Single-Dose Pharmacokinetics of Oral Fleroxacin in Bacteremic Patients

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Fleroxacin is a new broad-spectrum quinolone which can be given by the oral route. The present study was designed to assess the influence of bacteremia on the pharmacokinetics of a single oral dose of fleroxacin. Thirteen patients with proven bacteremia (one or more pairs of positive blood cultures, no hypotension) were given a single 400-mg fleroxacin dose orally on two occasions while also receiving standard antibiotic therapy. The first dose was administered 12 to 36 h after the last positive blood culture was drawn (day 1), and a second dose was administered 7 days later (day 7 ± 2) to compare the pharmacokinetics between the acute and the convalescent phases of the disease. Following each administration of fleroxacin, serial plasma samples were collected for up to 72 h and were analyzed for unchanged drug by a reversed phase high-pressure liquid chromatography technique. There were no significant changes in the following pharmacokinetic parameters (mean standard deviation) the maximum concentration of drug in serum (6.4 ± 1.5 versus 6.7 ± 1.9 mg/liter), the minimum concentration of drug in serum, defined as the concentration of drug in serum at 24 h postdose (3.0 ± 1.7 versus 2.5 ± 1.2 mg/liter), the time to the maximum concentration of drug in serum (2.3 ± 1.4 versus 2.0 ± 1.2 h), and the elimination half-life (19.7 ± 8.0 versus 17.9 ± 6.9 h). Fleroxacin clearances were compared for each individual patient. A positive correlation ($R^2 = 0.787$) was found between the values measured on day 1 and day 7. Oral clearance of fleroxacin ($CL = CL/F$, where F is bioavailability) was slightly, but not significantly, reduced during the bacteremic phase (oral clearance, 43.8 ± 23.5 versus 48.5 ± 17.5 ml/min). When compared with previous results obtained in healthy young subjects, longer times to the maximum concentration of drug in serum and elimination half-lives and higher areas under the curve were observed. This could be due to the bacteremic state, the old age of the patients (mean, 66 years), and the low renal clearance (mean calculated creatinine clearance, 71.1 ml/min). A single oral dose of 400 mg of fleroxacin provides sufficient levels in serum to cover susceptible microorganisms for at least 24 h in bacteremic patients. Renal function appeared to be the key element that had to be taken into consideration to adapt fleroxacin dosage profiles in our patient population. Bacteremia itself appeared to amplify that phenomenon, but to a much lesser extent than renal function did.

Fleroxacin is a new trifluorinated quinolone that differs from most other quinolones by its excellent bioavailability (reaching almost 100%) and a longer terminal half-life ($t_{1/2p}$; 10 h) following oral administration (53, 54). It is eliminated primarily by renal clearance, with about 60 to 70% of a dose being recovered unchanged in the urine within 96 h (53–55). These pharmacokinetic properties associated with a wide antibacterial spectrum (5, 7, 24, 35, 37, 55, 56) and a high degree of penetration into body fluids and tissues (12, 26, 27, 36, 44, 52) allow a once-a-day oral administration. The pharmacokinetic parameters of fleroxacin in healthy young volunteers are well known (33, 44, 53, 54). However, serious infections may lead to changes in these parameters through various mechanisms (1, 2, 4, 6, 13, 28, 49, 50). Moreover, severely ill patients are mostly elderly people who often suffer from other underlying diseases. Volunteers can be tested after an overnight fast, whereas patients must be treated at any time, whether they are fasting or not. Volunteers are administered only the drugs to be tested, whereas hospitalized patients typically need other drugs.

All of these factors, as well as the decreased renal function which is frequently observed in patients with severe infections, can influence the absorption and dispositions of drugs. Furthermore, the pharmacokinetics of orally administered antibiotics can change in the same patient as the disease goes from the acute phase to the convalescence phase. The pharmacokinetics of single oral doses of fleroxacin were therefore investigated in patients during bacteremia (acute disease phase) and about 1 week later (convalescent phase).

MATERIALS AND METHODS

Patients. Patients over 18 years of age hospitalized at the University Hospital of Geneva, Geneva, Switzerland, were considered for inclusion in the study, provided that they were able to give written informed consent and were able to take medication by mouth, did not have hypotension, and had at least one positive blood culture showing the same pathogen in both of a pair of bottles. To be included in the study, cultures had to be reported as positive by the microbiological laboratory within 24 h after the blood was drawn.

Pregnant or breast-feeding patients, patients allergic to quinolone antimicrobial agents, patients with severe renal impairment (creatinine clearance, ≤30 ml/min), patients already receiving a quinolone derivative for the treatment of their acute infection, and human immunodeficiency virus-positive patients were excluded from the study.
In addition to fleroxacin, all patients received standard antibiotic therapy with penicillins, aminoglycosides, or cephalosporins. The choice and duration of that antibiotic therapy were determined by the physician responsible for the patient exclusively on the basis of clinical considerations. Other orally administered medications were not to be given 1 h (2 h for antacids) prior to or following the administration of fleroxacin.

A medical history, a physical examination, and a panel of laboratory tests (renal and liver chemistries, complete blood cell counts) were obtained on days 1 and 7 of the study. Renal creatinine clearances were calculated as described by Cockcroft and Gault (14). The protocol was approved by the Geneva University Hospital's ethical review board.

**Study design.** The study described here was an open-label, nonrandomized, within-subject comparative pharmacokinetic trial. Patients consenting to be studied received one 400-mg tablet of fleroxacin orally no later than 3 h after the last positive blood culture was drawn (day 1). No special diet was required for the patients in the study. Blood samples of 5 ml were collected by using sodium fluoride and potassium oxalate as anticoagulants before fleroxacin intake and at 1, 2, 4, 12, 24, and 48 h after fleroxacin intake. Identical drug administration and sampling schedules were repeated 2 days later, at a time when the patient's condition had stabilized.

After centrifugation (1,000 × g for 15 min), plasma samples were transferred to polyethylene-stoppered glass tubes covered with aluminum foil to prevent photodegradation and were then stored at −20°C until they were assayed.

**Microbiological investigations.** Blood cultures were performed by using Roche Septi-Check and Oxoid Signal (F. Hoffmann-La Roche, Basel, Switzerland) bottles as a paired blood culture system; each bottle was inoculated with 10 ml of blood.

**Fleroxacin assay.** The concentrations of fleroxacin in plasma were determined by a reversed phase high-pressure liquid chromatography technique described by Dell et al. (15) and Heizmann et al. (22). The mobile phase was 5 mM tetrabutylammonium hydrogen sulfate-methanol (72/28; vol/vol), and separation was performed on a Toyo Soda ODS-120 T 5-μm column. Concentrations of fleroxacin in plasma were detected fluorimetrically (excitation at 290 nm; emission at 450 nm); the limit of quantification was 20 ng/ml (relative standard deviation, 3.6%) for 0.5-ml plasma samples were used. The mean interassay reproducibility was 4% relative standard deviation over the concentration range of 0.02 to 5 μg/ml. Recovery from plasma was 81% (relative standard deviation, 10%) over the concentration range 0.01 to 5 μg/ml. The coefficient of variation of multiple determinations was less than 15%.

**Pharmacokinetic analysis.** The software used for the fitting procedure was EXCEL 4.0 (Microsoft). Standard algorithms for nonlinear curve-fitting were implemented, and objective function was minimized with the solver module included in the EXCEL 4.0 package. Visual inspection of the log-linearized data showed a monophasic decline in the fleroxacin concentration in the plasma of all subjects and no absorption delay. Monophasic elimination with first-order absorption was therefore assumed, and a biexponential model without a lag time was fitted to the untransformed data, with weighting proportional to the inverse of the predicted values. The maximum concentration of drug in plasma (Cmax) and the time to reach Cmax (Tmax) were read directly from the observed data. The minimum concentration of drug in plasma (Cmin; defined as the concentration measured 24 h after drug intake) was recorded as fitted values. t1/2β was calculated as ln2/β, where β is the terminal rate constant of elimination. The area under the concentration-time curve extrapolated to infinity (AUC0–∞) was estimated by the trapezoidal rule from time zero to the last time of measurement and was extrapolated from the last estimated concentration (C) to infinity as C/β. The oral clearance of fleroxacin was calculated as dose/AUC0–∞, assuming complete absorption from the gastrointestinal tract.

**Statistical analysis.** For statistical comparison between the data obtained during the acute phase of disease and those obtained during the convalescent phase, a Wilcoxon signed rank test was used. Correlation was performed with a Spearman's rank test. For both analyses, the level of significance (α) was 0.05.

**RESULTS**

From June 1990 to December 1991, 18 patients were initially enrolled in the study, but only 13 patients completed the trial, and only data for these patients were considered in the data analysis. Five of the patients were excluded for the following reasons: refusal of repeated venipunctures during the study (n = 3), concomitant ciprofloxacin treatment for a group D salmonella infection (n = 1), and acute renal impairment in one patient suffering from chronic cardiac and renal failure. The study population was characterized by patients in a general hospital with regard to age and underlying conditions (Table 1). The mean ± standard deviation age, weight, creatinine levels in serum, and calculated creatinine clearance (14) for these subjects were 66.3 ± 15.8 years, 69.8 ± 11.4 kg, 97.2 ± 26.0 μmol/liter, and 71.1 ± 34.0 ml/min, respectively.

Both gram-positive (71.4% of isolates) and gram-negative aerobic microorganisms (28.6% of isolates) were isolated in blood cultures; one patient (patient 3) had polymicrobial bacteremia (Table 1).

Fleroxacin was well tolerated. No patient vomited, and liver enzymes, complete blood count, creatinine levels, and blood urea nitrogen levels did not show changes suggestive of side effects from the administration of fleroxacin.

**Pharmacokinetic parameters.** The mean concentration-time curves obtained during the acute phase of the disease and the convalescent phase are shown in Fig. 1. The pharmacokinetic parameters for fleroxacin on days 1 and 7 are presented in Table 2. There were no significant changes in the following mean ± standard deviation pharmacokinetic parameters: Cmax, 6.4 ± 1.5 versus 6.7 ± 1.9 mg/liter; Cmin, 3.0 ± 1.7 versus 2.5 ± 1.2 mg/liter; T1/2α, 2.3 ± 1.4 versus 2.0 ± 1.2 h; and t1/2β, 19.7 ± 8.0 versus 17.9 ± 6.9 h. Individual fleroxacin levels in serum 24 h after administration of the dose (Cmin) were all greater than 1 mg/liter on day 1 and day 7 ± 2. Tmaxs exhibited wide interindividual variabilities, but they seemed to be characteristic for each individual. Oral clearance was only slightly (10.8%), but not significantly (P = 0.15), reduced during the bacteremic (acute) phase compared with that during the convalescent phase. Individual fleroxacin clearances measured on days 1 and 7 were highly correlated for each individual patient (R2 = 0.877; P = 0.001). Drug clearances appeared to be related to creatinine clearances on day 1 (P < 0.001). However, this correlation was no longer statistically significant when the data obtained on day 7 were considered (Fig. 2). There was a trend (P = 0.06) toward a positive correlation between the age of the patients and the oral clearance of fleroxacin (Fig. 3).

**DISCUSSION**

The broad spectra of activity and the bactericidal nature of the fluoroquinolones, together with their high levels of absorption, rapid distributions, and elevated concentrations in tissues,
TABLE 1. Clinical data for 13 bacteremic patients to whom fleroxacin was administered

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Ht (cm)</th>
<th>Creatinine clearance (μmol/liter) on day 1</th>
<th>Sex</th>
<th>Underlying condition</th>
<th>Organisms isolated</th>
<th>Presumed origin of septicemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>80</td>
<td>160</td>
<td>61.6</td>
<td>F</td>
<td>Diabetes, congestive heart failure</td>
<td>Streptococcus pneumonia</td>
<td>Lungs</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>56</td>
<td>165</td>
<td>68.8</td>
<td>F</td>
<td>Diabetes, congestive heart failure</td>
<td>Streptococcus faecalis</td>
<td>Unknown</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>77</td>
<td>182</td>
<td>68.1</td>
<td>M</td>
<td>Diabetes</td>
<td>Klebsiella aeratis and Escherichia coli</td>
<td>Unknown</td>
</tr>
<tr>
<td>4</td>
<td>93</td>
<td>66</td>
<td>160</td>
<td>29.1</td>
<td>F</td>
<td>Diabetes, congestive heart failure</td>
<td>Escherichia coli</td>
<td>Biliary or digestive systems</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>70</td>
<td>165</td>
<td>53.2</td>
<td>M</td>
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<td>Enterococcus faecalis</td>
<td>Urinary tract</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>56</td>
<td>155</td>
<td>61.2</td>
<td>F</td>
<td>Alcohol abuse, cirrhosis</td>
<td>Staphylococcus aureus</td>
<td>Bone or soft tissues</td>
</tr>
<tr>
<td>7</td>
<td>76</td>
<td>81</td>
<td>170</td>
<td>72.4</td>
<td>M</td>
<td>Alcohol abuse, cirrhosis</td>
<td>Streptococcus pneumonia</td>
<td>Lungs</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>58</td>
<td>160</td>
<td>41.3</td>
<td>F</td>
<td>Alcohol abuse, cirrhosis</td>
<td>Escherichia coli</td>
<td>Urinary tract</td>
</tr>
<tr>
<td>9</td>
<td>48</td>
<td>85</td>
<td>176</td>
<td>165.7</td>
<td>M</td>
<td>Alcohol abuse, cirrhosis</td>
<td>Streptococcus bovis</td>
<td>Cardiovascular system</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>76</td>
<td>186</td>
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<td>M</td>
<td>Diabetes</td>
<td>Staphylococcus aureus</td>
<td>Bone or soft tissues</td>
</tr>
<tr>
<td>11</td>
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<td>50</td>
<td>165</td>
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<td>Escherichia coli</td>
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</tr>
<tr>
<td>12</td>
<td>53</td>
<td>78</td>
<td>180</td>
<td>68.9</td>
<td>M</td>
<td>Alcohol abuse, cirrhosis</td>
<td>Beta group B streptococcus</td>
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</tr>
<tr>
<td>13</td>
<td>66</td>
<td>75</td>
<td>162</td>
<td>51.7</td>
<td>F</td>
<td>Alcohol abuse, cirrhosis</td>
<td>Diabetes</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD: 66.3 ± 15.8, 69.8 ± 11.4, 168.2 ± 9.8, 71.1 ± 34.0

* F, female; M, male.

SINGLE-DOSE PHARMACOKINETICS OF FLEROXACIN

make them excellent therapeutic agents for the management of a number of complicated community-acquired and nosocomial infections (24, 45, 55). The possibility of using them as orally administered agents makes them even more attractive since it could simultaneously reduce the costs of therapy, not to mention the duration of a patient's hospital stay, and afford a more comfortable treatment. Many investigators have stressed the advantages of using quinolones in elderly patients (17, 34, 38). Most studies to date have included healthy young male volunteers, who ingest the test drug under carefully controlled conditions while the volunteer is in a stable state (23, 33, 47), or have focused on uninfected patients with impaired renal function (10, 18, 23, 41, 46, 51). Patients treated during infection might have totally different physiologic and metabolic conditions.

Several recent studies and reviews have dealt with the effects of bacteremia on drug disposition. Bacteremia by itself induces a variety of alterations: fever, inappetence, inhibition of gastric function (8, 13, 28), possible reduction of gastrointestinal transit time (6), synthesis of acute-phase proteins with altered protein binding (4), and changes in blood flow to various organs. Tachycardia is induced by fever, and the associated increase in cardiac output can enlarge the level of the perfusion in the gastrointestinal tract. Theoretically, this could lead to an increased absorption of orally administered drugs, but studies are scarce and their results are not conclusive (6, 28, 30, 49, 50). Alterations in disposition kinetics during pyrexia may be due to both the febrile reaction and the pathologic process responsible for the fever (1, 3, 28). Drug metabolism is also influenced by fever. The higher renal, hepatic, and splanchnic blood flows during fever (11, 20, 28), which may increase metabolic clearance, seem to be counterbalanced by an inhibition of liver enzyme activity (19). In summary, fever appears to have variable and apparently opposing influences on the pharmacokinetics of drugs.

The aim of the present study was therefore to investigate the pharmacokinetics of orally administered fleroxacin in bacteremic patients. Our study population was representative of patients typically found in general hospitals in terms of age, underlying diseases, and the multiple medications that they were receiving. Almost two-thirds of our patients presented at least one significant underlying pathology which could by itself significantly influence the pharmacokinetics of a drug. On the basis of both age (>65 years) and underlying pathologies, only one out of our patients (8%) could have been expected to present a drug disposition similar to those in healthy young volunteers.

The consequences of aging on the pharmacokinetics of fluoroquinolones have been studied previously (21, 29, 34, 39, 56). It appears that the most important change is due to the decline in renal function, in parallel with the decline in creatinine clearance in elderly people (29, 39). This process mainly affects drugs that are predominantly eliminated by this route, such as norfloxacin, enoxacin, ofloxacin, lomefloxacin, temafloxacin, and fleroxacin (10, 25, 33, 34, 43, 48). The $C_{max}$
as well as \( T_{\text{max}} \) values in our population of elderly patients were very close to those observed in healthy young volunteers (32, 33, 40, 44, 53–55) and suggest that the kinetics of absorption are not modified. However, \( T_{\text{max}} \) varied from 0.9 to 5.4 h in our patients, whereas they varied from 0.5 to 3.0 h in healthy young volunteers. Analysis of \( T_{\text{max}} \) strongly suggests a role for the characteristics of the individual patient in that broad distribution. Modifications of drug distribution are possible in the bacteremic (acute) phase of disease or in older people (48). However, this point was not assessed in our study since changes in the apparent volume of distribution cannot be independently estimated after oral administration.

A correlation \( (R^2 = 0.787) \) between fleroxacin clearances was observed on day 1 and day 7 in the same individuals. There was a 10% increase in fleroxacin clearance between the bacteremic (acute) phase and the convalescent phase which did not reach statistical significance or, probably, clinical relevance. Although fleroxacin clearance increased slightly between the acute phase of the disease and the convalescent phase, it was still much lower on day 7 in our patients than in healthy young volunteers (Table 2).

In marked contrast to the results of the present study in a previous study (16) performed under identical conditions after administration of a single oral dose of ciprofloxacin, peak concentrations varied by a factor of 14.5 and no correlation in the \( \text{AUC}_{\text{0–24h}} \) could be found in bacteremic patients between day 1 and day 5. A positive correlation was found in the same study (16) when ciprofloxacin was administered as a single intravenous dose, suggesting erratic absorption of ciprofloxacin during bacteremia. The pharmacokinetics of orally administered fleroxacin therefore appear to be more predictable than those of orally administered ciprofloxacin during bacteremia, possibly because of a more reliable absorption of fleroxacin (16).

Comparisons between different studies are hazardous because the experimental designs of and methods used in different studies are never strictly comparable. However, while care should be taken not to overinterpret the data in Table 2, it could well be that the extended \( t_{\text{1/2}} \) and lower clearance are of clinical importance. One striking difference is the important decrease in the clearance in our elderly patients compared with the clearance in healthy young volunteers (Table 2). Fleroxacin clearance on day 1 was clearly correlated to the estimated creatinine clearance (Fig. 2). This point is not surprising, since fleroxacin is eliminated mostly by the renal route (approximately 60 to 70%) (53–55), and even clinically small changes in renal excretion may have a significant impact on fleroxacin clearance. Taburet et al. (48) studied single-dose fleroxacin pharmacokinetics in 12 elderly patients and concluded that the results were similar to those for patients with mild or moderate renal insufficiency. This fact has also been described previously by Meyers and Wilkinson (29). The correlation between fleroxacin clearance and creatinine clearance (Fig. 2) was, however, no longer significant on day 7. This surprising finding could be due to the fact that creatinine clearance was calculated for day 1 and day 7.
labeled and not measured, thereby not precisely reflecting actual values. The influence of concomitant therapies known to affect renal function (e.g., aminoglycoside therapy) might also have played a role, but their contributions to the results of our study could not be precisely evaluated.

The effect of impaired liver function, which was found in five of our patients, did not seem to have a significant impact on fleroxacin pharmacokinetics. The pharmacokinetics of fleroxacin in these patients was not different from that in patients without prior hepatic dysfunction. Moreover, fleroxacin pharmacokinetics have been shown to be modified only slightly even after a major induction of hepatic enzymes (7-day concomitant rifampin administration) (40). Blouin et al. (9) reported clinically significant decreases in the systemic and renal clearances of fleroxacin only in patients suffering from ascites, not in those with liver cirrhosis. The prediction of the levels of the various quinolones in the sera of patients with alcoholic cirrhosis is difficult. Because ciprofloxacin is eliminated by both the renal and the hepatic routes, its kinetics are often modified when liver function is compromised. This effect is even greater for pefloxacin, which is mostly metabolized by liver enzymes (10, 31). Quinolones mainly eliminated by the kidneys, such as ofloxacin or fleroxacin, behave differently and are more dependent on the possible coexisting renal dysfunction (31). These considerations about quinolones and their metabolism have recently been reviewed (33, 43).

The slightly reduced oral clearance and prolonged t1/2bf of fleroxacin in our bacteremic patients led to a trend toward higher $C_{\text{min}}$ on day 1 than on day 7. On day 1, all patients had $C_{\text{min}}$ greater than 1 mg/ml, and more than half of them had $C_{\text{min}}$ greater than 2 mg/ml. These values are greater than the MICs for 90% of the most common pathogens that are susceptible to fleroxacin (37).

In conclusion, the pharmacokinetic effects observed in the present study appeared to be related mainly to the decrease in renal clearance typical of elderly patients. Bacteremia itself appears to amplify that phenomenon, but to a much lesser extent than age does. Fleroxacin dosage in bacteremic patients does not require any specific consideration. Adaptation of the fleroxacin dosage according to the usual procedure in patients with reduced renal function is recommended, however, whenever creatinine clearance is significantly lower (<40 ml/min) (23, 48, 51), with administration of a normal 400-mg loading dose followed by 200-mg maintenance doses (51).

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