhoeae, and Clostridium perfringens, is comparable to that of other quinolones such as norfloxacin, ciprofloxacin, enoxacin, and pefloxacin (4, 7, 11). Its pharmacokinetic characteristics, which can be summarized as an excellent absorption, wide distribution, and an almost complete absence of metabolism, favor its use in clinical practice. The aim of the present work was to establish the effect of renal impairment on the kinetic behavior of ofloxacin, specifically, its capacity to have access to and remain in blister fluid, which is representative of interstitial tissue fluid.

MATERIALS AND METHODS

Individuals included in the study. Plasma and blister fluid samples were obtained from 18 individuals divided into two groups. The first group was used as a control group and contained nine healthy volunteers (mean creatinine clearance [CLCR], 104.8 ± 23.1 ml/min; mean weight, 61 ± 4.5 kg; mean age, 24.3 ± 12.2 years). The second group was formed of nine patients with renal impairment (mean weight, 67.6 ± 14.5 kg); CLCR values ranged between 2.1 and 63.9 ml/min.

Neither the volunteers nor the renal impairment patients took another drug during the study. Drug administration. All individuals in the study received two 200-mg tablets of ofloxacin orally in 200 ml of water. In all cases, the dose (400 mg) was administered when the patients awoke in the morning and the individuals fasted until 2 h after administration. The subjects had fasted for 12 h with water ad libitum before receiving medication.

Sampling. The biological samples obtained from both the volunteers and the patients with renal impairment were plasma and blister fluid.

The corresponding blood samples taken at programmed times by direct venipuncture of the basilica, antecubital, and radial forearm veins were centrifuged to obtain the plasma samples. After the plasma was separated and the samples were placed in duly labeled tubes, the samples were frozen at −20°C until assay.

Samples of blister fluid were obtained by the method described by Kiistala and Mustakallio (12). The sampling times were as follows. For healthy volunteers, plasma samples were drawn at 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 8.0, 12.0, and 24.0 h, and blister fluid was obtained at 1.5, 2.0, 3.0, 4.0, 8.0, 12.0, and 24.0 h. For patients with renal impairment, plasma samples were taken at 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 12.0, 24.0, and 48.0 h, and blister fluid was obtained at 2.0, 4.0, 6.0, 12.0, 24.0, 36.0, and 48.0 h.

The plasma samples were divided into two samples; one was evaluated by bioassay, and the other was evaluated by high-performance liquid chromatography.

Analytical techniques. (i) Bioassay. A microbiologic plate diffusion method with Bacillus subtilis ATCC 6633 as the assay organism was used. The growth medium was antibiotic medium no. 5 (Difco Laboratories).

(ii) Chromatographic technique. (a) Treatment of samples. To 1 ml of plasma were added 100 μl of 0.05 N NaOH, 0.5 ml of a buffer solution (pH 7.4), and 100 μl of a solution of norfloxacin used as an internal standard. The mixture was shaken vigorously for 30 s, after which 8 ml of methylene chloride was added. Suitably closed, the tubes were shaken for 15 min and centrifuged at 4,000 rpm; 7 ml of the organic phase was removed and brought to dryness under a stream of nitrogen, keeping the tubes at 40°C in a water bath. The dry residue was redissolved in 150 μl of the mobile phase used for chromatography, and 100 μl was injected into the chromatograph.

(b) Chromatographic conditions. A Varian 5000 chromatograph was used; it was connected to a UV detector with a
variable wavelength adjusted to $\lambda = 270$ nm, a 12-cm-long column (4-mm internal diameter) packed with the reverse phase (Nucleosil 5-C18), and a mobile phase prepared as follows: a sufficient amount of tetrabutyl ammonium sulfate was added to a solution of ortho-phosphoric acid adjusted to pH 3.0 to ensure a final concentration of 6%, redressing the pH to 3.0.

To calculate the concentrations of ofloxacin in the problem samples, the internal standard method was used (8). The detection limit of the technique proved to be 0.1 $\mu$g/ml, with a variation coefficient of $<$10%. The variation coefficient was assayed at a concentration of 5 $\mu$g/ml.

There was no statistical difference between the analytical techniques (21).

Kinetic analysis. To characterize the time course of the levels in plasma as a function of time, a single-compartment kinetic model was used with first-order absorption processes. The time course of the levels in plasma was found to fit the following equation:

$$C_P = \frac{D}{V} \frac{k_a}{k_a - k_{el}} (e^{-k_{el}t} - e^{-k_at})$$

(1)

where $C_P$ is the plasma concentration at time $t$; $D$ is the dose administered; $V$ is the volume of distribution; $k_a$ is the absorption constant, and $k_{el}$ is the elimination constant from plasma. We assume that ofloxacin has a bioavailability of 100% when administered orally, so factor $F$ was not included in equation 1. Several studies done with this quinolone by other authors indicate that its oral absorption is rapid and complete (9, 13, 15).

In the present study, for treatment of the experimental data, we used the open single-compartment kinetic model in both the healthy volunteers and the patients with renal impairment. According to the selection criteria used to determine the goodness of fit of the experimental data (22), the best model for patients with CLCRs of 5 and 24.5 ml/min, respectively, proved to be an open two-compartment kinetic model. However, in these patients we forced the data fitting to a single-compartment model to provide a homogeneous treatment for all results and hence facilitate comparison of the parameters estimated.

To calculate the degree of absorption of ofloxacin in each renally impaired patient with respect to the control group of healthy volunteers, a comparison was made between the areas under the plasma level-time curve, suitably corrected by their corresponding elimination half-life (3) by the following equation:

$$f_{\text{plasma}} = \frac{\text{AUC}_{0-\infty} \text{ RI}}{\text{AUC}_{0-\infty} \text{ C}} \times \frac{t_{1/2} \text{ C}}{t_{1/2} \text{ RI}}$$

(2)

where AUC$_{0-\infty}$ RI is area under the plasma level-time curve in each renally impaired patient; AUC$_{0-\infty}$ C is median value of the area under the plasma level-time curve established for the group of healthy volunteers; $t_{1/2}$ RI is plasma elimination half-life in each renally impaired patient; and $t_{1/2}$ C is median value of the plasma elimination half-life established for the control group.

Similarly, to know the intrinsic access capacity of ofloxacin to blister fluid in the renally impaired patients with respect to the control group, $f$ was calculated from the data of levels in blister fluid by the following equation:

$$f_{\text{blister}} = \frac{\text{AUC}_{0-\infty} \text{ RI}}{\text{AUC}_{0-\infty} \text{ C}} \times \frac{t_{1/2} \text{ C}}{t_{1/2} \text{ RI}}$$

(3)

Each term of the equation represents the aforementioned parameters but calculated from the levels in blister fluid.

The type of relationship between the $k_a$ of ofloxacin and the CL$_{CR}$ was established by means of regression analysis.

<table>
<thead>
<tr>
<th>Specimen</th>
<th>AUC$_{0-\infty}$ (h-ml)</th>
<th>$C_{\text{max}}$ (\mu g/ml)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$k_a$ (h$^{-1}$)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>38.8 $\pm$ 10.3</td>
<td>3.8 $\pm$ 1.2</td>
<td>2.3 $\pm$ 1.3</td>
<td>3.8 $\pm$ 5.1</td>
<td>5.1 $\pm$ 1.8</td>
</tr>
<tr>
<td>Blister fluid</td>
<td>39.6 $\pm$ 13.2</td>
<td>2.8 $\pm$ 0.4</td>
<td>5.2 $\pm$ 1.4</td>
<td>0.6 $\pm$ 0.7$^b$</td>
<td>5.9 $\pm$ 3.2</td>
</tr>
</tbody>
</table>

$^a$ Values are means $\pm$ standard deviation.

$^b$ For blister fluid, $k_a$ refers to the constant rate of access of ofloxacin to this fluid.
Statistical analysis. After the normality of the data obtained was confirmed, statistical comparison of the results was performed by one-way analysis of variance (2).

Programs used. (i) AUTOAN 2. The AUTOAN 2 program allows one to obtain the initial estimate of the pharmacokinetic parameters and to make a prior fitting of the experimental results to the most appropriate model (22).

(ii) NONLIN 84. After finding the initial estimates of the parameters, the NONLIN 84 program carries out an optimum fitting of the experimental data to the model and calculates the corresponding parameters (16).

(iii) EPISTAT. The EPISTAT program comprises a series of statistical packages that permit different options (19).

RESULTS

Figure 1 shows the mean curves of ofloxacin levels in plasma and blister fluid in the group of healthy volunteers. At 24 h after administration, the concentrations in interstitial tissue fluid and plasma were 0.3 and 0.2 μg/ml, respectively. Table 1 shows the mean pharmacokinetic parameters in both fluids for the control group.

In the group of patients with renal impairment, significant alterations were observed regarding both the profiles of the plasma-time levels and those corresponding to interstitial tissue fluid, as may be seen by comparing the curves shown in Fig. 2 and 3 with those in Fig. 1.

On comparing the plasma kinetics of the control group with those observed in the patients with different degrees of renal impairment, an increase was observed in the maximum plasma concentrations ($C_{max}$), which rise from a mean value of $3.8 \pm 1.2$ μg/ml to values ranging between 5 and 8 μg/ml, depending on the degree of renal impairment. A similar situation was apparent in interstitial tissue fluid, in which the value of $C_{max}$ increased from $2.8 \pm 0.4$ μg/ml in the healthy volunteers to 3 to 5 μg/ml in the patients with renal impairment. Similarly, as the degree of renal impairment increased, a progressive maintenance of levels in plasma was observed, with concentrations of 1.5 to 2.0 μg/ml at 48 h after administration in patients with terminal renal impairment ($\text{CL}_{\text{CR}}, <5$ ml/min). Tables 2 and 3 show the pharmacokinetic parameters in plasma and blister fluid obtained in the patients with renal impairment. In all of these, the $\text{AUC}_{0,\infty}$ is the parameter subject to the most pronounced changes as a result of renal impairment. In the control group, this param-
TABLE 2. Pharmacokinetic parameters of ofloxacin obtained from levels in plasma of patients with renal impairment

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>CLCR (mL/min)</th>
<th>AUCOₕₐₘ (µg · h/mL)</th>
<th>kₙ₈ (h⁻¹)</th>
<th>Cmax (µg/mL)</th>
<th>T_max (h)</th>
<th>t₁/₂ (h)</th>
<th>V (liters/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>225.3</td>
<td>8.7</td>
<td>6.0</td>
<td>1.0</td>
<td>28.9</td>
<td>9.3</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>143.5</td>
<td>13.0</td>
<td>4.4</td>
<td>1.3</td>
<td>22.1</td>
<td>1.4</td>
</tr>
<tr>
<td>3</td>
<td>12.6</td>
<td>146.7</td>
<td>5.3</td>
<td>3.3</td>
<td>1.5</td>
<td>29.9</td>
<td>2.0</td>
</tr>
<tr>
<td>4</td>
<td>24.5</td>
<td>221.3</td>
<td>11.9</td>
<td>6.2</td>
<td>0.6</td>
<td>24.2</td>
<td>1.1</td>
</tr>
<tr>
<td>5</td>
<td>50.9</td>
<td>63.8</td>
<td>15.4</td>
<td>4.4</td>
<td>1.3</td>
<td>9.7</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>9.6</td>
<td>239.2</td>
<td>12.6</td>
<td>4.8</td>
<td>1.3</td>
<td>33.8</td>
<td>2.1</td>
</tr>
<tr>
<td>7</td>
<td>3.3</td>
<td>744.7</td>
<td>6.1</td>
<td>5.5</td>
<td>1.8</td>
<td>92.9</td>
<td>1.1</td>
</tr>
<tr>
<td>8</td>
<td>63.9</td>
<td>107.8</td>
<td>8.8</td>
<td>4.5</td>
<td>0.3</td>
<td>16.1</td>
<td>1.0</td>
</tr>
<tr>
<td>9</td>
<td>2.1</td>
<td>263.8</td>
<td>6.2</td>
<td>8.5</td>
<td>1.7</td>
<td>28.7</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* T_max. Time to maximum concentration of drug in plasma.

...Other had means of 38.8 ± 10.3 mg · h/liter in plasma and 39.6 ± 13.2 mg · h/liter in blister fluid, increasing to 744.7 and 694.7 mg · h/liter, respectively, in two patients with a CLCR of <3 mL/min. The kₙ₈ decreased progressively as the degree of renal impairment increased. Accordingly, a progressive increase occurred in the t₁/₂ in both plasma and blister fluid. Regarding the other parameters, no statistically significant differences were observed in the V (P > 0.8) in the two groups studied.

A linear relationship was found between the CLCR's and the kₙ₈ of ofloxacin defined by the following equation:

CLCR (mL/min) = -120 + 1,125.5 kₙ₈ (h⁻¹) r = 0.789 (4)

Table 4 shows the f values for both plasma and blister fluid.

It was not possible to establish any kind of relationship between the f values and CLCR; these were seen to show normal distribution, with mean values of 0.99 ± 0.3 and 0.97 ± 0.2 mL/min for plasma and interstitial tissue fluid, respectively.

**DISCUSSION**

In the control group, ofloxacin shows an excellent access capacity to blister fluid. On calculating the percentage of access to this fluid on the basis of the blister fluid AUCOₕₐₘ/plasma AUCOₕₐₘ ratio, a value of >100% is obtained, which is confirmed by the values obtained for the blister fluid/plasma partition coefficient (R). In all cases this proved to be >0.95, with a mean value of 1.33 ± 0.23. With respect to the elimination kinetics, no statistically significant differences were found among the parameters defining the elimination of ofloxacin in either fluid studied, with mean t₁/₂ values of 5.1

**TABLE 3. Pharmacokinetic parameters of ofloxacin obtained from levels in blister fluid of patients with renal impairment**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>CLCR (mL/min)</th>
<th>AUCOₕₐₘ (µg · h/mL)</th>
<th>Cmax (µg/mL)</th>
<th>T_max (h)</th>
<th>t₁/₂ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>228.1</td>
<td>4.8</td>
<td>9.0</td>
<td>34.8</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>122.1</td>
<td>3.4</td>
<td>8.2</td>
<td>18.1</td>
</tr>
<tr>
<td>3</td>
<td>12.6</td>
<td>104.8</td>
<td>2.3</td>
<td>13.0</td>
<td>18.8</td>
</tr>
<tr>
<td>4</td>
<td>24.5</td>
<td>194.2</td>
<td>4.8</td>
<td>7.0</td>
<td>24.0</td>
</tr>
<tr>
<td>5</td>
<td>50.9</td>
<td>48.9</td>
<td>2.6</td>
<td>6.1</td>
<td>9.8</td>
</tr>
<tr>
<td>6</td>
<td>9.6</td>
<td>327.3</td>
<td>3.3</td>
<td>3.3</td>
<td>67.3</td>
</tr>
<tr>
<td>7</td>
<td>3.3</td>
<td>484.1</td>
<td>5.3</td>
<td>11.6</td>
<td>53.4</td>
</tr>
<tr>
<td>8</td>
<td>63.9</td>
<td>85.8</td>
<td>3.0</td>
<td>4.1</td>
<td>16.3</td>
</tr>
<tr>
<td>9</td>
<td>2.1</td>
<td>694.7</td>
<td>4.9</td>
<td>9.1</td>
<td>89.9</td>
</tr>
</tbody>
</table>

* T_max. Time to maximum concentration of drug in blister fluid.

...To determine the relationship established between kₙ₈ and CLCR permits calculation of the kₙ₈ for all patients as a function of their CLCR, from the following equation:

kₙ₈ (h⁻¹) = 0.010 + 8.80 10⁻⁴ CLCR (mL/min) (5)

In summary, it may be concluded that renal impairment does not lead to changes in the absorption and distribution...
capacities of ofloxacin and that this pathologic condition only affects the elimination processes. Since the distribution characteristics of the drug in blister fluid depend on the drug’s plasma kinetics, in renal impairment an increase will occur in interstitial tissue fluid parallel to that taking place in the levels of the drug in plasma.

ACKNOWLEDGMENT

We thank Hoechst Iberica S. A., Barcelona, Spain, for supporting this study.

LITERATURE CITED