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Ciprofloxacin Pharmacokinetics in Patients with Normal and Impaired Renal Function

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The pharmacokinetics of ciprofloxacin following single oral doses of 500 and 750 mg in 32 patients with various degrees of renal function impairment were investigated in an open, randomized crossover fashion. Ciprofloxacin was administered after overnight fasting; the washout time between the two doses was 1 week. Serum and urine samples were collected serially between 0 and 24 h and subjected to bioassay and high-performance liquid chromatography. Pharmacokinetic parameters were analyzed, assuming an open two-compartment model with first-order input and elimination. A distinct difference was observed in pharmacokinetic parameters between patients with impaired renal function (creatinine clearance, <50 ml/min per 1.73 m^2) and those with normal renal function (creatinine clearance, ≥50 ml/min per 1.73 m^2). For the former group, the area under the curve of serum concentration versus time was doubled, the renal clearance of ciprofloxacin was cut to one-fourth, the total and nonrenal ciprofloxacin clearance was reduced by 50%, and the elimination half-life was prolonged by a factor of approximately 1.7. The correlation between renal drug clearance and creatinine clearance was highly significant ($r = 0.890$; $P < 0.001$). On the basis of these findings, it appears that a 50% dose reduction of ciprofloxacin in patients with impaired renal function (creatinine clearance, <50 ml/min per 1.73 m^2) may be indicated to achieve concentrations in serum similar to those observed in normal individuals. As the concentration of ciprofloxacin in urine after 24 h remained above the MIC for most urinary pathogens, this drug appears to be of potential benefit for the treatment of urinary tract infections in patients with impaired renal function.

Ciprofloxacin (Bay o 9867) is a new quinolone carboxylic acid derivative with broad antibacterial activity against gram-positive and gram-negative bacteria, including those resistant to aminoglycosides and β-lactam antibiotics (1, 12). Single- and multiple-oral-dose pharmacokinetic studies have shown that ciprofloxacin is rapidly absorbed and penetrates well into tissue (3, 5). Ciprofloxacin is eliminated from serum by renal excretion and by extrarenal routes (11). The purpose of this study was to investigate the pharmacokinetics of ciprofloxacin following single oral doses of 500 and 750 mg in patients with various degrees of renal function.

MATERIALS AND METHODS

Volunteers. Thirty-eight male patients with no known allergies to quinolone derivatives were enrolled in this study after written informed consent was obtained. Six of these subjects were subsequently excluded from analysis from both phases of the study (one vomited shortly after drug administration, one could not be assigned to a group because he had contradictory creatinine clearance [CL_{CR}] values, two had received magnesium hydroxide before drug administration, one received Metamucil, and one ingested food before drug administration). Of the remaining 32 subjects, 4 (2 in each dosing group) were included in analysis in only one phase of the study because they had received magnesium hydroxide on one study day.

The renal function was estimated by CL_{CR} determinations, with two 12-h urinary creatinine collections and two determinations of creatinine in serum prior to ciprofloxacin administration. Patients were initially assigned into four different groups according to their CL_{CR} values: group A, >80 ml/min per 1.73 m^2 (12 patients); group B, 50 to 79 ml/min per 1.73 m^2 (5 patients); group C, 20 to 49 ml/min per 1.73 m^2 (10 patients); and group D, <20 ml/min per 1.73 m^2 (5 patients). However, during subsequent analysis of these groups, it became obvious that there were no noticeable differences in pharmacokinetic parameters between groups A and B, and between groups C and D. Therefore, patients were reassigned to groups 1 and 2 with CL_{CR} of ≥50 ml/min per 1.73 m^2 and <50 ml/min per 1.73 m^2, respectively, for statistical evaluation of pharmacokinetic parameters (Table 1). Most patients had lower-urinary-tract obstruction because of carcinoma of the prostrate, hypertrophy of the prostate, or bladder tumors, and some had indwelling urinary catheters.

Study design. This study was an open, randomized crossover trial. Patients received either 500 mg of ciprofloxacin as a single oral dose with at least 7 days of washout time, followed by 750 mg of ciprofloxacin as a single oral dose, or vice versa. The drug was administered with 180 ml of tap water after an overnight fast. Patients were instructed to void before drug administration and to abstain from eating for 4 h after drug administration.

Drug safety was evaluated by measuring vital signs and by questioning the patients about side effects. The following parameters were also measured before and after ciprofloxacin administration: erythrocyte and leukocyte

TABLE 1. Personal data on study subjects

Group (no. of members)	Age range (yr) (median)	Wt range (kg) (median)	CL_{CR} (ml/min per 1.73 m^2) (range)
1 (17)	39–74 (60)	64–108 (76)	≥50 (51–157)
2 (15)	48–90 (70)	57–114 (77)	<50 (8–46)

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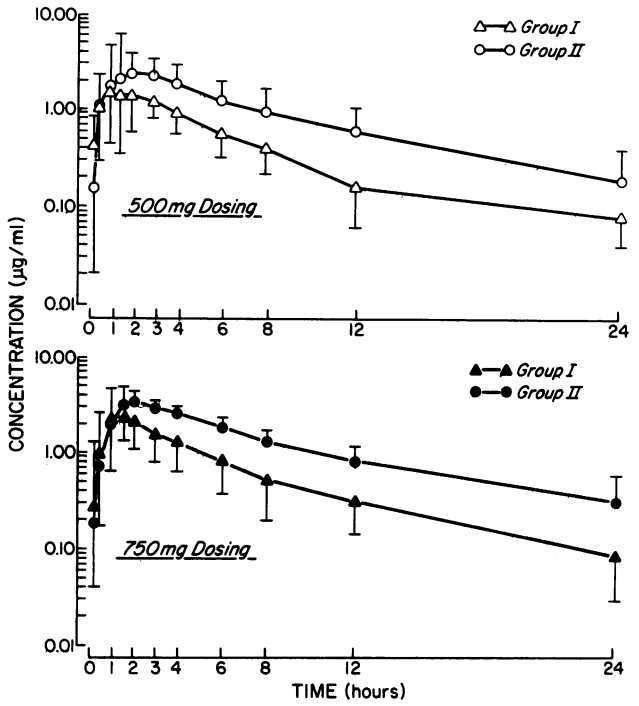

FIG. 1. Ciprofloxacin concentrations in serum after a single oral dose of 500 mg (top) or 750 mg (bottom) (geometric mean and standard deviation).

count, hemoglobin, hematocrit, platelet count, electrolytes, liver enzymes (bilirubin, alkaline phosphatase, serum glutamic oxalacetic transaminase, and serum glutamic pyruvic transaminase), serum creatinine, blood urea nitrogen, uric acid, total protein and albumin, and urinalysis.

Serum samples were drawn before dosing and at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, and 24.0 h after ciprofloxacin administration. Urine was collected before dosing and during the intervals from 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h thereafter. Urine samples were also taken 24 to 48 h after drug administration in group 2 only. Samples for bioassay were immediately frozen in plastic containers at −20°C; those for high-performance liquid chromatography (HPLC) were frozen at −70°C. All samples were assayed by both bioassay and HPLC.

Microbiological assay. Serum and urine samples were assayed by a plate diffusion method (10), with *Klebsiella pneumoniae* ATCC 10031 (Miles Pharmaceuticals, West Haven, Conn.) as a test organism. The test medium was neomycin assay agar at pH 7.9 (medium 11; Difco Laboratories, Detroit, Mich.). Standards were prepared with pooled normal human antibiotic-free serum for serum samples and a pH 7.0- phosphate buffer for urine. The plates were incubated overnight at 37°C. The standards, controls, and samples were run at least four times. The sensitivity of the assay was 0.01 μg/ml.

HPLC. HPLC serum assay procedures were performed by Miles Pharmaceuticals by a previously described reversed-phase method with fluorescence detection (4). The sensitivity of the assay was 0.008 μg/ml. Urine samples were assayed by a newly developed HPLC method to differentiate between ciprofloxacin and its three metabolites (G. J. Krol, A. J. Noi, and D. Beermann, J. Liq. Chromatogr., in press). Assay results by microbiological and HPLC methods were analyzed for comparability.

Pharmacokinetic analysis. The pharmacokinetic parameters of each subject were individually calculated by nonlinear least-squares regression analysis with a NONLIN program on an IBM-XT personal computer (C. M. Metzler, G. K. Elfring, and A. J. McEwen, Abstr. Biometrics 1984, 2215, p. 562–563).

The pharmacokinetic analysis of the serum values was based on an open, two-compartment model with first-order input and elimination, corresponding to the following equation (6):

$$C_p(t) = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-k_a t}$$

where $C_p(t)$ (in micrograms per milliliter) is the concentration in serum at time t, A and B (in micrograms per milliliter) are the zero intercepts of the tangents α and β with the y axis, C is $-(A + B)$, α and β (in reciprocal hours) are the slopes of the rapid initial distribution and the slow terminal elimination phases, respectively, and k_a is the absorption rate constant. The secondary parameters, i.e., area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), peak concentration (C_{max}), time at which C_{max} is achieved (T_{max}), distribution and elimination half-lives ($t_{1/2\alpha}$ and $t_{1/2\beta}$, respectively), and volume of the central compartment (V_1) were calculated from the initial parameters (A, B, α, and β) by standard methods (6). The systemic or total drug clearance (CL_{tot}) and the renal drug clearance (CL_R) were calculated from the relationship of dose/$AUC_{0-\infty}$ and $X_u/AUC_{0-\infty}$, respectively, where X_u is the total amount of unchanged drug excreted in the urine. Extrarenal clearance was defined as $C_{NR} = CL_{tot} - CL_R$. The predicted average steady-state concentration in serum was calculated as $AUC_{0-\infty}/T$, where T is the dosage interval.

Statistical analysis. The Wilcoxon rank sum test was used to compare pharmacokinetic parameters between the two groups of patients. The paired t tests was used to test changes in laboratory values.

RESULTS

In both groups 1 and 2, there were excellent correlations between HPLC values and bioassay values for serum (group 1: $r = 0.959$, $y = 0.15 + 0.85x$, $P < 0.001$; and group 2: $r = 0.94$, $y = 0.125 + 0.95x$, $P < 0.001$). Measurement of bias by comparing values from bioassay with those from HPLC revealed a mean difference of only 2.7% for samples in group 1 (310 paired observations) and 2.9% for samples in group 2 (271 paired observations). The correlation of values was not as good for urine ($r = 0.610$, $y = 29 + 0.59x$, $P < 0.001$; mean difference, 19.3%), with bioassay values being higher, probably owing to excretion of biologically active metabolites. These results were consistent with findings of previous studies (9). Therefore, we used bioassay results for serum and HPLC results for urine in our analyses.

Mean concentrations of ciprofloxacin in serum after 500- and 750-mg doses had been given to patients in groups 1 and 2 are shown in Fig. 1. In both groups, the 750-mg dose led to higher levels of ciprofloxacin in serum, higher C_{max}, longer T_{max}, and higher $AUC_{0-\infty}$ than the 500-mg dose (Table 2). Other parameters such as $t_{1/2}$, CL_{tot}, CL_R, and CL_{NR} were dose independent.

Patients in group 2 (those with impaired renal function) had higher dose concentrations in serum than those in group 1 (those with normal or slightly impaired renal function) after both doses. Compared with group 1, group 2 patients also had higher mean values for C_{max} and longer T_{max} (Table 2).

TABLE 2. Pharmacokinetic parameters for ciprofloxacin in patients with normal and impaired renal function[a]

Dose and group (no. of members)	C_{max} (μg/ml)	T_{max} (h)	V_1 (liters)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$AUC_{0-\theta}$ (μg · h/ml)	CL_{tot}/F[b] (ml/min)	CL_R/F (ml/min)	CL_{NR}/F (ml/min)
500 mg									
Group 1 (13)	2.2 ± 1.1	1.3 ± 1.0	123.4 ± 46.5	0.65 ± 0.30	4.3 ± 2.5	9.8 ± 4.0	1,002 ± 463	245 ± 101	780 ± 446
Group 2 (14)	2.5 ± 0.8 (NS)[c]	1.8 ± 0.5 ($P < 0.01$)	136.6 ± 11.7 (NS)	0.86 ± 0.61 (NS)	7.1 ± 2.9 ($P < 0.01$)	20.2 ± 9.9 ($P < 0.01$)	527 ± 288 ($P < 0.01$)	64 ± 62 ($P < 0.01$)	462 ± 294 ($P < 0.05$)
750 mg									
Group 1 (13)	2.8 ± 1.5	1.6 ± 0.5	158.0 ± 46.5	0.79 ± 0.35	3.5 ± 1.2	15.6 ± 9.1	1,173 ± 815	272 ± 160	901 ± 699
Group 2 (15)	3.7 ± 0.8 ($P < 0.01$)	2.3 ± 0.8 ($P < 0.01$)	113.8 ± 34.2 (NS)	1.02 ± 0.47 (NS)	6.3 ± 3.2 ($P < 0.01$)	26.8 ± 6.6 ($P < 0.01$)	490 ± 107 ($P < 0.01$)	72 ± 53 ($P < 0.01$)	419 ± 92 ($P < 0.05$)

[a] Results are expressed as the mean ± standard deviation.
[b] F, Bioavailability.
[c] NS, not significant.

The $AUC_{0-\infty}$ was approximately doubled, and $t_{1/2\beta}$ was prolonged by a factor of approximately 1.7. Group 2 patients had statistically smaller CL_{tot}, CL_R, and CL_{NR}. The predicted average concentrations in serum at steady state, assuming a 12-h dosage interval, were as follows: 500-mg dose: 0.82 μg/ml in group 1, 1.68 μg/ml in group 2; 750-mg dose: 1.30 μg/ml in group 1, 2.23 μg/ml in group 2.

The cumulative percentage of ciprofloxacin excreted and unchanged in the urine is shown in Fig. 2. While the percentage of excretion in urine was dose independent, it was only 15% of the dose administered to group 2 patients compared with 26% for group 1 patients. Concentrations in urine after administration of 500 mg of ciprofloxacin are shown in Fig. 3. Renal clearance of ciprofloxacin as a function of endogenous CL_{CR} is shown in Fig. 4. The correlation coefficient ($r = 0.890$) was highly significant ($P < 0.001$).

Ciprofloxacin was well tolerated by nearly all subjects. Four patients in the group given 500 mg and three in the group given 750 mg complained of side effects including headache, dizziness, nausea, vomiting, and diarrhea. Two of the patients experienced severe headache and diarrhea, while the remaining side effects were only of mild intensity, with no differences between groups 1 and 2. No significant changes occurred in the measured laboratory results before and after ciprofloxacin administration.

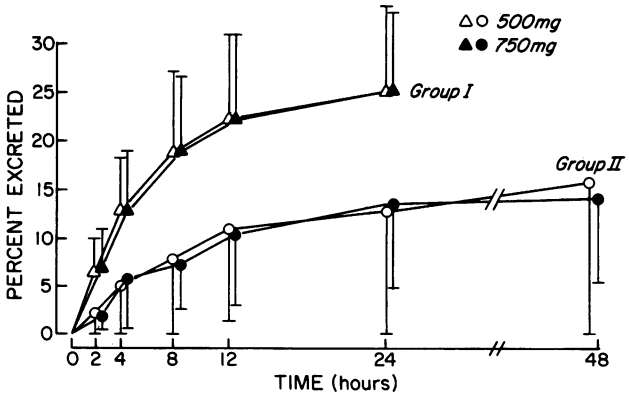

FIG. 2. Cumulative percentage of unchanged ciprofloxacin excretion in urine after single oral doses of 500 and 750 mg (mean and standard deviation).

DISCUSSION

This study demonstrates the relationship between the degree of renal function and ciprofloxacin clearance. Patients with moderate or severely impaired renal function ($CL_{CR} < 50$ ml/min per 1.73 m^2) experienced pharmacokinetic changes with ciprofloxacin administration compared with patients with normal or slightly impaired renal function ($CL_{CR} \geq 50$ ml/min per 1.73 m^2).

Patients with renal function impairment had higher C_{max} and longer T_{max} values, as well as a higher predicted average of steady-state concentrations of ciprofloxacin in serum. Assuming that the bioavailability of ciprofloxacin was the same in both groups, the total ciprofloxacin clearance was greatly reduced in group 2 patients, primarily owing to the lower CL_R. However, CL_{NR} was also significantly reduced in group 2 patients. This may be because the patients in this group were older, often bedridden, and in generally poor physical condition. Reduced CL_R in group 2 patients resulted in a 50% reduction in excretion of unchanged ciprofloxacin in urine. However, the 24-h ciprofloxacin concentration in urine for this group (Fig. 4) was still between 2 and 100 times the MIC for most urinary-tract pathogens, indicating that therapeutic ciprofloxacin levels in urine can be achieved in patients with renal dysfunction and that doses as high as 500 and 750 mg might not be necessary

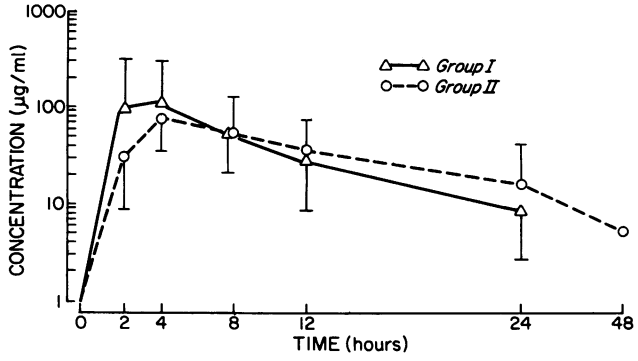

FIG. 3. Concentrations of ciprofloxacin in urine after a single oral dose of 500 mg (geometric mean and standard deviation).

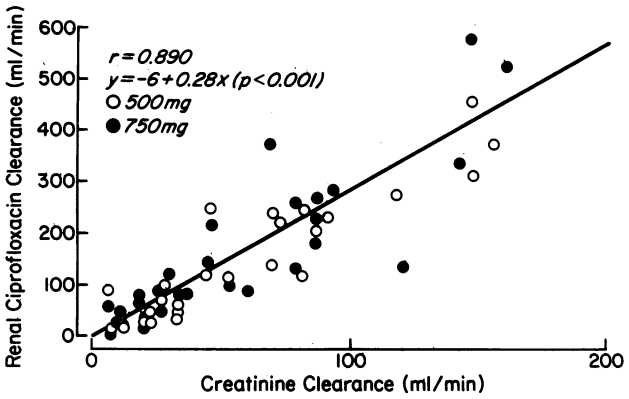

FIG. 4. Correlation between CL_R of ciprofloxacin and endogenous CL_{CR}.

for the treatment of urinary-tract infections in normal individuals.

The absorption of ciprofloxacin did not appear to be influenced by the age of the patients: the C_{max} and T_{max} values were consistent with those from studies of younger patients (11). The extent of absorption as a function of age or renal function was not determined. Other studies have revealed bioavailability values of 60 to 80% (7, 11).

Our study included only male subjects. However, since ciprofloxacin concentrations in serum and urine were sex independent in healthy volunteers in another study (8), we can assume that this would also be true for female patients with impaired renal function.

A study involving the administration of 250 mg of ciprofloxacin to patients with renal failure (CL_{CR}, <20 ml/min per 1.73 m^2) demonstrated alterations in pharmacokinetic parameters similar to those in this study (2). A 50% dose reduction was recommended for these patients. However, since only patients with CL_{CR} of either >60 ml/min per 1.73 m^2 or <20 ml/min per 1.73 m^2 were included in the study, dosage adjustment in patients with CL_{CR} between 20 and 60 ml/min per 1.73 m^2 was not addressed. On the basis of results of our study, the difference of the AUC for serum (and consequently the CL_{tot}) between groups suggests that dose adjustments should be considered for patients with impaired renal function. A reduction in the ciprofloxacin dose by 50% appears indicated for patients with CL_{CR} of <50 ml/min per 1.73 m^2 if concentrations in serum comparable to those in sera of individuals with normal renal function are desired. The high CL_{NR} of cirprofloxacin relative to CL_R, which is consistent with previous studies (11), confirms the importance of extrarenal elimination routes for ciprofloxacin. Therefore, further dose reduction should probably be considered for patients with both impaired renal and impaired hepatic function.

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