

Pharmacokinetics of Levofloxacin and Ciprofloxacin during Continuous Renal Replacement Therapy in Critically Ill Patients

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Received 4 December 2000/Returned for modification 27 March 2001/Accepted 10 July 2001

The pharmacokinetics of intravenously administered levofloxacin and ciprofloxacin were studied in intensive care unit patients during continuous venovenous hemofiltration (CVVH; four patients received levofloxacin, and five received ciprofloxacin) or hemodiafiltration (CVVHDF; six patients received levofloxacin, and five received ciprofloxacin). Levofloxacin clearance was substantially increased during both CVVH and CVVHDF, while ciprofloxacin clearance was affected less. The results of this study suggest that doses of levofloxacin of 250 mg/day and ciprofloxacin of 400 mg/day are sufficient to maintain effective drug concentrations in the plasma of patients undergoing CVVH or CVVHDF.

Continuous renal replacement therapy (CRRT), including continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF), is frequently used as an alternative to conventional hemodialysis in critically ill patients with acute renal failure (9, 15). However, relatively few clinical data are available regarding the removal of commonly used drugs during CRRT. Data regarding the clearance of drugs by conventional hemodialysis cannot be accurately extrapolated to CRRT because of differences in the membranes used; differences in blood, ultrafiltrate, and dialysate flow rates; and the continuous nature of the procedures compared to the intermittent nature of hemodialysis (9, 22, 25). Inadequate dosing of antimicrobials may lead to treatment failures and the potential for the development of antimicrobial resistance, while excessive dosing may predispose to drug toxicities. Basic knowledge regarding the disposition of antimicrobials during CRRT is thus important to the effective and safe treatment of the severe infections encountered in this patient population.

Levofloxacin and ciprofloxacin are extensively used as empirical or directed therapy for a variety of infections in critically ill patients due to their excellent activity against common gram-negative pathogens and moderate activity against many gram-positive organisms as well. No previous studies of levofloxacin pharmacokinetics during CRRT have been published. Ciprofloxacin has been previously studied during CRRT; however, patient numbers were small and somewhat inconsistent results were obtained (5, 7). The objective of the present study was therefore to characterize the pharmacokinetic disposition of levofloxacin and ciprofloxacin in critically ill adult intensive care unit patients during CVVH or CVVHDF.

This was a prospective open-label study of levofloxacin (Ortho-McNeil Pharmaceutical, Raritan, N.J.) and ciprofloxacin

(Bayer Pharmaceuticals, West Haven, Conn.). Adult patients greater than 18 years of age who were inpatients in a medical or surgical intensive care unit, who were prescribed either intravenous levofloxacin or ciprofloxacin as part of their required medical care, and who were receiving CRRT were eligible for inclusion in this study. Exclusion criteria included an age of less than 18 years or a requirement for conventional hemodialysis rather than CRRT. The study was approved by the Institutional Review Board of the hospital where the study was performed, and written informed consent was obtained from all patients or their legally designated representatives prior to study entry.

Levofloxacin and ciprofloxacin dosing regimens were determined by physicians caring for the patients and selected based on clinical indication. Levofloxacin regimens included 250- or 500-mg doses administered intravenously every 24 to 48 h. Ciprofloxacin regimens included 400-mg doses administered intravenously every 12 to 24 h. All levofloxacin and ciprofloxacin doses were infused over 1 h. Complete medical histories were obtained for each enrolled patient, and complete physical examinations were performed and serum chemistry and hematology profiles were determined and reviewed prior to collection of samples for pharmacokinetic analysis.

For all patients, CRRT was administered by using a Hospal BSM-22SC machine (CGH Medical, Lakewood, Colo.) with a Multiflow60 AN69HF 0.60-m² polyacrylonitrile hollow-fiber membrane (Hospal Industrie, Meyzieu, France). Vascular access was obtained by introduction of a 12 French, 20-cm double-lumen central venous catheter (Arrow, Reading, Pa.) into a femoral vein. CRRT was managed by the renal consult service caring for the patient, and parameters such as blood flow rate and dialysate flow rate for those receiving CVVHDF were adjusted as therapeutically necessary. During CVVHDF, dialysate fluids (Premixed Dialysate for Hemodiafiltration; Baxter Healthcare, Deerfield, Ill.) were delivered via volumetric pump into the dialysate compartment of the filter in a direction countercurrent to the blood flow. Replacement crystalloid fluids were delivered postmembrane via a volumetric pump, and additional electrolytes such as calcium and potassium were

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added to replacement and dialysate fluids as required. The extracorporeal circuit was anticoagulated as clinically indicated with heparin sodium at rates ranging from 100 to 1,200 IU/h.

Because of the unpredictability of drug elimination and uncertainty regarding the duration of CRRT in individual patients, pharmacokinetic sampling was performed as soon as possible after initiation of CRRT and drug therapy. Pre- and postmembrane venous blood samples were obtained from all patients at 1, 2, 4, and 8 h after completion of the drug infusion. Samples were also obtained from all patients just before administration of the next dose (either 12, 24, or 48 h after administration of the previous dose, depending on the specific dosing interval ordered) whenever possible. Finally, additional mid-interval samples were obtained at 12 and 24 h after completion of drug infusion, when applicable, in patients receiving doses at intervals of greater than 12 h. Samples (7 ml) were taken from the in-line blood access port in the extracorporeal circuit. Dialysate and/or ultrafiltrate samples (40 ml) were obtained simultaneously with blood samples at each time.

Blood samples were collected in glass tubes and promptly centrifuged. Serum was transferred to labeled polyethylene vials and stored at -70°C until assayed. Ultrafiltrate-dialysate samples were frozen immediately after collection. Drug concentrations in serum and dialysate-ultrafiltrate were determined by high-performance liquid chromatography with UV detection in accordance with adaptations of a previously published method (19). Coefficients of determination (r^2) over the levofloxacin standard curve concentration ranges (0.4 to 15.0 $\mu\text{g/ml}$ for serum and 0.2 to 10.0 $\mu\text{g/ml}$ for ultrafiltrate-dialysate) were in the range of 0.997 to 0.999 for the entire study. The inter- and intraday coefficients of variation for levofloxacin serum samples ranged from $\leq 4.1\%$ at 0.4 $\mu\text{g/ml}$ to $\leq 5.2\%$ at 10.0 $\mu\text{g/ml}$; ultrafiltrate-dialysate coefficients of variation were $\leq 9.8\%$ at 0.2 $\mu\text{g/ml}$ to $\leq 3.3\%$ at 5.0 $\mu\text{g/ml}$. Coefficients of determination over the ciprofloxacin standard curve concentration ranges (0.25 to 10.0 $\mu\text{g/ml}$ for serum and 0.2 to 10.0 $\mu\text{g/ml}$ for ultrafiltrate-dialysate) were also in the range of 0.997 to 0.999 for the entire study. The inter- and intraday coefficients of variation for ciprofloxacin serum samples ranged from $\leq 8.2\%$ at 0.5 $\mu\text{g/ml}$ to $\leq 5.6\%$ at 5.0 $\mu\text{g/ml}$; ultrafiltrate-dialysate coefficients of variation were $\leq 7.1\%$ at 0.2 $\mu\text{g/ml}$ to $\leq 2.2\%$ at 5.0 $\mu\text{g/ml}$. The lower limit of detection of both levofloxacin and ciprofloxacin was 0.1 $\mu\text{g/ml}$ in either serum or ultrafiltrate-dialysate.

Serum concentration-time data for levofloxacin and ciprofloxacin were analyzed by standard noncompartmental methods. Elimination of drugs was assumed to be first order. Pre-membrane drug concentrations in serum were used to determine pharmacokinetic parameters. The apparent terminal elimination rate constant (k_{el}) was determined by least-squares regression analysis of the terminal portion of the natural log concentration-time curve. Elimination half-life ($t_{1/2}$) was calculated as $0.693/k_{\text{el}}$. The maximum drug concentration in serum (C_{max}) was calculated as C_{first}/e^{-kt} , where C_{first} is the first measured drug concentration in serum (approximately 1 h postinfusion), k is k_{el} , and t is the time from end of the drug infusion to C_{first} . The minimum drug concentration in serum was determined by direct measurement or calculated as $C_{\text{last}} \times e^{-kt}$, where C_{last} is the last measured drug concentration in serum, k is k_{el} , and t is the time from C_{last} to the end of the

dosing interval. The area under the concentration-time curve from time zero to the end of the 24-h dosing interval (AUC_{0-24}) was calculated by the linear trapezoidal summation method. The total 24-h AUC was calculated by $\text{AUC}_{0-12} \times 2$ or $\text{AUC}_{0-48}/2$ for patients receiving ciprofloxacin every 12 h or levofloxacin every 48 h, respectively. Since the early sampling performed in many patients precluded assumptions of true pharmacokinetic steady-state conditions, volume of distribution was calculated by non-steady-state methods. Total systemic clearance (CL_S) was calculated by multiplying the volume of distribution by k_{el} .

The principles of drug clearance calculation during CRRT are reviewed elsewhere (2, 22, 25). Sieving coefficients (S) during CVVH were calculated by the formula $2 \times C_{\text{uf}}/(C_a + C_v)$, where C_{uf} is the drug concentration in ultrafiltrate, C_a is the drug concentration in premembrane blood, and C_v is the drug concentration in postmembrane blood. Clearance of drug across the membrane during CVVH (CL_{CVVH}) was calculated by the formula $S \times Q_{\text{uf}}$, where Q_{uf} is the ultrafiltration rate. Saturation coefficients (S_a) during CVVHDF were calculated by the formula $2 \times C_{\text{uf/d}}/(C_a + C_v)$, where $C_{\text{uf/d}}$ is the drug concentration in combined ultrafiltrate-dialysate. Drug clearance across the membrane during CVVHDF ($\text{CL}_{\text{CVVHDF}}$) was calculated by the formula $S_a \times (Q_{\text{uf}} + Q_d)$, where Q_d is the dialysate flow rate. The percentage of CL_S contributed by CL_{CVVH} or $\text{CL}_{\text{CVVHDF}}$ was calculated by either the formula $(\text{CL}_{\text{CVVH}}/\text{CL}_S) \times 100$ or the formula $(\text{CL}_{\text{CVVHDF}}/\text{CL}_S) \times 100$, respectively.

Differences between demographic variables among patients receiving either CVVH or CVVHDF during administration of each antibiotic were assessed for statistical significance by using a one-way analysis of variance fixed-effects model for continuous variables or a two-way chi-square test for categorical variables. Differences among calculated pharmacokinetic parameters were assessed by a two-tailed Mann-Whitney rank sum test for unpaired nonparametric data. All statistical tests were performed by using SPSS 8.0 for Windows (SPSS, Inc., Chicago, Ill.). P values of ≤ 0.05 were considered significant.

A total of 20 patients were enrolled in the study and completed sample collection. Levofloxacin was administered to four patients during CVVH and six patients during CVVHDF; five patients received ciprofloxacin during CVVH, and five additional patients did so during CVVHDF. Information regarding patient demographics, underlying illnesses, and CRRT therapy is presented in Tables 1 and 2. The mean \pm standard deviation age, weight, and APACHE II score of patients receiving levofloxacin were 48 ± 14 years, 89.4 ± 13.7 kg, and 30 ± 4 , respectively; those of patients receiving ciprofloxacin were 47 ± 18 years, 96.8 ± 15.7 kg, and 28 ± 5 , respectively. There were no statistically significant differences among patients receiving CVVH and CVVHDF in either the levofloxacin or the ciprofloxacin group. Levofloxacin and ciprofloxacin were apparently well tolerated by all of the patients, and no drug-related adverse effects were reported or observed during the study.

Calculated pharmacokinetic parameters are given in Table 3 for patients receiving levofloxacin and those receiving ciprofloxacin. Certain pharmacokinetic parameters, specifically, CL_S , $t_{1/2}$, and the minimum drug concentration in serum for levofloxacin and the C_{max} and AUC_{0-24} for ciprofloxacin, appeared to be somewhat dependent on whether patients were

TABLE 1. Demographic and clinical characteristics of the 20 patients in this study

Drug and patient no.	Age (yrs)	Ht (cm)	Wt (kg)	Sex ^a	APACHE II score ^b	Principal diagnosis ^c	Infectious diagnosis	Outcome
Levofloxacin								
1	34	168	99.9	F	23	Idiopathic thrombocytopenia purpura, respiratory failure	Pneumonia	Survived
2	23	170	91.8	F	29	Liver transplant with chronic rejection	Pneumonia	Survived
3	48	183	98.0	M	37	End-stage liver disease, acute GI bleeding	Pneumonia	Died
4	47	175	95.6	F	28	Pneumococcal sepsis, alcoholic liver disease	Pneumonia	Died
5	55	185	80.0	M	26	AAA repair with complications	Abdominal surgical wound infection	Died
6	41	163	69.9	M	34	End stage liver disease, acute GI bleeding	Pneumonia	Died
7	70	204	125.3	F	29	Sepsis, rhabdomyolysis	Cellulitis	Survived
8	46	182	79.4	F	25	Intra-abdominal sepsis	Intra-abdominal sepsis	Survived
9	66	173	80.0	M	31	Acetaminophen toxicity, acute liver failure	Pneumonia	Survived
10	52	178	83.2	F	35	End stage liver disease, intra-abdominal sepsis	Intra-abdominal sepsis	Died
Ciprofloxacin								
11	20	162	99.8	M	36	Acute liver failure, sepsis	Intra-abdominal sepsis	Died
12	54	182	89.0	M	31	End-stage heart disease	Pneumonia	Died
13	48	183	107.4	M	27	End-stage heart disease	Pneumonia	Died
14	42	169	88.4	M	25	End-stage liver disease	Intra-abdominal sepsis	Survived
15	23	185	91.8	F	18	Liver transplant with chronic rejection	Pneumonia	Survived
16	63	173	99.3	M	29	End stage heart disease, cardiogenic shock	Pneumonia	Survived
17	73	172	112.7	M	26	Sepsis, ARDS	Pneumonia	Died
18	41	178	133.8	M	32	Thoracic aortic dissection	Pneumonia	Survived
19	60	170	86.0	F	28	Necrotizing pancreatitis, ARDS	Necrotizing pancreatitis	Died
20	59	178	82.2	M	24	End stage liver disease, sepsis	Intra-abdominal sepsis	Died

^a F, female; M, male.

^b Score on admission to the intensive care unit.

^c AAA, abdominal aortic aneurysm; ARDS, acute respiratory distress syndrome; GI, gastrointestinal.

receiving CVVH or CVVHDF. However, this dependency was not consistent for all pharmacokinetic parameters and was not evident for both drugs.

The median levofloxacin S during CVVH and S_a during CVVHDF were estimated to be approximately 0.67 and 0.56, respectively. These calculated values were observed to be very consistent throughout the sampling periods among all of the patients and across various ultrafiltration rates. Approximately 26% of the levofloxacin CL_S was contributed by membrane clearance during CVVH, compared to 40% of the CL_S during CVVHDF, indicating that the clearance of levofloxacin was substantially enhanced during the use of both CRRT techniques. The mean ciprofloxacin S during CVVH and S_a during CVVHDF were estimated to be 0.67 and 0.63, respectively. These calculated values were also observed to be very consistent among all of the patients. Approximately 17% of the ciprofloxacin CL_S was accounted for by membrane clearance during both CVVH and CVVHDF. Compared to levofloxacin, the contribution of CRRT to total drug clearance thus appeared to be of less importance during ciprofloxacin therapy.

Levofloxacin elimination is nearly completely dependent on intact renal routes of excretion (3, 4); therefore, severe renal impairment causes very significant changes in CL_S and $t_{1/2}$. Previous studies of levofloxacin have demonstrated that the drug's $t_{1/2}$ is increased from 6.3 ± 0.6 h in subjects with normal renal function to 76 ± 42 h in patients with a creatinine clear-

ance of <20 ml/min and to 51 ± 24 h in anuric patients receiving hemodialysis (24; L. G. Gisclon, C. R. Curtin, S. C. Chien, R. Williams, M. Corrado, and V. Reichl, Abstr. 36th Intersci. Conf. Antimicrob. Agents Chemother., abstr. A13, 1996). A dosing regimen of 500 mg as a one-time loading dose, followed by 250 mg every 48 h, is currently recommended by the manufacturer for either dialyzed or undialyzed patients with a creatinine clearance of <20 ml/min (Levaquin [levofloxacin] prescribing information, Ortho-McNeil Pharmaceutical). The median levofloxacin $t_{1/2}$ of 27 h during CVVH and 19 h during CVVHDF determined in the present study are substantially shorter than the 51 to 76 h previously reported for anuric patients. However, the overall drug clearance in these patients was still markedly reduced despite the apparently enhanced elimination of levofloxacin by CRRT; the median CL_S was 0.42 to 0.58 ml/min/kg in study patients, compared to approximately 2.0 ml/min/kg in patients with normal renal function (3, 4, 8).

Adverse effects that may be frequently observed during fluoroquinolone therapy include central nervous system and gastrointestinal disturbances. Although relatively high sustained concentrations of levofloxacin were observed during this study (AUC_{0-24} of up to $155.3 \mu\text{g} \cdot \text{h/ml}$ compared to a mean AUC_{0-24} of up to $72.5 \mu\text{g} \cdot \text{h/ml}$ in patients with normal function receiving 500 mg intravenously per day) (21), no adverse events were reported or observed in patients receiving the drug. Studies of 1,000 mg of levofloxacin administered

TABLE 2. Etiologies of renal failure and details of continuous renal replacement therapy

Drug and patient no.	Etiology of renal failure ^a	Urine output/24 h (ml) ^b	Type of CRRT	Blood flow rate (ml/min)	Dialysis rate (liters/h) ^c	Ultrafiltration rate (ml/min)
Levofloxacin						
1	Idiopathic thrombocytopenia purpura	35	CVVH	150		14
2	ATN (unknown etiology)	0	CVVH	150		21
3	Hepatorenal syndrome	25	CVVH	150		20
4	Sepsis with MODS	40	CVVH	150		22
5	Ischemic ATN	15	CVVHDF	200	1.5	9
6	Hepatorenal syndrome	34	CVVHDF	150	1.0	17
7	Rhabdomyolysis	67	CVVHDF	150	1.0	23
8	Sepsis with MODS	106	CVVHDF	200	0.8	22
9	Acetaminophen toxicity	128	CVVHDF	150	1.0	17
10	Sepsis with MODS	62	CVVHDF	150	0.9	23
Ciprofloxacin						
11	Sepsis with MODS	5	CVVH	150		19
12	Sepsis with MODS	155	CVVH	150		15
13	ATN (unknown etiology)	134	CVVH	150		9
14	Hepatorenal syndrome	12	CVVH	150		19
15	ATN (unknown etiology)	0	CVVH	150		21
16	Ischemic ATN	0	CVVHDF	150	1.0	18
17	Sepsis with MODS	79	CVVHDF	150	1.0	14
18	Ischemic ATN	0	CVVHDF	150	1.0	14
19	Sepsis with MODS	90	CVVHDF	150	1.0	17
20	Sepsis with MODS	29	CVVHDF	150	0.8	24

^a ATN, acute tubular necrosis; MODS, multiple organ dysfunction syndrome.

^b During time of pharmacokinetic sampling.

^c Applicable only to patients receiving CVVHDF.

orally once daily to healthy volunteers demonstrated that a C_{\max} of $11.8 \pm 2.5 \mu\text{g/ml}$ and an AUC_{0-24} of $118 \pm 19 \mu\text{g} \cdot \text{h/ml}$ were well tolerated with no increased or unexpected drug-related adverse events (4).

Studies suggest that important pharmacodynamic predictors of the clinical efficacy of fluoroquinolones include the C_{\max}/MIC and $\text{AUC}_{0-24}/\text{MIC}$ ratios (10, 16, 17, 18, 20, 21, 27). Data from this study suggest that levofloxacin doses of approximately 250 mg/day in patients receiving CRRT are sufficient to produce C_{\max} and AUC_{0-24} values that are similar to those achieved following the administration of 500-mg intravenously to patients with normal renal function (i.e., C_{\max} of 6 to 7 $\mu\text{g/ml}$ and AUC_{0-24} of approximately 60 to 70 $\mu\text{g} \cdot \text{h/ml}$) (3, 4, 8). A levofloxacin regimen of 250 mg every 48 h, as recommended by the manufacturer for anuric patients receiving conventional hemodialysis, appears to be subtherapeutic in patients receiving CRRT since, based on the present study, that dose will not produce adequate C_{\max} or AUC_{0-24} values.

Total systemic clearance of ciprofloxacin in this patient population was noted to be highly variable, ranging from 0.34 to 1.70 ml/min/kg (compared to 7 to 8 ml/min/kg in patients with normal renal function) (1, 6, 11, 23, 26). This could possibly be attributed to variability in nonrenal mechanisms of drug clearance, as well as variations in the efficiency of clearance via CRRT. Normally, 30 to 50% of ciprofloxacin is eliminated through hepatic metabolism and biliary excretion. It has been demonstrated that ciprofloxacin CL_S does not always correlate well with creatinine clearance (1, 6, 11, 23, 26), and it has been suggested that increases in biliary clearance may effectively compensate for a reduction in renal clearance in patients with renal impairment (12, 13, 14). In the present study, 5 of the 10 patients receiving ciprofloxacin also had severe hepatic impair-

ment. Thus, it was expected that ciprofloxacin CL_S would be highly variable due to alterations in both renal and nonrenal routes of excretion, as well as the extracorporeal clearance by CRRT. However, the median percentage of CL_S represented by CRRT (17%) suggests that CRRT does not substantially contribute to ciprofloxacin clearance in patients with severe renal impairment. This is consistent with a previous case series of four patients in which only 6% of systemic ciprofloxacin clearance was attributable to CRRT (7). The CRRT clearance observed in the present study was also comparable to that previously reported in 10 patients receiving continuous arteriovenous hemodiafiltration or CVVHDF (5).

Ciprofloxacin doses of 200 to 400 mg administered intravenously every 18 to 24 h have been recommended for patients with creatinine clearances of 5 to 29 ml/min (Cipro I.V. [ciprofloxacin] prescribing information, Bayer Corporation). Drug concentrations observed in the present study suggest that a minimum dose of 400 mg/day is necessary to maintain effective concentrations of ciprofloxacin in patients receiving CRRT. Such a dose should achieve a C_{\max} of approximately 4 to 5 $\mu\text{g/ml}$, similar to peak concentrations achieved in patients with normal renal and hepatic functions. Doses of 400 to 800 mg/day have been recommended for patients receiving CRRT in previous studies as well (5, 7).

Previously published guidelines for drug dosing during CRRT recommend that the ciprofloxacin dosages recommended for anuric patients also be used for patients receiving CRRT (22). This is based on an estimated 2 to 4% CRRT removal calculated from protein binding and anuric clearance values found in the literature. Data from the present study, as well as two previous ones, suggest that CRRT clearance is higher than 2 to 4% but still represents a relatively minor

TABLE 3. Summary of levofloxacin and ciprofloxacin pharmacokinetic parameters for 20 patients receiving CRRT

Drug and patient no. or parameter	Dosing regimen	CRRT type	C _{max} (µg/ml)	C _{min} (µg/ml)	AUC ₀₋₂₄ (µg.h/ml)	V(liters/kg)	t _{1/2} (h)	CL _s		S/S _a	CRRT CL		
								ml/min	ml/min/kg		ml/min	ml/min/kg	% CL _s
Levofloxacin													
1	250 mg q24h	CVVH	7.0	3.1	155.3	0.7	19.6	42	0.42	0.84	12	0.13	30
2	500 mg q48h	CVVH	4.3	1.6	69.2	1.2	33.2	38	0.42	0.79	16	0.18	42
3	500 mg q48h	CVVH	7.6	2.1	113.7	0.8	24.9	35	0.36	0.29	6	0.06	16
4	500 mg q48h	CVVH	5.7	1.9	89.5	1.5	30.0	54	0.57	0.56	12	0.13	23
5	250 mg q24h	CVVHDF	4.3	1.5	72.2	1.1	18.6	54	0.68	0.45	15	0.19	28
6	250 mg q24h	CVVHDF	3.5	1.8	57.6	1.4	19.2	60	0.86	0.55	19	0.27	31
7	250 mg q24h	CVVHDF	5.0	2.1	82.7	0.7	18.5	52	0.41	0.93	36	0.29	70
8	500 mg q48h	CVVHDF	7.7	1.2	105.5	0.9	17.8	45	0.57	0.44	16	0.20	35
9	500 mg q48h	CVVHDF	7.4	1.3	102.1	1.0	19.1	47	0.58	0.63	22	0.27	46
10	500 mg q48h	CVVHDF	7.2	1.2	98.5	0.9	18.4	49	0.58	0.57	22	0.26	44
<i>P</i> value			0.25 ^a	0.04 ^a	0.48 ^a	0.84 ^b	0.07 ^b	0.05 ^b	0.05 ^b	0.12 ^b	0.006 ^b	0.006 ^b	0.12 ^b
Ciprofloxacin													
11	400 mg q24h	CVVH	7.2	4.7	138.0	1.1	38.1	34	0.34	0.65	13	0.13	37
12	400 mg q24h	CVVH	4.2	0.7	57.2	1.3	8.7	151	1.69	0.62	9	0.10	6
13	400 mg q24h	CVVH	6.3	3.0	106.7	1.0	21.5	55	0.51	0.73	7	0.06	13
14	400 mg q24h	CVVH	5.8	1.5	84.3	0.8	11.8	65	0.74	0.67	13	0.15	20
15	400 mg q24h	CVVH	3.2	0.9	46.8	1.4	12.3	117	1.27	0.95	20	0.21	17
16	400 mg q24h	CVVHDF	3.7	1.0	53.4	1.4	12.0	131	1.32	0.69	24	0.24	18
17	400 mg q24h	CVVHDF	3.2	0.3	40.3	0.9	6.9	208	1.56	0.63	19	0.14	9
18	400 mg q24h	CVVHDF	4.8	2.2	76.6	0.9	9.8	149	1.12	0.67	21	0.15	14
19	400 mg q12h	CVVHDF	5.8	2.4	89.8	1.1	8.6	122	1.42	0.62	21	0.24	17
20	400 mg q12h	CVVHDF	7.5	1.3	96.6	0.5	4.3	121	1.48	0.53	20	0.24	17
<i>P</i> value			0.06 ^c	0.13 ^c	0.07 ^c	0.50 ^d	0.13 ^d	0.14 ^d	0.14 ^d	0.20 ^d	0.06 ^d	0.06 ^d	0.55 ^d

^a Levofloxacin at 500 mg every 48 h (q48h) during CVVH versus levofloxacin at 500 mg q48h during CVVHDF; unable to compare levofloxacin 250-mg q24h regimens.

^b All levofloxacin CVVH regimens versus all levofloxacin CVVHDF regimens.

^c Ciprofloxacin at 400 mg q24h during CVVH versus ciprofloxacin at 400 mg q24h during CVVHDF.

^d All ciprofloxacin CVVH regimens versus all ciprofloxacin CVVHDF regimens.

fraction of CL_s. However, this and previous studies suggest that doses lower than 400 mg/day should be avoided during CRRT if adequate concentrations are to be maintained (5, 7).

This study was limited by the relatively small number of subjects enrolled and the high degree of pharmacokinetic variability observed during CRRT. However, patient numbers in this study are as large as or larger than those in the two previously published studies evaluating ciprofloxacin disposition during CRRT and the results obtained are comparable to those previously reported. This is also the only study to date evaluating levofloxacin disposition during CRRT. It should also be noted that patients not receiving CRRT were not included as controls for study patients; thus, relative alterations in pharmacokinetics must be compared with historical rather than study-derived data. Another limitation is that the potential for drug adsorption to membrane surfaces and a falsely increased apparent drug elimination rate was not evaluated. Because differences in ultrafiltration rates influence drug removal rates, failure to control CRRT parameters by a strict protocol may perhaps be seen as a further limitation to this study. However, because subjects were studied as they actually received CRRT and antibiotics for clinical indications without protocol-prescribed alterations in CRRT parameters or antibiotic dosing, the results are directly applicable to the clinical setting. Finally, possibilities for error in pharmacokinetic calculations are inherent in this study due to the fact that

collection of samples took place over relatively short periods of time in relation to the slow drug elimination rates and long half-lives.

Recommendations for drug dosing during CRRT that are based on calculated estimates of extracorporeal drug clearance rather than on actual clinical evaluations should be used cautiously and only in the absence of clinical data. The increasing frequency of use of CRRT in critically ill patients necessitates that clinicians active in this setting be knowledgeable concerning the potential of various CRRT techniques to markedly influence antimicrobial pharmacokinetics. Susceptibilities of suspected pathogens and desired drug concentrations should also be considered when selecting appropriate drug dosing regimens.

The results of this study suggest that levofloxacin doses of approximately 250 mg/day (250 mg every 24 h or 500 mg every 48 h) are appropriate for patients receiving either CVVH or CVVHDF. Ciprofloxacin elimination is highly variable in this population, and CRRT does not appear to contribute substantially to ciprofloxacin clearance. However, a ciprofloxacin dose of 400 mg/day appears to be necessary for the maintenance of typical drug concentrations in serum. The levofloxacin and ciprofloxacin dosing regimens recommended by the manufacturers for anuric patients and/or those receiving conventional hemodialysis appear to be unsuitable for patients receiving CRRT.

This investigator-initiated study was supported by grants from Ortho-McNeil Pharmaceutical and the Bayer Corporation.

REFERENCES

- Boelaert, J., Y. Valcke, M. Schurgers, R. Daneels, M. Rosseneu, M. Rousseel, and M. G. Bogaert. 1985. The pharmacokinetics of ciprofloxacin in patients with impaired renal function. *J. Antimicrob. Chemother.* **16**:87-93.
- Bressolle, F., J. J. Kinowski, E. de la Coussaye, N. Wynn, J. Eledjam, and M. Galtier. 1994. Clinical pharmacokinetics during continuous haemofiltration. *Clin. Pharmacokinet.* **26**:457-471.
- Chien, S.-C., M. C. Rogge, L. G. Gisclon, C. Curtin, F. Wong, J. Natarajan, R. R. Williams, C. L. Fowler, W. K. Cheung, and A. T. Chow. 1997. Pharmacokinetic profile of levofloxacin following once-daily 500-milligram oral or intravenous doses. *Antimicrob. Agents Chemother.* **41**:2256-2260.
- Chien, S.-C., F. A. Wong, C. L. Fowler, S. V. Callery-D'Amico, R. R. Williams, R. Nayak, and A. T. Chow. 1998. Double-blind evaluation of the safety and pharmacokinetics of multiple oral once-daily 750-mg and 1-gram doses of levofloxacin in healthy volunteers. *Antimicrob. Agents Chemother.* **42**:885-888.
- Davies, S. P., B. S. Azadian, W. J. Kox, and E. A. Brown. 1992. Pharmacokinetics of ciprofloxacin and vancomycin in patients with acute renal failure treated by continuous hemodialysis. *Nephrol. Dial. Transplant.* **7**:848-854.
- Drusano, G. L., M. Weir, A. Forrest, K. Plaisance, T. Emm, and H. C. Standiford. 1987. Pharmacokinetics of intravenously administered ciprofloxacin in patients with various degrees of renal function. *Antimicrob. Agents Chemother.* **31**:860-864.
- Fish, D. N., J. L. Bainbridge, and C. A. Peloquin. 1995. Variable disposition of ciprofloxacin in critically ill patients undergoing continuous arteriovenous hemodiafiltration. *Pharmacotherapy* **15**:236-245.
- Fish, D. N., and A. T. Chow. 1997. The clinical pharmacokinetics of levofloxacin. *Clin. Pharmacokinet.* **32**:101-119.
- Forni, L. G., and P. J. Hilton. 1997. Continuous hemofiltration in the treatment of acute renal failure. *N. Eng. J. Med.* **336**:1303-1309.
- Forrest, A., D. E. Nix, C. H. Ballow, T. F. Goss, M. C. Birmingham, and J. J. Schentag. 1993. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob. Agents Chemother.* **37**:1073-1081.
- Gasser, T. C., S. C. Ebert, P. H. Graversen, and P. O. Madsen. 1987. Pharmacokinetic study of ciprofloxacin in patients with impaired renal function. *Am. J. Med.* **82**(Suppl. 4A):139-141.
- Gonzales, M. A., F. Uribe, S. D. Moisen, A. P. Fuster, A. Selen, P. G. Welling, and B. Painter. 1984. Multiple-dose pharmacokinetics and safety of ciprofloxacin in normal volunteers. *Antimicrob. Agents Chemother.* **26**:741-744.
- Hoeffken, G., H. Lode, C. Prinzing, K. Borner, and P. Koeppe. 1985. Pharmacokinetics of ciprofloxacin after oral and parenteral administration. *Antimicrob. Agents Chemother.* **27**:375-379.
- Jones, E. M., C. M. McMullin, A. J. Hedges, A. M. Lovering, L. O. White, D. S. Reeves, and A. P. MacGowan. 1997. The pharmacokinetics of intravenous ciprofloxacin 400 mg 12 h in patients with severe sepsis: the effect of renal function and intra-abdominal disease. *J. Antimicrob. Chemother.* **40**:121-124.
- Joy, M. S., G. R. Matzke, D. K. Armstrong, M. A. Marx, and B. J. Zarowitz. 1998. A primer on continuous renal replacement therapy for critically ill patients. *Ann. Pharmacother.* **32**:362-375.
- Lacy, M. K., W. Lu, X. Xu, P. R. Tessier, D. P. Nicolau, R. Quintiliani, and C. H. Nightingale. 1999. Pharmacodynamic comparisons of levofloxacin, ciprofloxacin, and ampicillin against *Streptococcus pneumoniae* in an in vitro model of infection. *Antimicrob. Agents Chemother.* **43**:672-677.
- Lister, P. D., and C. C. Sanders. 1999. Pharmacodynamics of levofloxacin and ciprofloxacin against *Streptococcus pneumoniae*. *J. Antimicrob. Chemother.* **43**:79-86.
- Madaras-Kelly, K. J., B. E. Ostergaard, L. B. Hovde, and J. C. Rotschafer. 1996. Twenty-four-hour area under the concentration-time curve/MIC ratio as a generic predictor of fluoroquinolone antimicrobial effect by using three strains of *Pseudomonas aeruginosa* and an in vitro pharmacodynamic model. *Antimicrob. Agents Chemother.* **40**:627-632.
- Nix, D. E., J. M. DeVito, and J. J. Schentag. 1985. Liquid chromatographic determination of ciprofloxacin in serum and urine. *Clin. Chem.* **31**:684-686.
- Peloquin, C. A., T. J. Cumbo, D. E. Nix, M. F. Sands, and J. J. Schentag. 1989. Evaluation of intravenous ciprofloxacin in patients with nosocomial lower respiratory tract infections. Impact of plasma concentrations, organism, minimum inhibitory concentration, and clinical condition on bacterial eradication. *Arch. Intern. Med.* **149**:2269-2273.
- Preston, S. L., G. L. Drusano, A. L. Berman, C. L. Fowler, A. T. Chow, B. Dornseif, V. Reichl, J. Natarajan, and M. Corrado. 1998. Pharmacodynamics of levofloxacin. A new paradigm for early clinical trials. *JAMA* **279**:125-129.
- Reetze-Bonorden, P., J. Bohler, and E. Keller. 1993. Drug dosing in patients during continuous renal replacement therapy: pharmacokinetic and therapeutic considerations. *Clin. Pharmacokinet.* **24**:362-379.
- Roberts, D. E., and J. D. Williams. 1989. Ciprofloxacin in renal failure. *J. Antimicrob. Chemother.* **23**:817-823.
- Saito, A., K. Oguchi, and Y. Harada. 1992. Pharmacokinetics of levofloxacin in patients with impaired renal function. *Chemotherapy* **40**(Suppl. 3):188-195.
- Schetz, M., P. Ferdinande, R. Van den Berghe, C. Verwaest, and P. Lauwers. 1995. Pharmacokinetics of continuous renal replacement therapy. *Intensive Care Med.* **21**:612-620.
- Singlas, E., A. M. Taburet, I. Landru, H. Albin, and J. P. H. Ryckelincx. 1987. Pharmacokinetics of ciprofloxacin tablets in renal failure: influence of haemodialysis. *Eur. J. Clin. Pharmacol.* **31**:589-593.
- Thomas, J. K., A. Forrest, S. M. Bhavnani, J. M. Hyatt, A. Cheng, C. H. Ballow, and J. J. Schentag. 1998. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. *Antimicrob. Agents Chemother.* **42**:521-527.