Infectious complications in critically ill patients: focus on clinical, pharmacological and economic aspects

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CHAPTER 3

Ciprofloxacin pharmacokinetics in critically ill patients: a prospective cohort study*

INTRODUCTION

Since the mid-1980s fluoroquinolones have acquired a prominent position in the management of moderate-to-severe infections in critically ill patients. This class of synthetic antibiotics has an antimicrobial activity ranging from enterobacteriaceae and opportunists to some gram-positive pathogens. Due to excellent tissue penetration and favourable therapeutic ratio's fluoroquinolone antibiotics such as ciprofloxacin can be used in the management of a large range of infections, including infections of the genitourinary-, respiratory- and gastrointestinal tracts as well as skin, joint and soft tissue infections.

Due to their broad spectrum and relatively mild side effects, fluoroquinolones have gained great popularity in the treatment of various infections. However, antibiotic resistance to quinolones can be a problem. Fish *et al.* reviewed causes of treatment failure and reported that drug resistance was responsible for 80% of treatment failures in quinolone-treated patients [1]. An important issue in preventing antibiotic resistance is avoiding drug levels below the minimal inhibitory concentrations (MICs) especially in antibiotics with time-dependent killing mechanisms. Infections most often associated with resistance are those where pathogens are exposed to concentrations below MIC, such as in cystic fibrosis, endocarditis, osteomyelitis, prostatitis and lung abscesses [2]. Animal models and some clinical studies have suggested that quinolone underdosing could play a role in the development of antibiotic resistance [3,4]. Underdosing of antibiotics should therefore be avoided to prevent treatment failures and antibiotic resistance. This is particularly important in critically ill patients as resistance rates to ciprofloxacin have

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increased over the last decade for most species [5]. The development of resistance may further complicate optimal dosing.

The mechanisms of bacterial killing of various antibiotic classes are different. This implies that optimum pharmacokinetic profiles for these different classes will also differ. For instance, the bacterial killing capacity of aminoglycosides depends on the peak antibiotic concentration (C_{max}) [6]. In contrast, beta-lactam antibiotics (which have no significant "post-antibiotic effect") are most effective if the time during which drug concentrations exceed 4-5x MIC is at least 50-70% of each dosing interval [7]. Therefore, whereas aminoglycosides should be given in bolus doses once daily to achieve high peak values and low average values (to reduce toxicity), beta-lactam antibiotics may work better when they are given by continuous infusion [8].

In the case of quinolones the killing of bacteria is determined by the "area-under-the-curve" (AUC), which can be obtained by mathematical integration of the serum concentration-time curve (surface area) and the peak concentration (C_{max}). The ratio of the AUC to the MIC of the causative microorganism (AUC/MIC) is a good predictor of treatment efficacy. For ciprofloxacin, one of the oldest and most well-studied fluoroquinolones, various studies have suggested that an AUC/MIC-ratio of at least 125 is required for optimum clinical effects [9,10]. Forrest and co-workers reported clinical and bacteriological cure rates of 82% when AUC/MIC was ≥ 125, vs. cure rates of only 26% when AUC/MIC was < 125 [9]. This study did not report whether failures were due to low ciprofloxacin levels or high MIC levels. An alternative parameter to predict treatment success is a C_{max} to MIC ratio of 10 or higher; however, experimental evidence suggests that the AUC/MIC-ratio is a better predictor for efficacy than the C_{max}/MIC ratio [11]. In addition, some studies have indicated that not obtaining sufficient C_{max} : MIC ratios (*i.e.* < 10) is a primary cause of fluorochinolones-associated resistance [12-15].

The currently available clinical studies of this issue have been performed in a mix of patients with a wide variety of infections. Few data are available regarding the use of fluoroquinolones in critically ill patients, although these drugs are widely used in this population because they are well tolerated and have a broad microbiological spectrum.

These considerations led us to prospectively study the pharmacokinetics of ciprofloxacin in critically ill patients in our ICU.

METHODS

The study was performed according to guidelines for therapeutic drug monitoring of our hospital. It was designed as a prospective observational single-centre cohort study. ICU patients treated with ciprofloxacin (intravenous infusion of 400 mg twice daily, infused over a 20–minute period) were consecutively included after they had been treated for at least 36 hours. This is a commonly used dosage for the treatment of moderate to severe

infections, and this dosing regimen has been successfully used in clinical studies [16]. Indications for treatment were based on clinical suspicion of infection and/or cultured pathogens susceptible to ciprofloxacin, at the discretion of the attending physician/intensivist. The measured drug levels were correlated to MIC values of pathogens commonly found in our ICU population.

Measurements

The following clinical and biometric variables were scored on the actual day of drug sampling: underlying reason for ciprofloxacin administration, microbiological cultures, gender, age, length, weight, cumulative fluid balance calculated from the day of admission to the ICU (no correction for *perspiratio insensibilis* was used), plasma levels of bilirubin (µmol/l) and creatinin (µmol/l), and SOFA-scores [17]. Use of vasoconstrictors was defined as infusion of any dosage of epinephrin, norepinephrin or dopamine on the day of sampling.

Pharmacokinetic analysis

Ciprofloxacin pharmacokinetics were primarily predicted using a two-compartment first order kinetic model based on information from previous clinical studies [9,18]. We tested the hypothesis that AUC exceeded MIC values of 0.125, 0.25, 1.0 and 2.0 mg/l by at least 125 times, or C_{max} by at least 10 times. MIC values were chosen on the basis of resistance patterns of the pathogens most frequently cultured in our ICU patient population over the preceding 24 months. In addition, commonly occurring patient and clinical factors that could be associated with either high or low AUCs were analysed.

Seven blood samples were drawn at various time points (t=0.5 hours, t=1 hours t=1.5 hours, t=2 hours, t=3 hours, t=6 hours and t=12 hours after infusion of 400 mg of ciprofloxacin over a 20-minute period) to determine plasma concentrations of ciprofloxacin. All patients had been treated with ciprofloxacin for a period of 36 hours to achieve steady state concentrations. Blood samples were collected in tubes without anticoagulant and were centrifuged at 1500 rotations/minute for 10 minutes within one hour of sample collection to obtain plasma for the measurement of ciprofloxacin concentrations. Samples were frozen and stored at -20°C until analysis, which was performed within 1 month. Stability under these conditions has been reported for this duration [19]. Plasma ciprofloxacin levels were determined using high-pressure liquid chromatography (HPLC) [20] . We considered ciprofloxacin clearance to be linear and used a similar model as has been used by others in critically ill patients [9]. Therefore pharmacokinetic calculations of the elimination half-life ($t_{1/2}$), area under the curve ($AUC_{0\rightarrow24}$), total body clearance (CL) and volume of distribution (at steady state; Vss) were performed using a 2-compartment first order pharmacokinetic analysis model of the plasma ciprofloxacin concentration versus time, using a commercially available pharmacokinetic software program (MwPharm software version 3.15, Mediware, Heerenveen, The Netherlands).

Statistical analysis

Results are presented as mean±SD. Students' t-tests and chi squared tests were used for comparisons between the two study groups. Statistical significance was accepted for $P < 0.05$.

Linear regression was used to evaluate the impact of patient characteristics on the AUC. In order to remove skewness and heteroscedastity, the logtransformed AUC values were used for the analysis. The resulting estimates and confidence intervals were then backtransformed and are presented as ratio. For the multivariate analysis, a forward variable selection method was used. As an additional check on the robustness of the outcome, a backward selection method was carried out with the factors that had a p-value below 0.1 in the univariate analysis. The multivariate analysis was first done with the summary variable $SOFA_{cumulative}$ and was repeated with the subscales.

Table 1: Patient characteristics of 32 ICU patients treated with ciprofloxacin

	Mean±SD	Median	[range]
Gender (m/f)	24/8	NA	
Age (years)	68.7±17.4	73.5	[17-94]
Length (m)	1.75±0.11	1.75	[1.58-1.98]
Weight (kg)	77.7±15.0	77.5	[52.4-100.0]
BMI* (kg/m^2)	25.0±4.0	24.7	[18.6-36.7]
Fluid balancecum icu (l)	13.4±11.2	11.3	[-2.6-41.0]
BMI_{corr} (kg+fluid bal/m^2)	29.6±6.5	28.3	[17.9-44.6]
$SOFA_{cum}$+	7.3±3.4	7.5	[0.0-17.0]
$SOFA_{respiratory}$	2.7±1.0	3.0	[0.0-4.0]
$SOFA_{thrombocytes}$	0.7±0.9	1.0	[0.0-4.0]
$SOFA_{bilirubin}$	0.3±0.6	0.0	[0.0-2.0]
$SOFA_{circulatory}$	2.4±1.6	3.0	[0.0-4.0]
$SOFA_{EMV}$	0.1±0.4	0.0	[0.0-2.0]
$SOFA_{renal}$	1.2±1.4	1.0	[0.0-4.0]
Mechanical ventilation (y/n)	29/3	NA	
Vasoconstrictors (y/n)	22/10	NA	
Serum creatinin (µmol/l)	160±148	127	[31-853]
Serum bilirubin (µmol/l)	9.8±9.6	8 [2-35]	
CVVH‡ (y/n)	6/26	NA	

* BMI = Body mass index

\+ SOFA = Sequential organ failure score; 6 different categories are used

‡ CVVH = Continuous veno-venous hemofiltration

RESULTS

Thirty-two patients (24 males and 8 females) were included in the study. Patient characteristics are shown in Table 1. Our study patients were severely ill, with an average cumulative SOFA-score of 7.3±3.4 [range 0-17] . Twenty-nine patients (91%) were mechanically ventilated and 22 (69%) were receiving vasopressors at the moment of inclusion in our study.

Positive cultures from blood, sputum/tracheal aspirate or peritoneal fluids were found in 30/32 patients (94%). *Pseudomon*as species were found in 8 patients (25%), *Klebsiella* species in 6 (19%), *Enterobacter* species in 5 (16%), *Stenotrophomonas* in 3 (9%), *Escherichia Coli* in 2 (6%), *Acinetobacter baumannii* in 1 (3%), *Citrobacter freundii* in 1 (3%), and *Salmonella* group C in 1 patient (3%). Gram-positive micro-organisms were cultured in the other patients. MIC values that would represent the 90th percentile of values for these gram-negative pathogens (MIC_{90}) in our ICU population are shown in table 2.
Usually, drug levels exceeding MIC_{90} will effectively treat infections in 90% of cases. The clinical course of the infections in individual patients was not assessed, as this was not the goal of our study. No adverse effects of ciprofloxacin (which can include seizures, allergic rash, or elevation of liver or pancreatic enzymes) were observed in our study group.

Table 2: MIC_{90} of cultured pathogens based on data from our general ICU patient population. These values may vary between different hospitals, patient populations and countries.

Pathogens	MIC_{90} Mg/l
Acinetobacter baumannii	≤ 0.5
Citrobacter freundii	≤ 0.5
Enterobacter species	≤ 0.5
Escherichia Coli	≤ 0.5
Klebsiella species	≤ 1.0
Pseudomonas species	≤ 0.5
Salmonella group C	≤ 1.0
Stenotrophomonas maltophilia	≤ 1.0

The pharmacokinetic data after intravenous administration of ciprofloxacin 400 mg *bid* are shown in table 3. We observed large (up to 5-fold!) variations in distribution volume in steady state (Vd1), ranging from 51.7 to 248.9 liters. Vd1, $AUC_{0\rightarrow24}$ and $T_{1/2}$ data for individual patients are shown in figure 1. No significant correlations were seen between Vss and weight, length, body mass index, cumulative fluid balance, weight corrected for fluid balance or corrected body mass index (corrections were made for "extra" volume acquired during ICU stay, based on cumulative fluid balance). We observed a nine-fold variation in

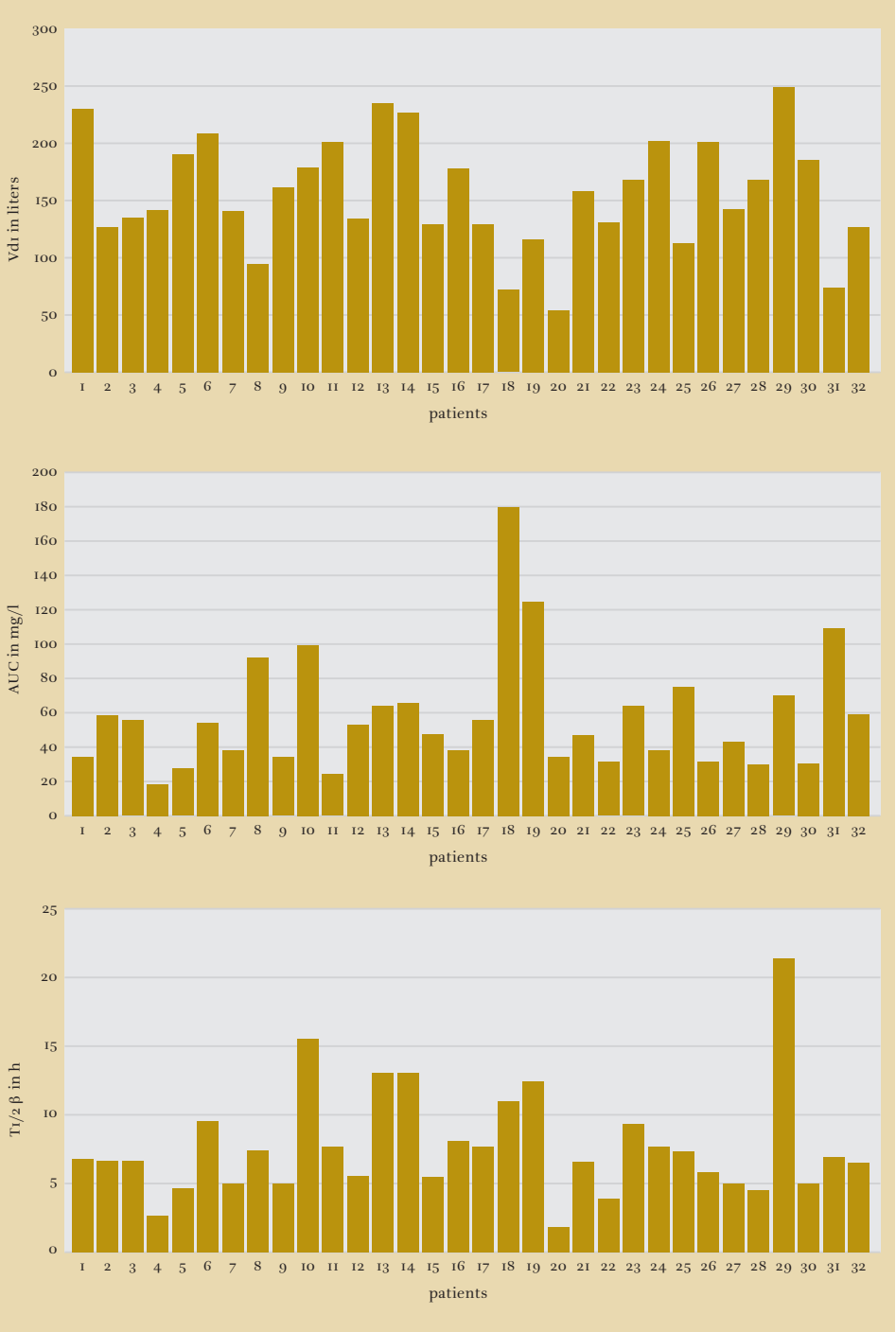

Figure 1: Volume of distribution (Vd1) in liters, AUC in mg/l and T½(β) in hours of ciprofloxacin 400 mg bid IV in 32 individual critically ill patients during steady state

Table 3: Pharmacokinetic variables of 32 ICU patients treated with ciprofloxacin 400 mg bid IV			
Ciprofloxacin pharmacokinetics	Mean±SD	Median	[range]
Volume of distribution in steady state (Vd1 in l)	66.0±40.6	52.1	[22.5-156.0]
Volume of distribution per kilogram (Vd1/kg in l/kg)	0.86±0.52	0.61	[0.25-2.12]
Volume of distribution in steady state (Vd2 in l)	154.7±4.7	149.5	[51.7-248.9]
Volume of distribution per kilogram (Vd2/kg in l/kg)	2.01±0.65	1.96	[0.90-3.59]
Serum half-life (T1/2 (α) in h)	0.44±0.24	0.41	[0.16-1.16]
Serum half-life (T1/2 (β) in h)	7.43±3.97	6.54	[1.48-21.16]
Maximum serum concentration (C_{max} in mg/l)	6.92±3.53	5.5	[2.2-18.0]
Minimum serum concentration (C_{min} in mg/l)	1.22±0.98	1.1	[0.0-4.6]
Mean serum concentration (C_{mean} in mg/l)	2.37±1.40	2.0	[0.9-7.5]
Area under concentration curve / 24 h ($AUC_{0\to24}$ mg*h/l)	56.8±33.5	48.8	[22.6-180.0]

$AUC_{0\to24}$. In individual patients with long maximum half-lives we retrospectively checked treatment duration and were able to demonstrate that even in these patients serum drug samples were obtained during steady-state conditions.

Figure 2 shows the area under the curve ($AUC_{0\to24}$ in mg*24h/l) of ciprofloxacin concentrations over a 24-hour period in our 32 patients. Based on the assumption that an AUC/MIC >125 is required for optimal bacterial killing and prevention of antibiotic resistance, figure 2 also depicts three theoretical lines representing MIC levels of 0.125, 0.5 and 1.0, respectively. For micro-organisms with MIC values of 0.125 (implying very high susceptibility to ciprofloxacin), AUC/MIC>125 was achieved in all patients (32/32). For MIC values of 0.25, 0.5, 1.0 and 2.0 these results were 27/32 (84%), 10/32 (31%), 1/32 (3%), and 0/32 (0%), respectively.

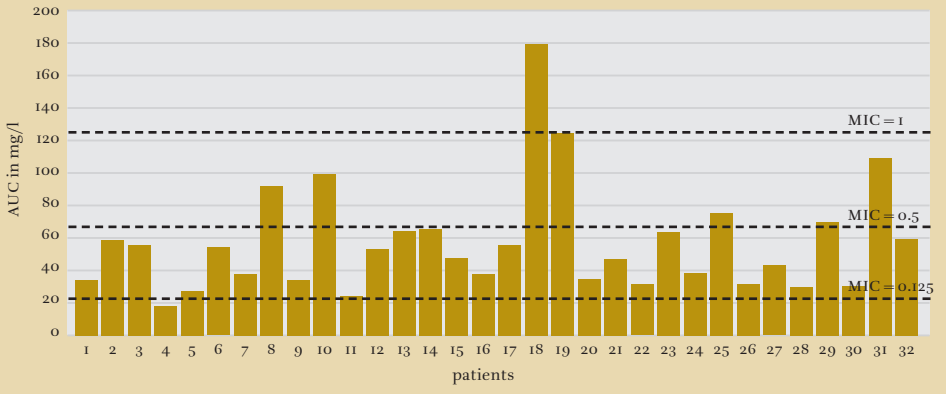

*Figure 2: Area under the curve ($AUC_{0\to24}$) in mg*24h/l of ciprofloxacin concentrations over 24 hours in 32 individual critically ill patients treated with ciprofloxacin 400 mg bid IV and AUC/MIC>125 for different theoretical MIC levels of 0.125, 0.5 and 1.0.*

C_{max} /MIC concentration-ratios of 10 or greater were achieved in 32/32 (100%) of patients when MIC was 0.125, in 31/32 (97%) when MIC was 0.25, in 22/32 (69%) when MIC was 0.5, in 8/32 (25%) when MIC was 1, and in 0/32 (0%) when MIC, was 2.0. These data are shown in table 4, based on administered doses of 400 mg *bid*, an AUC/MIC of 125 and C_{max}/MIC of 10.

Table 4: Fractional attainment of $AUC_{0\to24}$/MIC ratio of 125 and $AUC_{0\to24}/C_{max}$ ratio of 10 at each MIC based on ciprofloxacin dosages of 800 mg/day (400 mg bid)

Organism MIC	C_{max}/10 › MIC	AUC/MIC › 125
	%	%
0.125	100	100
0.25	97	84
0.5	69	31
1	25	3
2	0	0
8	0	0
32	0	0

Figure 3 shows a simulated fractional attainment of $AUC_{0\to24}$/MIC ratio of 125 at MIC's of 0.25, 0.5, 1.0 and 2.0 mg/l, for ciprofloxacin doses ranging from 800 to 3200 mg/day based on the pharmacokinetic data obtained in our ICU patient population at doses of 800 mg/day. In the simulation dosing frequencies of 2,3,4,5,6,7,8 times daily 400 mg were used. In this figure the percentages of patients of effective treatment (attainment rate) related to the MIC of the pathogen are depicted.

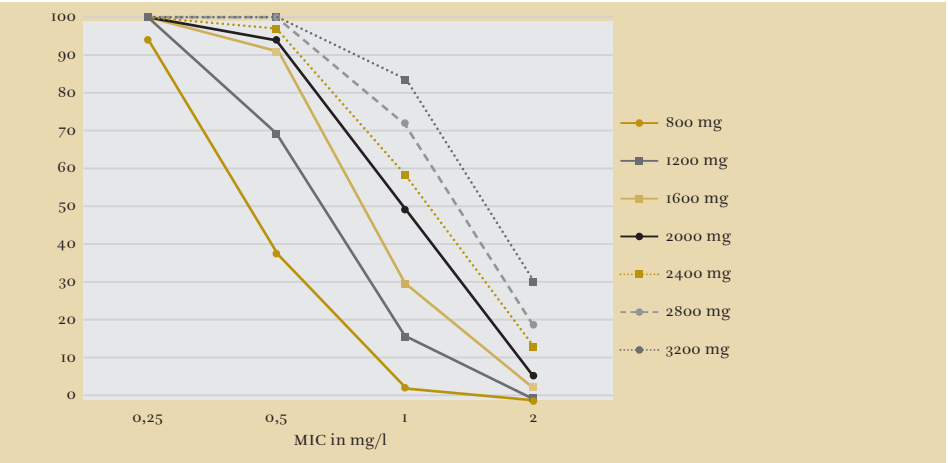

Figure 3: Simulated fractional attainment of $AUC_{0\to24}$/MIC ratio of 125 at MIC 0.25. 0.5. 1.0 and 2.0 mg/l for ciprofloxacin dosages ranging from 800-3200 mg/day based on ICU patient population pharmacokinetics obtained at 800 mg/day. In the simulation dosing frequencies of 2,3,4,5,6,7,8 times daily 400 mg were used.

We also compared different subgroups within our study population in regard to AUC, based on a number of different clinical variables. The results are shown in table 4. Significant univariate effects were demonstrated for gender (women had higher AUC values than men (89%)), length (lower AUC in longer patients), SOFA renal scores (higher AUC values in patients with more impaired renal function), SOFA pulmonary scores (higher AUC values in more severe disturbances of pulmonary gas exchange) and cumulative SOFA scores (high cumulative SOFA-scores were the best predictors of a high AUC). In the multivariate model length was no longer significant, probably due to the gender effect. Apart from the observed gender effect (higher drug levels in females) higher cumulative, pulmonary and renal SOFA scores predict higher AUC. The largest independent significant effect on AUC was caused by the cumulative SOFA score (7% higher per SOFA point).

Table 5: Univariate and multivariate analysis of the impact of patient characteristics and clinical variables on Ciprofloxacin AUC_{1-24}.

	Univariate analysis			MV analysis forward			MV analysis backward		
	P-value	Mean	95%CI	P-value	Mean	95%CI	P-value	Mean	95%CI
Gender (f:m)	0.001	1.89	1.33-2.69	0.005	1.60	1.16-2.20	0.001	1.71	1.29-2.28
Age (y)	0.714	1.00	0.99-1.01						
Length (m)	0.024	0.16	0.03-0.77						
Weight (kg)	0.477	1.00	0.98-1.01						
BMI* (kg/m^2)	0.512	1.02	0.97-1.06						
Fluid $balance_{cum\ icu}$ (l)	0.067	1.02	1.00-1.03						
BMIcorr (kg+fluid bal/m^2)	0.137	1.02	0.99-1.05						
$SOFA_{cumulative}$	0.000	1.09	1.05-1.14	0.002	1.07	1.03-1.12			
$SOFA_{pulmonary}$	0.035	1.22	1.02-1.46				0.047	1.14	1.00-1.30
$SOFA_{thrombocytes}$	0.099	1.18	0.97-1.45						
$SOFA_{bilirubin}$	0.177	1.22	0.91-1.62						
$SOFA_{circulatory}$	0.118	1.09	0.98-1.22						
$SOFA_{EMV}$	0.333	1.26	0.78-2.02						
$SOFA_{renal}$	0.002	1.21	1.08-1.36				0.001	1.18	1.08-1.30
Creatinin (µmol/l)	0.136	1.28	0.68-2.39						
CVVH	0.068	1.51	0.97-2.37						
Mechanical ventilation	0.430	1.28	0.68-2.39						
Vasoconstrictors	0.136	1.33	0.91-1.96						

Effects are reported as mean ratio and 95% confidence intervals. P< 0.05 is considered significant. For the multivariate analysis (MV), a forward variable selection method was used. As an additional check on the robustness of the outcome, a backward selection method was carried out with the factors that had a P-value < 0.1 in the univariate analysis. The multivariate analysis was first done with the summary variable SOFAcumulative and was repeated with the subscales.

DISCUSSION

The results of our study clearly demonstrate that a huge variability occurs in the pharmacokinetic variables of ciprofloxacin following intravenous administration in critically ill patients. Up to five-fold differences in volumes of distribution in steady state were observed. These differences could not be explained by differences in patient biometry, or by excessive volume loading (acquired fluid volume) during treatment in the ICU. These observations have been confirmed by Gous and coworkers who have studied ciprofloxacin levels in sepsis[21]. The authors concluded that fluid shifts have no influence on ciprofloxacin pharmacokinetics in intensive care patients with intra-abdominal sepsis. In addition, greater variability was observed for other pharmacokinetic variables such as $t_{1/2}$, C_{max}, C_{min}, and C_{mean} as well as for the most important pharmacokinetic and pharmacodynamic parameter, the AUC.

Our finding that AUC values were higher in women has previously been observed in a study by Overholser and co-workers in healthy volunteers, following oral administration of ciprofloxacin [22]. This gender effect could not be explained by differences in body weight, and as the route of administration was different in our study it is unlikely that this played an important role, because similar gender effects were observed in both studies; although bioavailability of antibiotics may be a problem in oral administration, this is not a factor when patients are treated intravenously. Thus serum clearance for ciprofloxacin appears to be lower in females than in males.

Ciprofloxacin is eliminated through metabolisation, renal clearance (glomerular filtration and tubular excretion) and by transintestinal elimination. In patients with renal failure higher drug levels may be expected and dose reduction has been suggested [23]. Gasser and co-workers recommended a 50% reduction in the doses of ciprofloxacin in patients with impaired renal function (defined as a creatinin clearance <50 ml/min per 1.73 m^2) to achieve serum concentrations similar to those seen in individuals with normal renal function [24]. We found an average increase in AUC of about 50% in critically ill patients with impaired renal function, which is in line with the observations and recommendations of Gasser *et al*. However, based on our findings we do not recommend reducing the dose in critically ill patients with renal failure, for the following reasons. Firstly, large variations in individual AUCs were observed, and therefore low AUC values may occur in individual patients with impaired renal function. This is in line with observations by Pea and coworkers who studied 89 critically ill patients retrospectively treated with ciprofloxacin 200 mg or 400 mg *bid* [25]. Even in renal failure patients no significant accumulation was observed. However in that study also lower dosages (200 mg *bid*) were used. Secondly, a 50% dose reduction would lead to drug levels below the overall average in the general ICU population. Finally, AUC's are already often relatively low in relation to the MIC of the causative micro-organism. Further reductions could lead to treatment failures and/or induction of resistance. Thus, although in some cases renal failure can lead to

higher drug levels, daily doses should not be lowered in most cases for reasons of clinical efficacy.

In antibiotics with no or only marginal post-antibiotic effects, such as beta-lactam antibiotics, the duration of concentrations above the MIC for the causative pathogen is most predictive for favourable outcomes in terms of clinical and microbiological cure rates [7,8]. Therefore, the duration of drug levels above MIC should be 50-70% or higher for each dosing interval [7,8]. This can be most easily achieved by continuous intravenous infusion [26]. In contrast, for aminoglycosides the most important factor determining bacterial killing rates and prevention of resistance is the ratio of C_{max} (peak concentration) to the MIC of the causative micro-organism [26]. This has led to important changes in dosing regimens over the past few years, from 2-3 times daily to once daily dosing, thereby reducing aminoglycoside-associated toxicity [27].

For the antibiotic category of fluoroquinolones, AUC/MIC was found to be the most important factor determining efficacy according to the criteria outlined above. Schentag and Forrest previously demonstrated that AUC/MIC ratios above 125 should be targeted to achieve optimum efficacy [9,10].

In our study this threshold was reached in all patients only when MIC was ≤ 0.125 mg/l. However, many of the gram-negative pathogens commonly found in our ICU population have MIC_{90} values of 0.25-0.5 mg/l; these values are likely to be significantly higher in many other countries, as the Netherlands have a relatively low level of antibiotic drug resistance [28]. Furthermore, ciprofloxacin is frequently chosen because of its activity against *Pseudomonas* species. *Pseudomonas* bacteria often have relatively high MIC values at the onset of treatment, with high risk of induction of resistance to quinolones. Our results underscore the importance of using higher dosages of ciprofloxacin in patients with severe infections, especially when infections with pathogens with high MIC-values such as *Pseudomonas* or enterobacteriaceae is suspected. In fact this was already suggested by Forrest and coworkers in 1993 and is underlined by our present data [9]. Recently Zelenitsky and coworkers studied clinical outcome and pharmacodynamic endpoints based on Monte Carlo simulations and concluded that the highest recommended ciprofloxacin dose of 400 mg i.v. q8h should be used in the treatment of *P. aeruginosa* infection to improve pharmacodynamic target attainment and clinical cure [15]. Moreover they concluded that even this dosing regimen appears to be ineffective if pathogen MICs are 1 mg/l. Still, it seems that these recommendations have been poorly adopted in international clinical practice and therefore ciprofloxacin underdosing must be common.

The study by Forrest and co-workers in which the pharmacodynamic endpoint of AUC/MIC ratios >125 was determined as the best parameter to predict bacterial killing did

not specify whether clinical treatment failures linked to AUC/MIC ratio's lower than 125 were due to low ciprofloxacin levels, or high MIC levels [9]. Based on the results of our study, the former seems the more likely explanation.

Our findings imply that starting doses of ciprofloxacin in ICU patients should probably be increased to at least 1200 mg per day, particularly in cases were infections with microorganisms with relatively high MICs cannot be ruled out. This can be achieved either by increasing the doses (to 600 mg *bid*) or by decreasing the dosing intervals from 12 to 8 hours (400 mg *tid*). From a pharmacokinetic perspective the first option offers the additional advantage that administration of 600 mg will theoretically lead to higher peak serum antibiotic concentrations, thereby increasing the likelihood of reaching a C_{max}/MIC-ratio of 10 or higher. In addition, although the drug acquisition costs will be the same for both regimens there may be difference in factors such as workload and administration costs which are likely to be higher when an 8-hourly dosing interval is used. The importance of this is illustrated by the results of a cost-effectiveness study performed by our study group in which costs for treating pneumonia or intra-abdominal infections in the ICU or general ward using 5 different antibiotic regimens were compared [29]. We observed that antibiotic treatment was associated with significant hidden costs that were largely determined by the mode of administration. These differences were mainly due to the fact that direct intravenous administration or piggy back infusion of intravenous antibiotics requires more time expenditure by relatively expensive medical and nursing staff members. Therefore, from a pharmacokinetic, pharmacodynamic and financial viewpoint the 12-hourly administration at higher doses appears superior to the more frequent administration at the same dose. However, from the perspective of preventing side effects the *tid* regimen may be more favourable. Further studies will be required to determine which dosing regimen is superior.

A limitation of these recommendations is that it rests in part on an extrapolation of the pharmacokinetic data of AUC obtained using a daily dose of 800 mg of ciprofloxacin; these data were then used to predict serum drug levels at doses of 1200 mg or higher. In our model we have assumed that the changes in drug clearance would be linear; however, in theory the use of higher doses could lead to either an increase and a decrease in drug clearance. Previous studies in healthy volunteers have shown that distribution and elimination of ciprofloxacin is linear for doses of 50 mg, 100 mg and 250 mg IV [30]. Few data on higher doses are available, and variations in drug levels may be extremely large especially in critically ill patients [8]. During antibiotic administration of beta-lactam antibiotics at higher dosages, saturable renal tubular reabsorption has been described leading to higher concentrations [31]. In contrast, following ciprofloxacin administration in patients with renal failure the trans-intestinal elimination of ciprofloxacin has been shown to increase substantially, thereby decreasing drug levels [32]. Therefore, our

extrapolations from doses of 800 mg to higher doses based on the kinetic data reported in this manuscript should be tested in new prospective studies. Some preliminary data suggest that increasing the daily doses of ciprofloxacin is safe, for example a small prospective study by Lipman and associates in 16 critically ill patients with severe sepsis and bacteraemia but without renal failure [33]. Additional studies will be needed to determine safety, efficacy and antibiotic resistance at these higher doses with a greater degree of certainty.

Our study has some limitations. The pharmacodynamic analysis is based on the assumption that AUC/MIC-ratios › 125 are important [9]. This threshold value has been obtained in a study of patients with mainly lower respiratory tract infections, and no precise information is available regarding where these patients were treated (in the ICU or regular wards). Some authors have suggested that AUC/MIC-ratios lower than 125 may be sufficient to achieve the desired clinical efficacy [34]. On the other hand, in *P. aeruginosa* infections AUC/MIC ratios around 50 have been shown to increase resistant subpopulations, and a ratio of 157 was necessary to suppress resistance [35]. Thus, although AUC/MIC ratio's ‹125 may in some cases be acceptable, the risk of inducing resistance in specific micro-organisms such as *P. aeruginosa* and (more importantly) the risk of treatment failure is probably too high in critically ill patients to accept AUC/MIC ratio's lower than 125 in this setting. In addition, because various host defence factors may be negatively affected by critical illness in ICU patients (particularly in later stages following sepsis, when the syndrome of so-called immunoparalysis may develop) [36], it can be expected that this threshold for antibiotic efficacy is unlikely to be lower in this patient population and may well be even higher. Moreover in critically ill patients immediate adequate treatment is of paramount importance, which makes adequate antibiotic dosing essential. Although our data are relevant to steady state conditions and no first-dose kinetics are available the results of our study suggest that in many patients with high MIC pathogens also higher initial dosing should be considered. However, although all this seems plausible, a prospective evaluation in critically ill patients has not yet been performed.

In conclusion, the results of our study demonstrate that the most commonly used daily dose of 800 mg of ciprofloxacin IV (400 mg *bid*) often leads to drug levels and pharmacokinetic profiles that are inadequate to treat infections in critically ill patients. This can occur even when drug concentrations are expected to be higher due to factors such as renal failure. We therefore recommend an increase in ciprofloxacin doses to at least 1200 mg per day (600 mg *bid* or 400 mg *tid*) in case infections with pathogens which might have an MIC › 0.25 mg/l cannot be ruled out. Clinicians should be aware of inadequate drug levels in at least 30% of cases if pathogens present MIC= 0.5 mg/l or higher.

Given the large variation in ciprofloxacin pharmacokinetics in critically ill patients, individualising the dose by means of therapeutic drug monitoring should be considered. In our opinion, high doses should also be used initially when ciprofloxacin is used as an empiric treatment; the dose can subsequently be decreased if a highly susceptible microorganism is found to be the cause of infection. Further studies are needed to determine whether the findings reported here also apply to other types of quinolones such as levofloxacin and moxifloxacin. Physicians treating critically ill patients in the ICU should be aware of the differences in pharmacokinetics between various classes of antibiotics, and the risk for under-dosing in specific situations as outlined above. Future strategies may include combining known patient characteristics (gender, biometry, liver and renal function, etc.) with microbiological data (culture results, in vitro bacterial susceptibility, local antibiotic resistance patterns etc.) and with data obtained by therapeutic drug monitoring (kinetic profiles, AUC etc.) to determine optimum therapeutic strategies. This may help us to improve microbiological and clinical outcomes in critically ill patients in the ICU, and to avoid induction of antibiotic resistance.

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