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Population pharmacokinetics and dosing simulations of cefuroxime in critically ill patients: non-standard dosing approaches are required to achieve therapeutic exposures

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Objectives: To investigate the population pharmacokinetics of cefuroxime in critically ill patients.

Methods: In this observational pharmacokinetic study, multiple blood samples were taken over one dosing interval of intravenous cefuroxime. Blood samples were analysed using a validated ultra HPLC tandem mass spectrometry technique. Population pharmacokinetic analysis and dosing simulations were performed using non-linear mixed-effects modelling.

Results: One hundred and sixty blood samples were collected from 20 patients. CL_{CR} ranged between 10 and 304 mL/min. A two-compartment model with between-subject variability on CL, *V* of the central compartment and *V* of the peripheral compartment described the data adequately. Twenty-four hour urinary CL_{CR} was supported as a descriptor of drug CL. The population model for CL was $CL = \theta_1 \times CL_{CR}/100$, where θ_1 is the typical cefuroxime CL in the population, which is 9.0 L/h. The mean *V* was 22.5 L. Dosing simulations showed failure to achieve the pharmacokinetic/pharmacodynamic target of 65% $fT_{>MIC}$ for an MIC of 8 mg/L with standard dosing regimens for patients with $CL_{CR} \geq 50$ mL/min.

Conclusions: Administration of standard doses by intermittent bolus is likely to result in underdosing for many critically ill patients. Continuous infusion of higher than normal doses after a loading dose is more likely to achieve pharmacokinetic/pharmacodynamic targets. However, even continuous infusion of high doses (up to 9 g per day) does not guarantee adequate levels for all patients with a CL_{CR} of ≥300 mL/min if the MIC is 8 mg/L.

Keywords: β-lactams, cephalosporins, antibiotics, PK/PD, critical care medicine, ICUs

Introduction

Cefuroxime is a second-generation cephalosporin that has been in clinical use for over two decades.

Like other β-lactam antibiotics, cefuroxime is a time-dependent antibiotic, which means antibacterial activity is related to the time for which the unbound concentration is maintained above the MIC during a dosing interval ($fT_{>MIC}$). The $fT_{>MIC}$ required for optimal bactericidal activity for cefuroxime has been reported to be somewhere between 40% and 70% from *in vitro* animal models.[1] Although this may be adequate for minor infections, for treatment of serious infection in critically ill patients, higher pharmacokinetic/pharmacodynamic targets such as 100% $fT_{>MIC}$ or even 100% $fT_{>4\times MIC}$ have been associated with better outcomes, both clinical and microbiological.[2,3]

Research has shown that the pharmacokinetics of hydrophilic antibiotics in critically ill patients may differ from that in healthy volunteers and non-critically ill patients. Subtherapeutic concentrations using standard dosing have been reported for many antibiotics.[4–12] This shows that pharmacokinetic data from healthy volunteers cannot just be extrapolated to critically ill patients and that population pharmacokinetic studies are needed to define robust drug doses for this specific patient population.

Table 1. Simulated dosages

Intermittent	Extended	Continuous
no loading dose	no loading dose	loading dose: 750 mg over 0.5 h
infusion time = 0.5 h	infusion time = half of dosing interval	constant infusion over 24 h
1.5 g every 8 h	1.5 g every 8 h	4.5 g over 24 h
	1.5 g every 6 h	6.0 g over 24 h
		7.5 g over 24 h
		9.0 g over 24 h

Table 2. Patient characteristics

Age (years), median (range)	69 (26–85)
Weight (kg), median (range)	80 (65–100)
Number of doses between start of therapy and start of study, median (range)	3 (3–5)
Body mass index, median (range)	28 (22.6–35)
Sex, % male/% female	73/27
APACHE II score on ICU admission, median (range)	19 (13–32)
SOFA score on ICU admission, median (range)	9 (3–13)
SOFA score on day of sampling, median (range)	7 (1–12)
CL_{CR} (mL/min), median (range)	57 (10–304)
Albumin concentration (g/L), median (range)	28.5 (17–42)

To date, there are few data to guide dosing of cefuroxime in critically ill patients, which may preclude the use of cefuroxime in this setting. Cefuroxime is not commonly used as empirical therapy in critically ill patients because it has a relatively narrow spectrum and does not cover most nosocomial pathogens. However, it may have a role in de-escalation when the pathogens are found to be susceptible to the drug. Therefore, knowledge about its pharmacokinetics in the critically ill is important for using the drug appropriately.

Therefore, the aim of this study was to evaluate the population pharmacokinetics of cefuroxime in critically ill patients and investigate if pharmacokinetic/pharmacodynamic targets are achieved with current dosing strategies, as well as to investigate the potential of alternative dosing regimens and strategies.

Methods

Patients

This prospective, open-label pharmacokinetic study was conducted at the intensive care unit (ICU) of Ghent University Hospital, Belgium between March 2012 and January 2014. The trial was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of Ghent University Hospital (registration number 2012/078) and was registered with the European Union Drug Regulating Authorities Clinical Trials (EudraCT, registration number 2011-006107-35). Written informed consent was obtained from all patients or a legally authorized representative before enrolment. Patients were enrolled in the study if they were admitted to the ICU and were prescribed cefuroxime. The exclusion criteria included the following: <18 years of age, a haematocrit of <21%, absence of an arterial catheter or need for renal replacement therapy.

Drug administration

Cefuroxime (Zinacef®, GlaxoSmithKline, Genval, Belgium) was infused intravenously over 30 min using a syringe pump. The dose was 1500 mg every 8 h for all patients except for those with renal impairment (defined as a CL_{CR} <20 mL/min), for whom the dose was reduced to 750 mg every 8 h.

Study procedures

Blood samples for assay were obtained after ≥24 h of therapy through a separate arterial catheter. Blood samples were collected just before the start of infusion (time 0) and after 0.25, 0.5, 0.75, 1, 2, 4 and 8 h in lithium-heparinized collection tubes (Venosafe, Terumo, Leuven, Belgium). The blood samples were centrifuged for 10 min at 3000 **g** (ALC Centrifugette 4206, Analis, Ghent, Belgium) immediately after sample collection and then frozen on dry ice and finally stored at −80°C (within 1 h after sample collection) for a maximum of 4 weeks until assay.

In order to determine 24 h CL_{CR}, the patient's urine was collected, starting at the time of initiation of the antibiotic infusion. The plasma sample at time 0 was also used to determine the concentration of creatinine in blood. Additional data were obtained from the medical record and included participant demographics, clinical details, measures of illness severity, microbiological results and laboratory investigations.

Analytical methods

The plasma concentrations of cefuroxime were determined by a validated ultra HPLC method coupled to tandem mass spectrometry. The details of this method have been previously described elsewhere.[13] Observed concentrations for cefuroxime were corrected for protein binding (33%).[14,15]

Creatinine was measured in both plasma and urine using the rate-blanked compensated and uncompensated Jaffe technique, respectively (Modular P and Cobas 8000, Roche Diagnostics GmbH, Mannheim, Germany).

Pharmacokinetic analysis

The concentration–time data were analysed using non-linear mixed-effects modelling (NONMEM version 7.3, Globomax LLC, Hanover, MD, USA). A Digital Fortran compiler was used and the runs were executed using Wings for NONMEM (http://wfn.sourceforge.net). The first-order conditional estimation method with interaction was used throughout the model building.

Model development

For the population pharmacokinetic analysis, the plasma cefuroxime concentrations were fitted to one-, two- or three-compartment linear models using subroutines from the NONMEM library. Between-subject variability (BSV) was evaluated using an exponential variability model. Various models for residual unexplained variability were also tested.

Model diagnostics

Visual inspection of diagnostic scatter plots and the NONMEM objective function value (OFV) were used to evaluate goodness of fit. Statistical comparison of nested models was undertaken in the NONMEM program on the basis of a χ^2 test of the difference in OFV. A decrease in the OFV of 3.84 units ($P < 0.05$) was considered statistically significant for 1 degree of freedom. Decreases in BSV of one of the parameters of ≥10% were also accepted for inclusion in a more complicated model.

Covariate screening

Covariate model building was performed in a stepwise fashion with forward inclusion based upon the aforementioned model selection criteria for those clinical parameters that showed significant correlation with

Table 3. Isolated microorganisms and their susceptibility

Microorganism	Number of positive cultures	Breakpoint MIC (mg/L)[a]
Escherichia coli	4/12	8
Staphylococcus aureus	2/12	4
Haemophilus influenzae	1/12	2
Klebsiella oxytoca	1/12	8
Raoultella ornithinolytica	1/12	ND
Proteus mirabilis	1/12	ND
Streptococcus pneumoniae	1/12	1
Morganella morganii	1/12	ND

ND, not determined.
[a]As described by EUCAST.[21]

one of the pharmacokinetic parameters. CL_{CR}, serum albumin concentration, age, sex, weight, Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sequential Organ Failure Assessment (SOFA) score were evaluated as covariates.

Bootstrap

A non-parametric bootstrap method ($n=1000$) using NONMEM was used to study the uncertainty of the pharmacokinetic parameter estimates in the final model. From the bootstrap empirical posterior distribution, we obtained the 95% CI (2.5%–97.5% percentile) for the parameters as described previously.[16]

Dosing simulations

Different dosing regimens were simulated using Monte Carlo simulations. The CL_{CR}s simulated were 50, 100, 200 and 300 mL/min. Five hundred subjects were simulated per dosing strategy and per CL_{CR}. The simulated

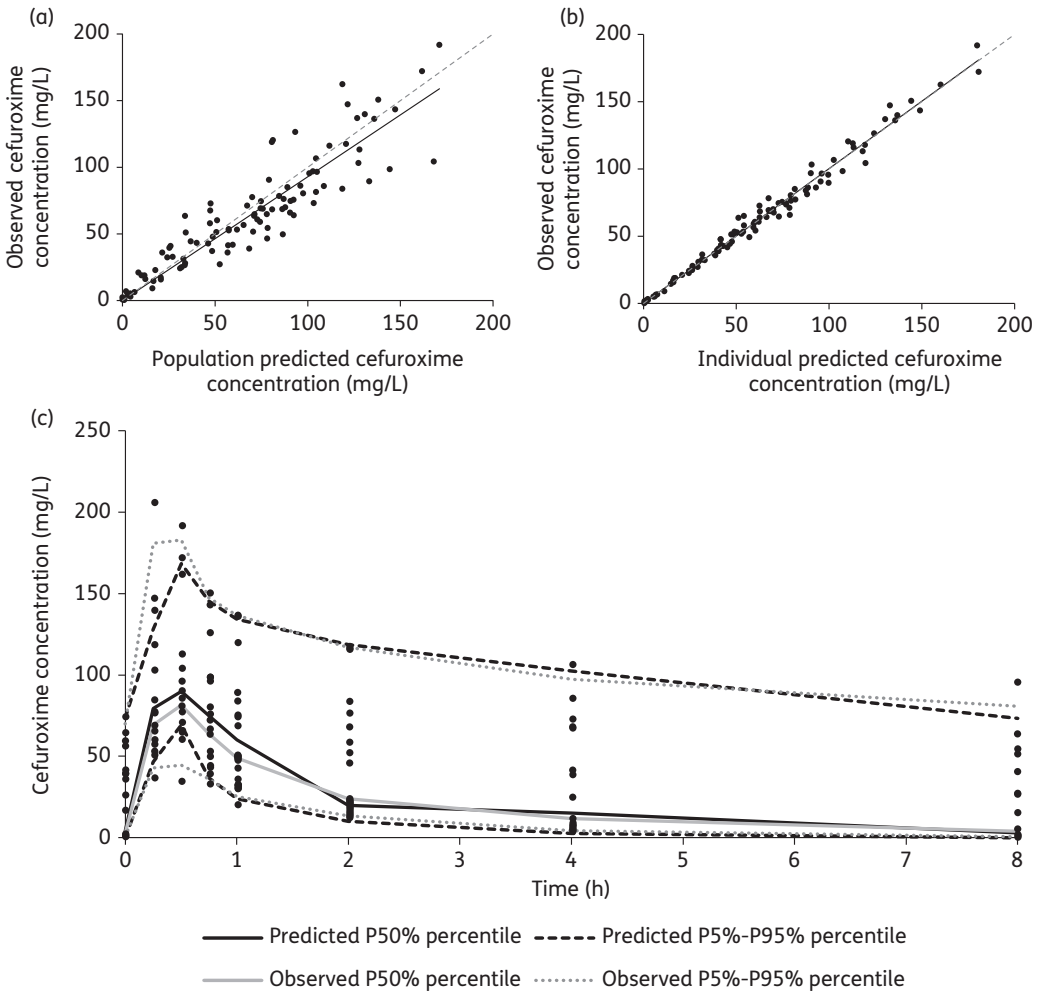

Figure 1. Diagnostic plots for the final population pharmacokinetic covariate model. (a) Population predicted cefuroxime concentrations versus observed concentrations ($R^2=0.86$). (b) Individual predicted cefuroxime concentrations versus observed concentrations ($R^2=0.99$). The non-linear regression line of fit is shown by the black continuous line and the line of identity *xy* is shown by the grey broken line. (c) Visual predictive check generated from a Monte Carlo simulation ($n=1500$) and showing that the estimated population pharmacokinetic model has adequate performance. The raw data are shown as black dots.

Table 4. Bootstrap parameter estimates of the final covariate model

	Model	Bootstrap		
			95% CI	
	median	median	2.5%	97.5%
Fixed effects				
CL (L/h)	9.0	9.0	8.0	10.1
V of the central compartment (L)	10.5	10.5	8.8	12.9
V of the peripheral compartment (L)	12.0	12.0	9.3	14.6
intercompartmental CL (L/h)	18.7	18.4	11.8	23.8
Random effects, BSV (% CV)				
CL (L/h)	28.0	27.1	19.0	34.6
V of the central compartment (L)	23.7	22.0	3.3	33.0
V of the peripheral compartment (L)	29.5	26.0	4.8	43.6
Random error				
proportional (% CV)	10.3	10.4	7.3	13.9
additive (SD, mg/L)	0.46	0.43	0.01	0.7

CV, coefficient of variation.

dosages are summarized in Table 1. Each Monte Carlo simulation generated concentration–time profiles for 500 subjects per dosing regimen using the parameters from the final covariate model. From these data, the $fT_{>MIC}$ was calculated for each simulated subject using linear interpolation. The probability of target attainment was obtained by counting the subjects who achieved 65% $fT_{>MIC.}$ The target MICs were 0.5, 1, 2, 4, 8 and 16 mg/L.

Results

Patient characteristics

A total of 160 blood samples and 20 CL_{CR}s were analysed from 20 patients enrolled in this study. The demographic and general clinical characteristics of the patients used for model building are shown in Table 2. Eighteen patients received antibiotic therapy for treatment of a pulmonary infection and two for prevention of a pulmonary infection after aspiration. Twelve causative microorganisms were cultured from nine patients, and are described in Table 3.

Pharmacokinetic analysis

The best base model consisted of a two-compartment linear model with zero-order input (ADVAN3 TRANS4 subroutine) with combined additive-proportional residual unknown variability. BSV was supported on CL, for *V* of the central compartment and for *V* of the peripheral compartment.

The only covariate that statistically improved the base model was CL_{CR}, normalized to the population's mean CL_{CR} (100 mL/min), which decreased the OFV by 37.9 points and decreased BSV on CL from 0.94 to 0.29. All other covariates showed no correlation with any of the pharmacokinetic parameters and were therefore not further investigated.

The final model is represented as follows: typical value of $CL = \theta_1 \times CL_{CR}/100$.

The typical value of CL was calculated as a function of CL_{CR}, normalized to the population's mean CL_{CR} (100 mL/min), where θ_1 is the typical value of cefuroxime CL in the population.

Figure 1 displays the goodness-of-fit plots for the final covariate model. The fit of the model was acceptable in terms of visual or statistical biases for the prediction. The plots in Figure 1 show that the final pharmacokinetic model describes the measured concentrations adequately. All subsequent dosing simulations were then based on this model.

The values of the parameters for the final models are given in Table 4 and include the 95% CIs for the parameters computed from all bootstrap runs.

Dosing simulations

The probability of target attainment for different dosing regimens and different CL_{CR}s is shown in Figure 2.

The standard dose of 1.5 g cefuroxime three times daily results in inadequate target attainment for patients with a CL_{CR} $\geq$50 mL/min. This standard dose leads to an 87% probability of target attainment for patients with a CL_{CR} of 50 mL/min and organism MIC of 8 mg/L.

Discussion

This is the first paper to investigate the population pharmacokinetics of cefuroxime in critically ill patients. We found that antibiotic CL was proportional to CL_{CR}, with important variability between patients for antibiotic CL. Current dosing schemes are not adequate for critically ill patients with a CL_{CR} $\geq$50 mL/min when conservative pharmacokinetic/pharmacodynamic targets are used.

Two pharmacokinetic studies in ambulatory and general ward patients who were treated with cefuroxime have been published before. The first study evaluated patients with a CL_{CR} between 60

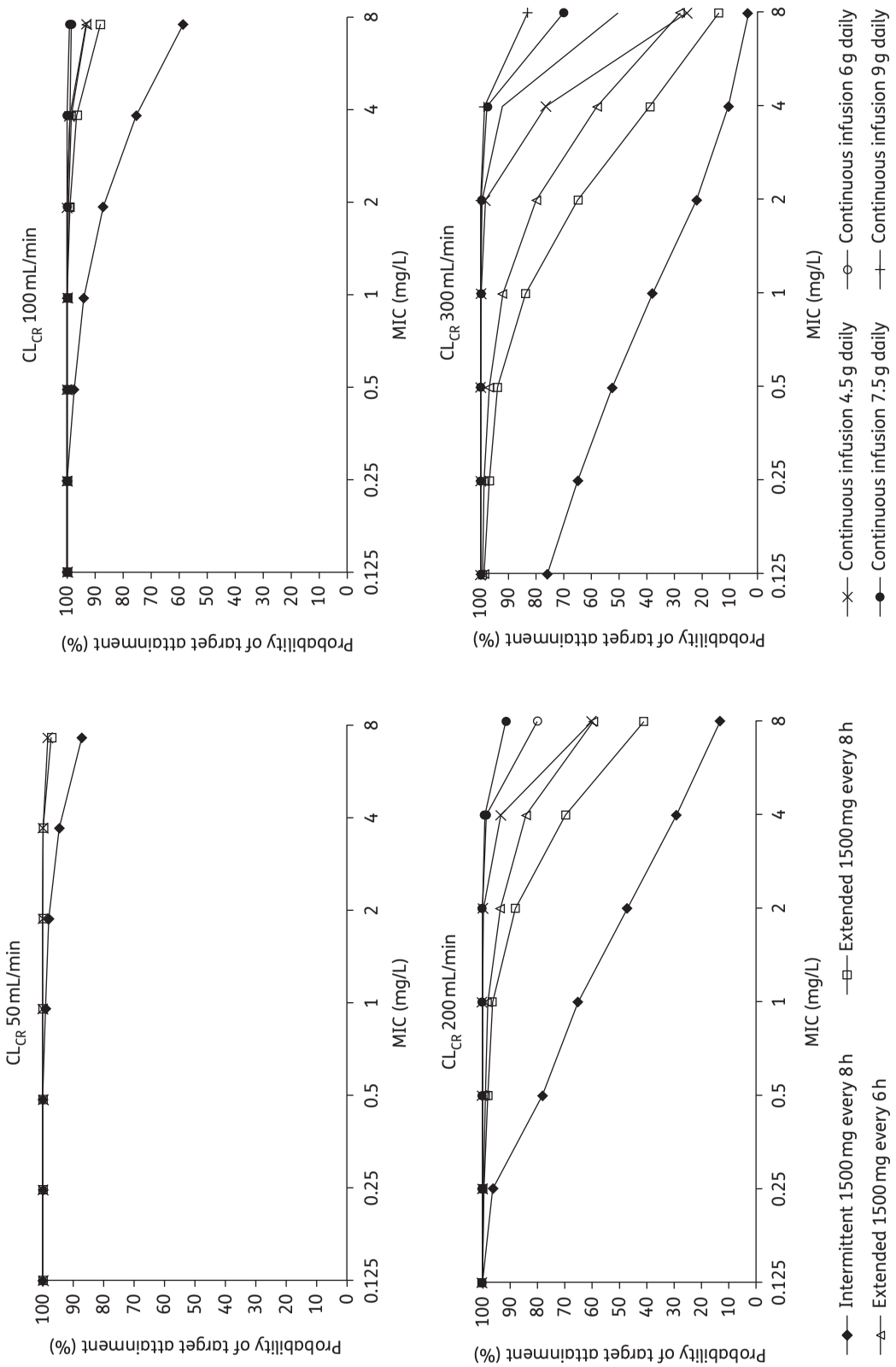

Figure 2. Probability of target attainment for different dosing strategies for CL_{CR}s of 50, 100, 200 and 300 mL/min.

and 120 mL/min and reported a mean *V* of 16.5 L and a CL of 7.4 L/h.[17] Another study in general ward patients found a typical population value for CL of 6.0 L/h and also a *V* of 16.5 L.[18] This value for CL is slightly lower than our findings, most likely because of their study population, which had a lower CL_{CR} than our study population. The values observed for *V* from these studies are lower than the value reported in our study (22.5 L). A larger than normal *V* is one of the typical pathophysiological changes in critically ill patients, a finding reported by multiple pharmacokinetic studies in critically ill patients.[7,8,19,20] These differences from healthy volunteers highlight once again the importance of performing population pharmacokinetic studies and dosing simulations in our specific patient population.

By performing dosing simulations and investigating the probability of target attainment, we have demonstrated that intermittent infusion of 1.5 g of cefuroxime 8 hourly will not ensure 90% probability of target attainment (plasma free concentrations > MIC for at least 65% of the dosing interval) for MIC 8 mg/L—The EUCAST breakpoint for cefuroxime for *Escherichia coli*—for patients with a CL_{CR} ≥50 mL/min.[21] This problem is exacerbated in patients with higher CL_{CR}s such as 100, 200 or even 300 mL/min. These patients have a high probability of underdosing, even for lower and frequently encountered MIC values such as 4, 2 and 1 mg/L.

It is important to point out that there may be other covariates that may also influence plasma concentrations, such as body weight on *V*, or SOFA score. However, only CL_{CR} could be retained in the final covariate model, as none of the other patient characteristics statistically significantly improved the model and, therefore, they could not be included. The reason for this is most likely the relatively small sample size of this study.

Previous research has already demonstrated that patients with augmented renal clearance have a low probability of target attainment.[6,22,23] In our study population of 20 patients, 8 patients had a CL_{CR} >150 mL/min, 4 of which were >200 mL/min. Research in critically ill patients shows that higher pharmacokinetic/pharmacodynamic targets may be associated with better outcomes.[2,3] If one aims to achieve these higher targets such as 100% $T_{>MIC}$ or even 100% $T_{>4\times MIC}$, other strategies are necessary for all patients without renal dysfunction.

In order to achieve sufficient exposure for an MIC of 8 mg/L, patients with a CL_{CR} ≥50 mL/min should be treated with other dosing strategies, such as extended or continuous infusion. Patients with CL_{CR}s ≥100 mL/min need higher dosages and/or alternative dosing strategies such as extended and continuous infusion. Some patients with very high CL_{CR}s (≥300 mL) need up to 9 g as a continuous infusion in order to achieve adequate concentrations. However, the clinical superiority of continuous infusions of high doses of cefuroxime compared with standard intermittent dosing has yet to be demonstrated. It should also be noted that continuous infusion of high doses does not guarantee adequate concentrations for all patients with a CL_{CR} of 300 mL/min if the MIC for the microorganism is 8 mg/L.

This paper has a number of limitations. First, we have not investigated free concentrations or concentrations at the site of infection. Instead, we have measured total drug concentrations with correction for protein binding based on the literature.[14,15] This is an oversimplification, but research has shown that this approach is acceptable for low to moderately protein-bound drugs such as cefuroxime, although it is not accurate for more highly protein-bound drugs.[24] Also, the small cohort of 20 patients could be considered a limitation of this study, given the variability of patient sickness severity. This small cohort may have also prevented other covariates from being shown to be significant and predictive of the variability of pharmacokinetic parameters, such as body weight on *V*. Due to the inclusion criteria of the study, the dose recommendations derived from the data analysis cannot be extrapolated to other critically ill patient populations such as patients with renal replacement therapy or that are obese.

Conclusions

In this study in critically ill patients treated with cefuroxime, we found important variability in antibiotic CL and a larger than normal *V* compared with general ward patients. The results of the dosing simulations show that current dosing regimens of 1.5 g of cefuroxime administered 8 hourly as a bolus infusion lead to underdosing for many patients, whereas continuous infusion of higher than normal doses after a loading dose is more likely to achieve pharmacokinetic/pharmacodynamic targets. However, even continuous infusion of high doses (up to 9 g per day) does not guarantee adequate concentrations for all patients with a CL_{CR} of ≥300 mL/min if the MIC is 8 mg/L.

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Transparency declarations

None to declare.

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