

## Pharmacokinetic Profiles of High-Dose Intravenous Ciprofloxacin in Severe Sepsis

J. LIPMAN,<sup>1\*</sup> J. SCRIBANTE,<sup>2</sup> A. G. S. GOUS,<sup>2</sup> H. HON,<sup>2</sup> S. TSHUKUTSOANE,<sup>2</sup>  
AND THE BARAGWANATH CIPROFLOXACIN STUDY GROUP†

*University of Queensland, Brisbane, Queensland, Australia,<sup>1</sup> and  
University of Witwatersrand, Soweto, South Africa<sup>2</sup>*

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The pharmacokinetics of 400 mg of ciprofloxacin given intravenously (i.v.) every 8 h (q8h) in severely septic adults was documented in a multidisciplinary, tertiary referral intensive care unit (ICU). Sixteen evaluable patients (three pharmacokinetic profiles) without renal dysfunction and with severe sepsis were studied. Ciprofloxacin at a dosage of 400 mg given i.v. q8h was administered over 1 h. Plasma samples for assay (high-pressure liquid chromatography) were taken at timed intervals (preinfusion, at the end of infusion, and at 1, 2, 3, 5, and 7 h postinfusion) for first-dose kinetics (day 0 [D0]), D2, and between D6 and D8. All pharmacokinetic variables were calculated by noncompartmental methods. Standard intensive care was provided. Peak ciprofloxacin concentrations were as follows: D0,  $6.01 \pm 1.93$  mg/liter; D2,  $6.68 \pm 2.01$  mg/liter; and D6 to D8  $6.45 \pm 1.54$  mg/liter. Trough levels were as follows: D0,  $0.6 \pm 0.5$  mg/liter; D2,  $0.7 \pm 0.4$  mg/liter; and D6 to D8  $0.6 \pm 0.4$  mg/liter. The areas under the concentration curves (8 h) were as follows: D0,  $13.3 \pm 3.8$  mg · h/liter; D2,  $16.8 \pm 5.4$  mg · h/liter; and D6 to D8,  $15.5 \pm 4.7$  mg · h/liter. No drug-related serious adverse events occurred. For 17 of 18 patients enrolled in the study, the causative organisms were susceptible to ciprofloxacin. One patient developed renal failure (non-drug related) after the administration of three doses of ciprofloxacin. One patient was infected with ciprofloxacin-resistant organisms on enrollment. Nine of 16 evaluable patients had clinical cures, and 8 had bacteriological cures. One patient developed a ciprofloxacin-resistant superinfection. In two patients the clinical course was indeterminate. Two bacteriological failures occurred. We conclude that in critically ill adults ciprofloxacin at a dosage of 400 mg given i.v. q8h is safe. Its pharmacokinetic profile provides bactericidal activity against most organisms encountered in an ICU. Except for some initial accumulation on D2, no further accumulation occurred in patients without renal failure. Ciprofloxacin should be administered i.v. at a dosage of 400 mg q8h for severe sepsis.

Ciprofloxacin is a fluoroquinolone with markedly increased activity over those of other members of its class, such as nalidixic acid and norfloxacin. The compound is active against a wide variety of gram-negative organisms as well as many gram-positive organisms, with MICs generally in the range of 0.01 to 2.0 mg/liter (5). It should therefore be ideal for use against many nosocomial infections.

The initial enthusiasm and excitement over the use of ciprofloxacin in the management of severe infections (particularly nosocomial infections) have been tempered by reports of clinical failure (15, 18).

Original registration data for ciprofloxacin were for the use of oral dosages of 500 mg twice daily (b.i.d.) or, for severe infections, 750 mg b.i.d. Initial registration data for intravenous (i.v.) use were for the use of 200 mg b.i.d., with problems stressed much later (8). Data suggest that the area under the plasma concentration-time curve (AUC) for 750 mg given

orally b.i.d. is similar to that for 400 mg given three times daily i.v. (25).

Initial data (8), confirmed more recently (3, 4, 12, 19, 22), have indicated the development of resistance to ciprofloxacin if the drug is used at inappropriately low doses.

The limited pharmacokinetic data for 400 mg given to volunteers i.v. every 8 h (q8h) have been encouraging, with adequate AUCs being achieved (25, 26).

For i.v. use, particularly in severe infections or when the MICs for the organisms may be high, e.g., in intensive care units, it would seem that 400 mg q8h may be the better dosing option.

**Aim.** Because there is a paucity of clinical studies with a dosage of 1,200 mg/day (10, 11) we studied the pharmacokinetics of ciprofloxacin given by i.v. injection at a dosage of 400 mg q8h in critically ill patients who had severe sepsis.

### MATERIALS AND METHODS

**Clinical setting.** Baragwanath Hospital is a 3,000-bed university and tertiary referral hospital in Soweto, South Africa. The intensive care unit is a 24-bed multidisciplinary unit that admits almost 1,000 patients per year and that runs at about a 95% bed occupancy rate.

Institutional Review Board and University Ethics Committee approval was obtained. When the trial started, a dose of 400 mg was not registered for use in South Africa, and thus, South African Medicines Control Council approval was also obtained.

**Study design.** We conducted a consecutive open-label study.

**Study patients.** Critically ill patients in the intensive care unit with nosocomial infections (nosocomial severe sepsis) who needed antibiotics and from whom informed consent could be obtained were given ciprofloxacin i.v. at a dosage of 400 mg q8h by continuous infusion over 1 h. Patients with diagnosed intra-abdominal sepsis were part of another trial being performed concomitantly and so they were not enrolled in the trial described here.

\* Corresponding author. Mailing address: Intensive Care Facility, Royal Brisbane Hospital, Division of Anaesthesiology and Intensive Care, University of Queensland, Brisbane 4029, Queensland, Australia. Phone: 61 7 3253 1847. Fax: 61 7 3253 7202. E-mail: jlipman@gasbone.herston.uq.edu.au.

† The Baragwanath Ciprofloxacin Study Group comprises M. Pinder, R. Piccolo, and E. Nel of the University of Witwatersrand, Soweto, South Africa; L. Verhoef of Bayer SA, South Africa; and K. Klugman, M. Khoosal, G. L. Saunders, and H. H. Crewe-Brown of the South African Institute of Medical Research, Johannesburg, South Africa. The study was conducted at Baragwanath Hospital, University of Witwatersrand, Soweto, South Africa.

(i) **Severe sepsis.** For the purpose of this study, the ACCP-SCCM Consensus Conference definitions for sepsis, severe sepsis, and organ failure were used (1). In brief, sepsis was defined as (i) clinical evidence of an infection (a primary site, other than intra-abdominal, or radiologic studies which revealed potentially infected material) (ii) plus at least two of the following: fever (rectal or core;  $>38.3$  or  $<35.6^{\circ}\text{C}$ ), tachycardia ( $>90$  beats/min), respiratory rate of  $>20$  breaths/min while spontaneously breathing or mechanically ventilated due to primary pulmonary disease, or a leukocyte count of  $>12,000$  cells/ $\text{mm}^3$ ,  $<4,000$  cells/ $\text{mm}^3$ , or  $>10\%$  immature (band) forms. Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension.

(ii) **Exclusion criteria.** Patients were excluded from the study if their age was  $<18$  years; if they had a history of allergy to ciprofloxacin, other quinolone derivatives, or metronidazole; if they had renal insufficiency with a creatinine clearance ( $\text{CL}_{\text{CR}}$ ) of  $<30$  ml/min or were on hemodialysis (we do not perform peritoneal dialysis); if they were pregnant or nursing or if the possibility of pregnancy could not be excluded, if they were taking drugs which have a significant influence on liver enzyme induction, i.e., benzodiazepines, barbiturates, phenytoin, rifampin, and isoniazid; or if they were taking drugs which have a significant influence on liver enzyme inhibition, i.e., theophylline and cimetidine.

(iii) **Evaluable patients.** For study purposes, patients needed to have received ciprofloxacin for a minimum period of 7 days (day 0 [D0] to D6) and to have had three pharmacokinetic profiles done (first dose [D0], D2, and between D6 and D8). If clinically indicated, the drug could be continued for up to 14 days.

**Specimen collection.** The pharmacokinetic profiles of ciprofloxacin in plasma were obtained for the first dose (D0), D2, and between D6 and D8. For each profile arterial blood was collected just before the administration of the antibiotic (time zero [T0]). Four hundred milligrams of ciprofloxacin was then infused i.v. via a dedicated i.v. line over 1 h. Arterial blood samples taken after a half hour (T0.5) and at T1 (just before the end of infusion), T2 (2 h after the start of infusion), T3, T4, T6, and T8 (just before administration of the next dose). Blood was placed into ammonium heparinized tubes, the tubes were immediately centrifuged at room temperature for 2 min, and the plasma was separated. The plasma was then stored at  $-20^{\circ}\text{C}$  until analysis.

**Ciprofloxacin assay.** The concentrations of ciprofloxacin in plasma were determined by high-pressure liquid chromatography with fluorescence detection by using on-column focusing. Reversed-phase chromatography with gradient elution and fluorescence detection was applied to quantify the analytes by the external standard procedure. Plasma samples were prepared by dilution involving a protein precipitation step for plasma with an acetonitrile buffer mixture. Four hundred microliters of plasma was diluted with 400  $\mu\text{l}$  of sample solvent; for concentrations above 2 mg/liter, 200  $\mu\text{l}$  of plasma was diluted with 800  $\mu\text{l}$  of sample solvent. The assay was linear over the range of 0.01 to 2 mg/liter. The concentrations for the quality control samples ranged between 0.01 and 2.0 mg/liter. The intra- and interassays coefficient of variation, determined with quality control samples, ranged from 2.4 to 8.4%.

**Pharmacokinetic analysis.** Mean and individual plasma ciprofloxacin concentrations were tabulated with relevant descriptive statistics. The mean and individual concentration-time profiles were also plotted. The following pharmacokinetic variables were calculated from the concentrations in plasma. In the present study the peak concentration ( $C_{\text{max}}$ ) was the concentration at the end of the infusion period and the trough concentration ( $C_{\text{min}}$ ) was the concentration 8 h after the start of the infusion. The terminal half-life ( $t_{1/2}$ ) was calculated from the adjustment of a triple-exponential-function ( $C_1e^{-z_1t} - C_2e^{-z_2t} + C_3e^{-z_3t}$ ) plasma concentration-versus-time profile. Here  $C_1$ ,  $C_2$ , and  $C_3$  are concentrations at three different times;  $z_1$ ,  $z_2$ , and  $z_3$  are the rate constants; and  $t$  is time. The regressions were done by the method of weighing nonlinear least squares with weights that are inversely proportional to the concentrations. The  $t_{1/2}$  was then calculated as  $t_{1/2} = (\ln 2)/z_3$ . The AUC from time zero to infinity ( $\text{AUC}_{0-\infty}$ ) for D0 and the AUC during the dosing interval for D2 and D6 to D8 ( $\text{AUC}_{\tau, \text{SS}}$ ) were calculated according to the linear trapezoidal rule from 0 h to the last quantifiable concentration after drug administration.  $\text{AUC}_{\tau, \text{SS}}$  was extrapolated to infinity by adding  $C_{\text{last}}/z$ , where  $C_{\text{last}}$  is the final concentration measured. Total body clearance (CL) was calculated as  $\text{CL} = \text{dose}/\text{AUC}$ , and the apparent volume of distribution (V) was calculated as  $V = \text{CL} \times \text{MRT}$ , where MRT is the mean residence time. MRT was calculated by the equation  $\text{MRT} = \text{AUMC}_{0-\infty}/\text{AUC}$ , where  $\text{AUMC}_{0-\infty}$  is the area under the first statistical moment curve from time zero to infinity. The AUC/MIC ratio was calculated as the AUC over 24 h divided by the MIC. The AUC over 24 h was calculated as the AUC over the 8-h dosing interval multiplied by 3.

The accumulation ratios were calculated by the equation  $\text{AUC}_{0-8\text{h}}/\text{AUC}_{0-8\text{h, dose } 1}$ , where  $\text{AUC}_{0-8\text{h}}$  is the AUC from time zero to 8 h at steady state and  $\text{AUC}_{0-8\text{h, dose } 1}$  is the AUC from time zero to 8 h after administration of the first dose.

**Statistical analysis.** Descriptive and summary statistics were used. Variables on D0 (see Table 2) were compared to variables on D2 and D6 to D8 by Student's  $t$  test.

**Concomitant antimicrobial therapy.** If it was thought to be clinically applicable (with or without microbiological confirmation), vancomycin was added for the treatment of enterococcal coinfection. Similarly, if anaerobic organisms were suspected or isolated, metronidazole was used. Amphotericin B was added to the therapy if fungi were suspected or isolated.

**Other concomitant therapy.** Standard intensive care techniques were used, and full supportive therapy was provided to all patients as needed.

**Clinical and microbiological evaluations.** (i) **Criteria for evaluation of clinical response.** Patients were evaluated at the conclusion of therapy as follows. (i) Cure was the disappearance of all signs and symptoms related to the infection. (ii) Improvement was a marked or moderate reduction in the severity and/or number of signs and symptoms of infection. (iii) An indeterminate response was an insufficient lessening of the signs and symptoms of infection to qualify as improvement. (iv) Failure was the complete failure of treatment.

(ii) **Criteria for evaluation of bacteriological response.** Cure (bacteriological response) for this study was defined when a culture of a clinical sample became negative and remained negative upon continued culturing. Cure was presumed if repeat samples for culture were not obtained due to the absence of material for culture for a patient who had responded to therapy. Failure was defined as the lack of eradication of the original organism and clinical failure as a result of infection with the original organism. Superinfection was deemed to have occurred if during or immediately after the end of therapy there was growth of a new organism that was judged to be causing an infectious process. Secondary infections were infections occurring after the trial.

Bacterial isolates were identified by genus and, usually, species. Susceptibility to relevant antibiotics was tested by the disc diffusion and/or the broth or agar dilution technique according to standards of the National Committee for Clinical Laboratory Standards (17) in tests with American Type Culture Collection control strains. The MICs of ciprofloxacin were obtained.

## RESULTS

To obtain 16 evaluable patients, 18 critically ill patients were enrolled in the study. Their ages ranged from 18 to 54 years. Their Apache II scores on the day of enrollment ranged from 5 to 23, with a mean of 14 (Table 1).

The relevant pharmacokinetics are presented in Table 2.

Figure 1a, b, and c display the plasma ciprofloxacin concentrations for D0, D2, and D6 to D8, respectively.

At least one organism susceptible to ciprofloxacin, assessed to be the possible pathogen and therefore to be the causative agent, was isolated from 17 of the 18 patients (Table 1). Twelve patients were assessed to have demonstrated infections and 6 had suspected infections (27).

One patient was enrolled in the study and was subsequently found to have a polymicrobial infection including infection with gram-negative organisms resistant to ciprofloxacin (the patient had a gunshot wound to the chest, paraplegia, and empyema) and so was technically regarded as a dropout. One patient developed renal failure after receipt of the third dose of ciprofloxacin (assessed as non-drug related) and soon after that died of multiple organ failure from overwhelming sepsis. Four other patients died after the trial was completed.

No drug-related serious adverse events were directly attributable to ciprofloxacin. Some adverse events which may have occurred were attributed to either the drugs that were used concomitantly or the intrinsic disease process and its severity. One patient had a generalized seizure while still on ciprofloxacin subsequent to the D6 to D8 pharmacokinetic profile. Although this could have been related to ciprofloxacin, it could just as likely have been due to withdrawal from benzodiazepine, the drug used to sedate the patient while the patient was on a ventilator. All other adverse events that were noted during the trial were assessed to be unrelated to ciprofloxacin and were assessed to be related to the patients' underlying disease profiles (e.g., hemodynamic compromise, severe hypoxemia, and tension pneumothorax).

The clinical and microbiological data are summarized in Table 1. Of the 16 evaluable patients, 9 had clinical cures and 8 had bacteriological cures (no causative organism was isolated from 1 patient). While on ciprofloxacin one patient developed a superinfection with an *Acinetobacter* isolate resistant to ciprofloxacin. For two patients assessment of antibiotic therapy was impossible because there was inadequate source control (inadequate abscess drainage or persistent drainage of pus from the infected site). In two patients, organisms (both *Acinetobac-*

TABLE 1. Relevant clinical and microbiological data for all patients enrolled in the study

Patient no.	Apache II score	Infective diagnosis	Bacteriological outcome	Clinical outcome	Organism	Site <sup>a</sup>	MIC (µg/ml)
1	14	Nosocomial pneumonia	Cure	Cure	<i>Acinetobacter baumannii</i>	TA	0.25
2	17	Nosocomial pneumonia	Failure	Failure	<i>Klebsiella</i> species	TA	<0.13
3	17	Nosocomial pneumonia		Dropped out	<i>Acinetobacter baumannii</i>	TA	0.50
					<i>Klebsiella</i> species	TA	<0.13
					<i>Acinetobacter baumannii</i>	TA	>64
4	16	Sepsis (bacteremia)		Resistant organism	<i>Acinetobacter baumannii</i>	BLD	>64
5	16	Nosocomial pneumonia	Cure	Cure	<i>Serratia marcescens</i>	BLD	<0.13
					<i>Klebsiella</i> species	BLD	<0.13
					<i>Serratia marcescens</i>	TA	<0.13
6	5	Nosocomial pneumonia	Cure	Cure	<i>Enterococcus faecalis</i>	BLD	0.25
					<i>Klebsiella oxytoca</i>	TA	<0.13
					<i>Staphylococcus epidermidis</i>	TA	<0.13
7	12	Nosocomial pneumonia	Cure	Cure	<i>Acinetobacter baumannii</i>	BLD & TA	<0.13 & <0.13
8	19	Nosocomial pneumonia		Superinfection	<i>Pseudomonas aeruginosa</i>	TA	<0.13
					<i>Klebsiella</i> species	TA	1.00
9	13	Nosocomial pneumonia	Cure	Cure	<i>Staphylococcus aureus</i>	PF	<0.13
					Viridans group streptococcus	PF	<0.13
10	19	Nosocomial pneumonia	Failure	Failure	<i>Klebsiella</i> species	BLD & PF	<0.13 & 0.13
					<i>Pseudomonas aeruginosa</i>	PF	0.13
					<i>Staphylococcus aureus</i>	PF	0.13
11	23	Empyema		Inadequate source control	<i>Streptococcus equinus</i>	BLD & ICD	4.00 & 1.00
					<i>Staphylococcus aureus</i>	TA	0.25
					<i>Klebsiella</i> species	TA	0.13
					<i>Klebsiella</i> species	ICD	0.13
					<i>Proteus mirabilis</i>	TA	0.13
					<i>Streptococcus milleri</i>	ICD	0.50
					<i>Acinetobacter baumannii</i>	BLD	0.25
12	14	Nosocomial pneumonia	Cure	Cure	None	None	None
13	11	Soft tissue infection	No organism	Cure	None	None	None
14	9	Nosocomial pneumonia		Resistant organism	<i>Acinetobacter baumannii</i>	TA	>64
15	15	Soft tissue infection	Cure	Cure	<i>Staphylococcus aureus</i>	BLD	0.25
16	11	Neck abscess		Inadequate source control	<i>Proteus mirabilis</i>	Pus	<0.13
					<i>Streptococcus milleri</i>	Pus	0.25
					<i>Pseudomonas aeruginosa</i>	TA	0.50
17	8	Empyema		Dropped out	<i>Enterococcus faecalis</i>	PF	None
					<i>Acinetobacter baumannii</i>	PF	None
18	13	Nosocomial pneumonia	Cure	Cure	<i>Acinetobacter baumannii</i>	TA	0.13

<sup>a</sup> TA, tracheal aspirate; BLD, blood; PF, pleural fluid; ICD, intercostal drain.

ter isolates; one in blood and one in sputum) resistant to ciprofloxacin were isolated ab initio. The clinical course for these two patients was indeterminate, i.e., they were assessed neither to improve nor deteriorate while on ciprofloxacin. There were two antibiotic (bacteriological) failures due to the apparent emergence of resistance; i.e., two patients had an unresponsive clinical course while they were on ciprofloxacin and newly ciprofloxacin-resistant organisms were isolated.

Four patients developed secondary infections after receiving ciprofloxacin and needed another course of antibiotics; only one of the four patients eventually recovered.

## DISCUSSION

By means of in vitro testing it has been shown that beta-lactam antibiotics eradicate organisms by a slow continuous killing characteristic. For this group of antibiotics it is the actual time that the antibiotic concentration is maintained above the MIC for the organisms that is all important (2, 9, 23, 28). Beta-lactam antibiotics have no postantibiotic effect (PAE) (16, 28). This is in contrast to the aminoglycosides, which have a dose-dependent killing characteristic with a significant PAE (16). Fluoroquinolones in general have killing characteristics that differ from those of both these classes of antibiotics. They have a dose-dependent killing initially and then a slower killing curve (4, 5, 19) and also exhibit a PAE (4-7, 19).

Like many other antibiotics the optimal i.v. dose of cipro-

floxacin is unknown (8). Various theoretical suggestions for optimal dosing regimens have been put forward.

High peak concentrations in plasma/MIC ratios and AUC/MIC ratios (area under the inhibitory curve cumulative over 24 h/MIC) of >100 to 150 have been suggested to be a guide to better i.v. dosing (11, 13, 19-21).

From a theoretical point of view, then, for the quinolones, a high  $C_{max}$  would help in the killing of the organism, as would the time above the MIC and the AUC. All of this integrated into one is the AUC/MIC ratio. Any PAE of the quinolones would be an added benefit to the killing characteristics. It has been suggested that a  $C_{max}$  of up to eight times the MIC would be optimal (21). Our average  $C_{max}$  was almost 6.4 mg/ml. In relation to our data this would mean that our  $C_{max}$  is eight

TABLE 2. Values of pharmacokinetic parameters for ciprofloxacin given i.v. at 400 mg q8h for the treatment of severe sepsis<sup>a</sup>

Day	$C_{max}$ (mg/liter)	$C_{min}$ (mg/liter)	$t_{1/2}$ (h)	CL (liter/h/kg)	V (liters/kg)	AUC <sub>0-8</sub> (mg · h/liter)
0 (n = 18)	6.01 (1.93)	0.6 (0.5)	3.9 (1.7)	0.4 (0.2)	1.4 (0.3)	13.3 (3.8)
2 (n = 17)	6.68 (2.01)	0.7 (0.4)	3.2 (0.9)	0.4 (0.2)	1.2 (0.3)	16.8 (5.4)
6-8 (n = 16)	6.45 (1.54)	0.6 (0.4)	3.3 (2.0)	0.4 (0.1)	1.3 (0.5)	15.5 (4.7)

<sup>a</sup> Values are given as means (SDs). There was no statistical significance between the groups (Student's *t* test).

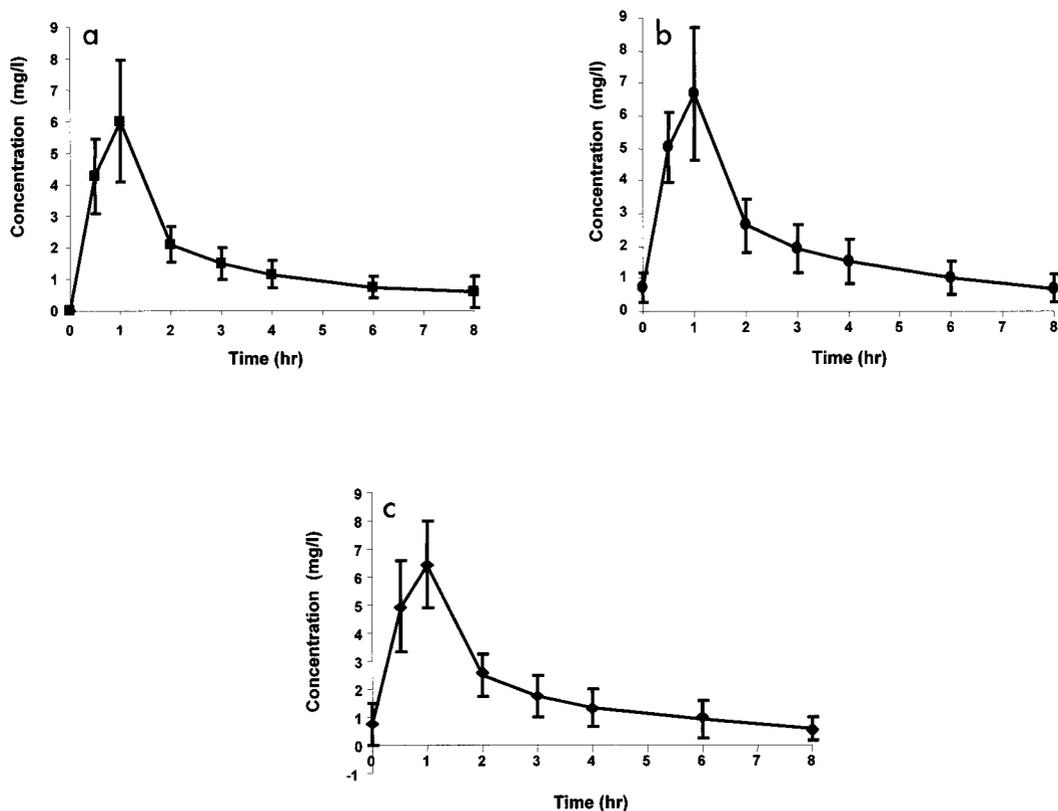


FIG. 1. Mean  $\pm$  SD plasma ciprofloxacin concentration versus time on D0 (a), D2 (b), and D6 to D8 (c).

times the MIC (0.8 mg/liter). Another suggestion for optimal dosing is an AUC/MIC ratio of  $>100$  to  $150$  (11, 13, 19–21). Our AUC/MIC ratio (Table 2; AUC [which is for a dose given q8h] multiplied by  $3/\text{MIC}$ ) was above  $100$  for organisms for which MICs were roughly below  $0.5$  mg/liter. The  $C_{\min}$  from our data was above  $0.5$  mg/liter. This means that ciprofloxacin was maintained above the MIC for most of the dosing period. Our data therefore mean that the theoretical optimal dosing criteria are almost met in most aspects, i.e., a high  $C_{\max}$ , a high AUC/MIC ratio, and a long period of time above the MIC. All of this was obtained with only one possible drug-related side effect: a seizure in one patient. Any lower dose or longer duration between doses would produce less optimal pharmacokinetics. Higher doses may well produce more side effects because accumulation would almost certainly occur.

Although our MIC data presented here are thorough (Table 1), the numbers in the study are too small to comment solely on the bactericidal effect of AUC/MIC ratios. These data will be part of a larger study to be reported later.

The accumulation ratios between D0 and D2 and D6 to D8 revealed some initial accumulation but no subsequent accumulation. No accumulation was noted between D2 and D6 to D8. Calculated accumulated ratios between D0 and D2 and D6 to D8 were  $1.3$  (standard deviation [SD] =  $0.3$ ) and  $1.3$  (SD =  $0.4$ ), respectively. The ratio between D2 and D6 to D8 was  $1$  (SD =  $0.2$ ). There were no statistical differences when comparing  $C_{\min}$  between the 3 study days (Table 2). We demonstrated that, except initially, no further accumulation of ciprofloxacin with our dosing regimen of  $400$  mg q8h occurred. This is an important finding because it means that the frequency of dosing in this dosing regimen cannot be regarded as being too frequent.

These findings lead us to believe that the ideal i.v. dosage of ciprofloxacin for the severely ill patient is  $400$  mg q8h. It provides a high  $C_{\max}$ , a high AUC/MIC ratio, and a long period of time above the MIC, all without accumulation at the end of the dosing interval. Any PAE that ciprofloxacin may exhibit would be an added advantage to these characteristics.

We stress that none of our patients had renal failure, which was an exclusion criterion for the trial, and if renal failure had developed, the trial would have been discontinued for those patients. Shah et al. (24) have shown that ciprofloxacin accumulates in the presence of renal dysfunction. The dosage of  $400$  mg q8h should be decreased to every  $12$  h for patients with  $\text{CL}_{\text{CRS}}$  of between  $31$  and  $60$  ml/min/ $1.73$  m<sup>2</sup> and should be decreased further to a daily dose if  $\text{CL}_{\text{CRS}}$  are less than  $30$  ml/min/ $1.73$  m<sup>2</sup>.

Our data are the first that fully document the pharmacokinetics of and the clinical response to ciprofloxacin given i.v. at a dosage of  $400$  mg q8h to critically ill patients, more particularly, patients with severe sepsis. Fink et al. (10) reported good clinical results in a study of severe pneumonia when they administered  $400$  mg of ciprofloxacin q8h with imipenem at  $1$  g q8h. They showed high clinical ( $69\%$ ) and bacteriological (also  $69\%$ ) cure rates with ciprofloxacin, a finding in keeping with our results. The low rate of side effects ( $1\%$  seizures) in their study was similar to that in our study. A dosage of  $400$  mg q8h would therefore seem to be the preferred dose for the treatment of severe infections. This has been suggested from in vitro studies by Bauernfeind (4). Our clinical and bacteriological results are in keeping with those of Fink et al. (10), although it is difficult to compare the two studies, because the design of our study was not similar to that of the study of Fink et al. (10).

In a study with vancomycin, we have previously shown a change in pharmacokinetic parameters between D2 and D7, particularly in  $V$  and  $C_{\max}$  (14); hence, we determined the pharmacokinetic profiles on D2 and D6 to D8 in this study. In the present study we did not find such differences (Table 2).

The values of  $C_{\max}$  and  $t_{1/2}$  obtained in this study are comparable to the values obtained by Shah et al. (26) and Nix et al. (20) in studies with healthy volunteers. CL and  $V$ , however, were lower in our severely septic patients. Initially, the mean CL for our patients was 84% of the CL reported for healthy volunteers. In our patients the CL over the treatment course remained relatively constant and was similar to that reported at D5 for the healthy volunteers. The  $V$  for patients with severe sepsis was 69% of that obtained for healthy subjects. We cannot definitively explain this.

The ranges of the normalized CL (0.17 to 0.82 liter/h/kg) and  $V$  (0.77 to 2.52 liters/kg) values were very wide, showing a diversity in the septic critically ill patients. Further studies may be necessary to accurately individualize ciprofloxacin dosing in this patient population.

It is worth noting that our patient population is largely young African patients without concomitant diseases. Their mean Apache II scores of 14 (which are not their admission scores) gives an indication that they were very ill and were often on a ventilator and in respiratory failure. The severity of illness and disease profiles for our patients are similar to those for the patients in the study of Fink et al. (10), although the patient populations may differ. It is thus feasible to extrapolate data from these two studies into similar other intensive care unit patients. Less sick patients, patients with smaller body structures, or patients who metabolize ciprofloxacin differently may not necessarily need 1,200 mg/day.

**Conclusion.** Ciprofloxacin is safe when it is given to critically ill adult patients i.v. at 400 mg q8h. This dosage produces adequate  $C_{\max}$ /MIC ratios and results in adequate AUC/MIC ratios, and concentrations in plasma are maintained above the MIC for most of the dosing interval. This ensures bactericidal activity against most organisms found in intensive care units. In our patients, who did not have renal failure, there was no accumulation of ciprofloxacin. We conclude that 400 mg of ciprofloxacin given i.v. q8h should be the dose administered for severe sepsis in the critically ill adult.

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