Population pharmacokinetics of ceftriaxone in critically ill septic patients: a reappraisal

Denis Garot,¹ Renaud Respaud,² Philippe Lanotte,³ Nicolas Simon,⁴ Emmanuelle Mercier,¹ Stephan Ehrmann,¹ Dominique Perrotin,¹ Pierre-François Dequin¹ & Chantal Le Guellec²

¹CHRU de Tours, Université François Rabelais, Service de réanimation médicale, Tours, ²CHRU de Tours, Université François Rabelais, Département de pharmacologie, Hôpital Bretonneau, Tours, ³CHRU de Tours, Université François Rabelais, Département de microbiologie, Tours and ⁴Université de la Méditerranée, APHM, Département de pharmacologie, CHU Timone, Marseille, France

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Intensive care unit patients exhibit altered pharmacokinetics for many drugs and suboptimal exposure may be detrimental.
- Despite frequent use of ceftriaxone in critically ill patients, its pharmacokinetics have not been studied in large cohorts of critically ill patients.
- Population pharmacokinetic analysis provides pharmacokinetic parameter estimates, estimates of inter- individual and intra-individual variability in these parameters and allows patient characteristics explaining inter-individual variability to be quantified.
- Coupled with pharmacodynamic analysis, this approach can help in simulating an optimal dosing regimen based on individual characteristics.

WHAT THIS STUDY ADDS

- Our population model characterized the pharmacokinetic profile of ceftriaxone in patients with highly variable characteristics
- Creatinine clearance was identified as the main covariate influencing ceftriaxone pharmacokinetics, particularly for high values. Haemofiltration had no effect.
- Model-based simulations showed that the risk of being under threshold concentrations is low for infections due to common pathogens, but exists in patients with high glomerular filtration rates.

Correspondence

Dr Denis Garot MD, CHRU Bretonneau, service de réanimation médicale, 2 Bd Tonnellé, 37044 Tours cedex, France.
Tel.: +33 0 24 747 3718
Fax: +33 0 24 739 6536
E-mail: garot@med.univ-tours.fr

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AIMS

To investigate the population pharmacokinetics of ceftriaxone in critically ill patients suffering from sepsis, severe sepsis or septic shock.

METHODS

Blood samples were collected at preselected times in 54 adult patients suffering from sepsis, severe sepsis or septic shock in order to determine ceftriaxone concentrations using high-performance liquid chromatography-ultraviolet detection. The pharmacokinetics of ceftriaxone were assessed on two separate occasions for each patient: on the second day of ceftriaxone therapy and 48 h after catecholamine withdrawal in patients with septic shock, or on the fifth day in patients with sepsis. The population pharmacokinetics of ceftriaxone were studied using nonlinear mixed effects modelling.

RESULTS

The population estimates (interindividual variability; coefficient of variation) for ceftriaxone pharmacokinetics were: a clearance of 0.88 l h⁻¹ (49%), a mean half-life of 9.6 h (range 0.83–28.6 h) and a total volume of distribution of 19.5 l (range 6.48–35.2 l). The total volume of distribution was higher than that generally found in healthy individuals and increased with the severity of sepsis. However, the only covariate influencing the ceftriaxone pharmacokinetics was creatinine clearance. Dosage simulations showed that the risk of ceftriaxone concentrations dropping below the minimum inhibitory concentration threshold was low.

CONCLUSIONS

Despite the wide interpatient variability of ceftriaxone pharmacokinetic parameters, our results revealed that increasing the ceftriaxone dosage when treating critically ill patients is unnecessary. The risk of ceftriaxone concentrations dropping below the minimum inhibitory concentration threshold is limited to patients with high glomerular filtration rates or infections with high minimum inhibitory concentration pathogens (>1 mg l⁻¹).

Introduction

Sepsis is the leading cause of death in critically ill patients. In patients presenting organ dysfunction, mortality rates range from 30% to 70% [1, 2]. Although the outcome of severe sepsis depends on multiple factors, the accuracy of initial antimicrobial treatment, i.e. the right molecule at the right dosage, is crucial [3].

Dosage regimens for drugs used in critically ill patients are frequently based on pharmacokinetic data obtained from healthy or less severely ill patients. Yet, the pharmacokinetics in severely ill patients may be altered due to renal or hepatic dysfunction, increased vascular permeability, fluid imbalance, altered protein metabolism and low albumin concentrations. Altered pharmacokinetic variables have been observed in critically ill patients for various drugs, including antibiotics such as aminoglycosides or cephalosporins [4–6].

Ceftriaxone is a well-tolerated third-generation cephalosporin with a broad-spectrum activity against gram-positive and gram-negative bacteria, commonly used in intensive care units (ICU) for the empirical or documented treatment of a wide range of infections, such as pulmonary, urinary, intra-abdominal and central nervous system infections. As a time-dependent antibiotic, the major pharmacokinetic/pharmacodynamic parameter determining the *in vivo* efficacy of ceftriaxone is the time period during which serum concentrations exceed the minimal inhibitory concentration (MIC) [7]. Despite being a commonly used antibiotic, very few data are available on ceftriaxone pharmacokinetics in critically ill patients. A correlation between ceftriaxone clearance and creatinine clearance (CL_{cr}) was found in two studies, each involving 12 patients [4, 5]. When compared with healthy subjects, a 90% increase in the volume of distribution of ceftriaxone was noted in critically ill patients with normal renal function [4]. The ceftriaxone volume of distribution in critically ill patients with acute renal failure was similar to that observed in normal renal function patients [5]. The protein binding of ceftriaxone is concentration-dependent, ranging from 95% at low concentrations ($<100\text{ mg l}^{-1}$) to approximately 60% at high concentrations ($>400\text{ mg l}^{-1}$) [8]. Hypoalbuminaemia may be marked in critically ill patients, thus modifying the free fraction of ceftriaxone. However, the impact of this phenomenon has not yet been described in detail.

The purpose of this study was to assess the population pharmacokinetics of ceftriaxone in a large group of critically ill patients suffering from sepsis, severe sepsis or septic shock. Furthermore, the effects of several clinical and biological covariates on pharmacokinetic parameters were investigated. The model was used to simulate different dosing regimens in order to determine whether any dosage would produce concentrations below the MIC of common ICU pathogens.

Methods

Setting

This prospective study was conducted in the 25-bed medical ICU of a tertiary level university-affiliated hospital between July 2006 and March 2008. The protocol was approved by the Comité de Protection des Personnes Tours Ouest-1. Prior to enrolment in the study, written informed consent was obtained either from the patients or their relatives.

Patient population and data collection

Patients were eligible for study entry if they were at least 18 years of age, hospitalized in the ICU for sepsis, severe sepsis or septic shock, and treated with ceftriaxone. Excluded from the study were patients with haemopathies or allergies to cephalosporin, as well as patients under guardianship, undergoing chronic dialysis, not expected to live beyond 7 days, or having been treated with ceftriaxone for more than 24 h.

Personal data collected at admission included age, gender, height and weight. Laboratory data included serum creatinine, CL_{cr} measured using 24 h urine collection, gamma glutamyltranspeptidase (GGT), bilirubin, prothrombin time, Factor V, albumin and haematocrit. These parameters were measured on two occasions. Sepsis severity scores (SAPS II [9] and SOFA [10]) were calculated. The type, dose and length of catecholamine support, daily fluid balance and use of renal replacement therapy were noted.

Administration of treatment

Ceftriaxone was reconstituted according to the manufacturer's guidelines, diluted in 50 ml of NaCl 0.9%, and administered intravenously over 20 min via a syringe pump. The dose of ceftriaxone was chosen by the attending physician based on clinical and microbiological data (1 g or 2 g once a day except in the case of meningitis). No recommendations were made for the purpose of the study. Ceftriaxone was discontinued if the isolated micro-organism was shown to be resistant.

Blood sampling and drug assay

The pharmacokinetic profile (PK) was obtained on two occasions for each patient. Samples for the first PK (PK1) were drawn on day 2 of ceftriaxone therapy. The second PK (PK2) was aimed at evaluating if ceftriaxone pharmacokinetics had changed following the resolution of sepsis. Samples for PK2 were drawn on day 5 of ceftriaxone therapy for patients in sepsis or severe sepsis and 48 h after catecholamine discontinuation in patients with septic shock.

In the initial study design, two distinct sampling schedules had been planned, as our intention was to set up a Bayesian procedure, using a limited number of samples per patient to predict individual concentrations at the end of

treatment. We had planned to develop the population pharmacokinetic model in a subset of patients using a sparse sampling scheme and to validate the Bayesian procedure in a separate patient subset for which a full profile was available as a reference. Upon data analysis, we discovered that concentrations were quite homogeneous among patients, with no marked outliers. Therefore, there was no apparent need to adapt the dose individually and we decided to pool the data sets. Twenty patients participated in the full pharmacokinetic study, during which 10 blood samples were taken per patient: one prior to the infusion, then 15 min, 30 min, 1, 2, 6, 8, 12 and 18 h after the completion of the infusion. Lastly, one sample was taken immediately prior to the next infusion (trough concentration). Thirty-four patients took part in the sparse sampling scheme, which consisted of taking a blood sample prior to the infusion and five more times, including a trough measurement. Samples were centrifuged within 30 min, and plasma was stored at -20°C until analysis, which was conducted within 3 months.

Ceftriaxone plasma concentrations were determined using a validated high performance liquid chromatography (HPLC) adapted from Al-Rawithi *et al.* [11], with cefotaxim as the internal standard. The extraction was performed using methylcyanide. A nucleosil 100 C18 column (Merck, Germany) was used for separation. The mobile phase consisted of 0.02 M phosphate buffer, 0.01 M N-acetyl-N,N,N-trimethylammonium bromide, and methyl cyanide (20:30:50; pH 7.0). The flow rate was 1.2 ml min^{-1} and ceftriaxone was quantified using ultraviolet detection at 280 nm. The lower limit of quantification was $2\text{ }\mu\text{g ml}^{-1}$. Calibration curves were linear between this lower limit of quantification and $200\text{ }\mu\text{g ml}^{-1}$. The accuracy was calculated as the percent deviation from the target value and ranged from 2.4 to 5.9% for three quality control concentrations (0.5 mg l^{-1} , 5 mg l^{-1} , 25 mg l^{-1}). The intraday and interday coefficients of variation (CVs) ranged from 1.8% to 9.8% and 9.1% to 11.5%, respectively, for concentrations ranging from 2 to $200\text{ }\mu\text{g ml}^{-1}$.

Microbiology

Blood cultures were performed for all patients. A 3–10 ml blood sample was collected from each patient, and inoculated into one BD Bactec Plus Aerobic/F[®] vial and into one BD Bactec Lytic Anaerobic/F[®] vial. Blood cultures were then incubated in a Bactec 9240 (BD Diagnostics, Germany) for 5 days. Other bacteriological samples were taken depending on the clinical situation. The MIC of bacterial isolates to ceftriaxone was determined using the E-test method (AB Biodisk, Sweden).

Population pharmacokinetic analysis

Ceftriaxone concentration data were used to develop a population model by nonlinear mixed effects modelling

(NONMEM version 6) [12]. The first-order conditional estimation (FOCE) method was used throughout the model-building process.

One- and two- compartment structural models with zero-order input and first-order elimination were evaluated as potential pharmacokinetic models. The selection of the base model was determined by the Akaike information criterion (AIC value) and a number of goodness-of-fit plots. The model with the lower AIC was chosen as the superior model. Inter-individual variability in ceftriaxone pharmacokinetics was assumed to follow a log normal distribution and was modelled according to an exponential error model. Several error models (additive, proportional or both) were investigated to describe residual variability. Standard errors of estimates (SEs) were obtained by the COVARIANCE function of NONMEM.

A total of 14 potential covariates were evaluated. They were composed of (i) demographic and anthropometric measurements (age and body weight obtained on the same day as PK), (ii) blood chemistry and haematology measurements on the day PK was taken (serum creatinine, measured CL_{cr} , bilirubin, albumin and haematocrit), (iii) concomitant therapy and disease-related factors: sepsis severity scores (SAPS 2 and SOFA), type of sepsis (sepsis, severe sepsis or septic shock), catecholamine support, daily fluid intake, ventilation and renal replacement therapy. Individual empirical Bayesian (POSTHOC) parameters were plotted against covariate values to assess correlations. Correlations between continuous covariates and pharmacokinetic parameters were assessed using linear proportional models and power models. They were parameterized so that the covariate was centred on the median value in the population. Non-continuous variables were categorized. Diagnostic plots, changes in the objective function and changes in parameter variability were used to select covariates that improved the model prediction. A decrease in the objective function value of at least 6.61 (χ^2 distribution with one degree of freedom for $P < 0.01$) relative to the base model was required for adding a single covariate to the model.

Between occasion variability (BOV) was analyzed in order to assess any within-subject difference in PK1 and PK2 parameters.

The ability of the final population pharmacokinetic model to describe adequately the observed data was evaluated using visual predictive check (VPC). The final population pharmacokinetic model and parameters (including interindividual and residual variability) were used to perform Monte Carlo simulations ($n = 200$). The mean of simulated concentrations and their 95% confidence intervals were then superimposed on the observed concentrations at 1 g and 2 g doses.

A non-parametric bootstrap analysis was performed in order to evaluate the precision and stability of the final parameter estimates. Patients were randomly sampled with replacement from the data set used for building the

model to create bootstrap data sets with the same sample size as the original. The final model was used to generate and analyze 500 bootstrap data sets. The 2.5th and 97.5th percentiles of the parameter estimates were taken in order to build the 95% bootstrap confidence intervals.

Dosing simulations

Various dosing regimens were simulated with Monte Carlo simulations using the final pharmacokinetic model. Two dosing regimens (1 g and 2 g once a day) were evaluated for four CL_{cr}s (= 30, 60, 120 or 180 ml min⁻¹). Each simulation generated concentration–time profiles from 1000 patients per dosage regimen. Based on this data, the time period during which concentrations remained higher than the MIC (T > MIC) was estimated graphically.

Aa antibacterial activity is rather dependent on free concentrations, we computed them from observed concentrations. The free concentrations (C_{free}) were estimated from total concentrations (C_{tot}) using *in vivo* binding parameters of ceftriaxone [13] and the following equation, as described by Kodama *et al.* [14]:

$$C_{free} = \frac{1}{2} \left[- \left(nP + \frac{1}{K_{aff}} - C_{tot} \right) + \sqrt{ \left(nP + \frac{1}{K_{aff}} - C_{tot} \right)^2 + \frac{4C_{tot}}{K_{aff}} } \right]$$

The following binding parameters of ceftriaxone were used: the total concentration of protein binding sites (nP) 517 μmol l⁻¹ and the binding affinity constant (K_{aff}) 0.0367 l μmol⁻¹ [15].

Results

Patient characteristics

In total, 54 patients (39 men) were enrolled from July 2006 to March 2008. Table 1 summarizes demographic data: 19 patients suffered from sepsis, nine presented with severe sepsis and 26 were in septic shock. For the 26 septic shock patients, the mean duration of catecholamine support was 4 days (range 1–14 days). A total of 40 patients were mechanically ventilated and 12 had haemofiltration (HF) (11 at PK1, six at PK2 and one between PK1 and PK2). For the other patients, the median CL_{cr} was 68.5 ml min⁻¹ (range 5.5–214). Renal function improved from PK1 to PK2, with median CL_{cr} values of 63 ml min⁻¹ (range: 5.5–195) and 70 ml min⁻¹ (range: 25.7–214), respectively. The median (range) serum albumin was 25 (13–37) g l⁻¹. Six patients died in the ICU.

In our study, 33 infections were microbiologically documented, with 36 isolated pathogens. Blood cultures were positive for 16 patients. MIC was determined for all micro-organisms except *P. aeruginosa* (Table 2). MIC values ranged from 0.016 mg l⁻¹ (*Streptococcus pneumoniae*) to

Table 1

Demographic and clinical characteristics of enrolled patients

Total number of patients	54
Gender (male)	39
Age (years) (mean, range)	68 (35–86)
SAPS II (mean, range)	50 (9–87)
Type of sepsis	
Sepsis	19
Severe sepsis	9
Septic shock	26
Mechanical ventilation	40
Creatinine clearance (range)	5.5–214 ml min ⁻¹
Renal replacement therapy	12
Clinical infection site	
Lung	33
Urinary tract	10
Intra-abdominal	6
Central nervous system	1
Skin and soft tissue	2
ENT	1
Undetermined	1

Table 2

Pathogens (n = 36) isolated with their MIC value

Pathogen	n	MIC (range)
<i>Escherichia coli</i>	10	0.032–0.064
<i>Staphylococcus aureus</i> (meti-5)	5	4–8
<i>Streptococcus pneumoniae</i>	4	0.016–0.5
<i>Klebsiella pneumoniae</i>	4	0.032–0.38
<i>Klebsiella oxytoca</i>	1	0.19
<i>Other streptococcus</i>	3	0.016–0.38
<i>Branhamella catarrhalis</i>	2	0.023–1
<i>Haemophilus influenzae</i>	2	0.016–0.06
<i>Proteus mirabilis</i>	2	0.016–0.064
<i>Providencia stuartii</i>	1	0.06
<i>Pasteurella multocida</i>	1	0.016
<i>Pseudomonas aeruginosa</i>	1	ND

ND, not determined.

1 mg l⁻¹ (*Branhamella catarrhalis*), except for the five *Staphylococcus aureus* isolates for which MICs varied from 4 mg l⁻¹ to 8 mg l⁻¹.

Ceftriaxone doses and serum concentrations

The median daily dose of ceftriaxone was 2 g. Of the patients, 41 received 2 g once a day at each period, five were administered 1 g once a day at each period, one received 2 g twice a day and the remaining patient took 2 g three times a day. For five patients, the ceftriaxone dose was modified between the two periods.

All patients underwent pharmacokinetic analysis at the first period (PK1), while six patients did not undergo the second analysis (PK2) for the following reasons: death (2), discharge from ICU (1), discontinuation of ceftriaxone (1)

and refusal (2). In total, 709 concentrations from 54 patients were available for model building, among which 168 were trough concentrations. No obvious differences between PK1 and PK2 concentrations were seen.

Trough concentrations, measured 24 h after the end of the infusion, ranged from 2.6 mg l⁻¹ to 93.2 mg l⁻¹ (0.22 to 13.5 mg l⁻¹ for the corresponding free concentrations) for the patients who received 1 g once a day, and from 5.9 mg l⁻¹ to 212.8 mg l⁻¹ (0.45 to 39.1 mg l⁻¹ for the free concentration) for those who received 2 g once a day. For all patients, trough concentrations (based on total concentration) exceeded the MIC of the pathogen involved. When considering the free concentration determined from the theoretical binding parameters, the trough concentration was below 1 mg l⁻¹ in 15/146 (10%) measurements at the dose of 2 g and in 1/22 (4%) at the dose of 1 g once a day.

Population pharmacokinetic modelling

A two-compartment model resulted in a better fit to describe ceftriaxone serum concentration data. The inter-subject variability regarding the clearance (CL), volume of the central compartment (V1), and volume of the peripheral compartment (V2) were modelled as exponential. No variability was implemented for intercompartmental clearance (Q). The residual variability was modelled as proportional. The population estimates (interindividual variability; CV) of ceftriaxone pharmacokinetic parameters were: CL 0.88 l h⁻¹ (49%), V1 10.3 l (47%), and V2 7.35 l (65%). In the entire population, the mean half-life was 9.6 h (range 0.83–28.6), and the total volume of distribution was 19.5 l (range 6.48–35.2).

The effects of covariates on ceftriaxone pharmacokinetics were first investigated for disease-related factors in order to determine whether the clinical status was influential. Neither SOFA nor SAPS 2 scores were correlated with any of the parameters. The V1 value increased with the severity of sepsis: V1 = 8.21 ± 3.55 l for sepsis, V1 = 9.77 ± 3.83 l for severe sepsis and V1 = 11.5 ± 4.16 l for septic shock. However, including sepsis in the model resulted in a non-significant change in the objective function value. Neither the clearance nor the volume of distribution was correlated with serum albumin. CL_{cr} was the only covariate to describe ceftriaxone clearance. Its inclusion in the model decreased the objective function by 12 points and the interindividual variability from 59% to 49%. As shown in Figure 1, ceftriaxone clearance was independent of CL_{cr} for values <60 ml min⁻¹ and then increased linearly with increasing glomerular filtration rates (GFR). In the 12 patients who underwent haemofiltration (HF), ceftriaxone parameter values were similar to those obtained in non-epurated (non-HF) patients. The median clearance was 0.82 l h⁻¹ (range 0.31–2.22) and 0.89 l h⁻¹ (0.27–3.12) in HF and non-HF patients, respectively. The total volume of distribution was 20.1 l (range 13.4–30.2) and 18.5 l (range 6.48–35.2) in HF and non-HF

Figure 1

Correlation between ceftriaxone clearance and creatinine clearance (CL_{cr})

patients, respectively. The model did not support interoccasion variability on any parameter. The final model thus included CL_{cr}, normalized to the population median in our patients (4.26 l h⁻¹) (Table 3). Table 3 also shows the medians and 95% confidence intervals obtained from the bootstrap procedure. Figure 2 reveals the excellent match between predicted and observed concentrations in the final model.

Figure 3 illustrates the plots of VPC obtained for the simulations using the final model. At the dose of 2 g, 2.01% and 1.85% of the predictions were outside the 2.5th and 97.5th percentile, respectively. Results were slightly less satisfactory at the 1 g dose, with 0.95% and 13.3% of the predictions outside these bounds. These results indicate that the final model correctly described the data, enabling the model to be used for subsequent simulations.

Dosing simulations

Simulations performed for two different ceftriaxone doses and four different renal functions indicated that most patients were likely to reach high total concentrations, even at a dose of 1 g day⁻¹. However, this was not the case for patients with a high GFR, who are at risk of presenting low total concentrations.

The median (range) simulated free fraction in our patients was 11 (9–19) % and 14 (9–41) %, for doses of 1 and 2 g, respectively. The simulated trough concentration and time > MIC following a single dose of ceftriaxone at 1 or 2 g in patients with different degrees of renal function are presented in Table 4. Simulated total and free ceftriaxone concentrations for the dose of 1 g and 2 g in patients with normal renal function are illustrated in Figure 4.

Table 3

Population pharmacokinetic parameters of ceftriaxone

Parameter	Estimation Final estimate	SE of the estimate	95% CI *		Bootstrap Median	95% CI†	
PK							
CL (l h ⁻¹) = θ ₁ + θ ₂ × (CL _{cr} /4.26)							
θ ₁	0.56	0.11	0.34	0.78	0.56	0.37	0.85
θ ₂	0.32	0.12	0.08	0.56	0.32	0.005	0.56
V1 (l)	10.3	0.89	8.56	12.04	10.0	6.24	13.4
V2 (l)	7.35	0.75	5.88	8.82	7.48	4.81	10.9
Q (l h ⁻¹)	5.28	1.37	2.59	7.97	5.12	1.16	14.4
BSV ω ² (% coefficient variation)							
ω ² (CL)	0.24 (49)	0.05	0.14	0.34	0.25	0.15	0.38
ω ² (V1)	0.23 (48)	0.06	0.11	0.35	0.24	0.11	0.43
ω ² (V2)	0.42 (65)	0.11	0.20	0.64	0.38	0.18	1.76
Residual variability σ ²							
σ ² proportional (%)	24	0.009	21	28	24	21	28

* (mean estimate $\pm$ 1.96 SE of the estimates) for θ ; (mean estimate $\pm$ 1.96 SE of the estimates)^{1/2} for ω and σ . †The 2.5th and 97.5th percentiles of 500 bootstrap distribution of parameter estimates. V1, volume of the central compartment; V2, volume of the peripheral compartment; CL, clearance of ceftriaxone; CL_{cr}, clearance of creatinine; Q, intercompartmental clearance.

Figure 2

Plot of observed vs. individual predicted concentrations of ceftriaxone for the final model

Discussion

A wide interpatient variability in ceftriaxone pharmacokinetics was found in critically ill septic patients. To our knowledge, this is the first report to describe ceftriaxone pharmacokinetics in ICU septic patients using a population modelling approach. By investigating widely varied patients (severity of sepsis, CL_{cr}, serum albumin, cholestase, etc.), this approach appears very useful as it allows for a

Figure 3

Plots of visual predictive checks obtained for the simulations with ceftriaxone 2 g i.v. once per day using the final model (median and 95% confidence interval)

quantitative evaluation of the effect of various pathophysiological and clinical covariates on the drug's pharmacokinetic profile. Our results show that the only parameter that influenced ceftriaxone pharmacokinetics was CL_{cr}. Nevertheless, the correlation was weak and found only when CL_{cr} was $>60 \text{ ml min}^{-1}$, suggesting that ceftriaxone clearance

Table 4

Minimum concentration and time > MIC following the administration of 1 or 2 g of ceftriaxone in patients with various degrees of renal function. Simulations are based on free concentration

Ceftriaxone dose and renal function	Trough concentration (mg l ⁻¹) median (25th–75th centiles)	Time > MIC (%) (MIC = 1 mg l ⁻¹) median (25th–75th centile)	Time > MIC (%) (MIC = 8 mg l ⁻¹) median (25th–75th centile)
1 g daily			
CL _{cr} = 30 ml min ⁻¹	1.10 (1.71–2.40)	100 (100–100)	2 (0–6)
CL _{cr} = 120 ml min ⁻¹	1.02 (0.52–1.58)	100 (70–100)	2 (0–5)
CL _{cr} = 180 ml min ⁻¹	0.74 (0.34–1.26)	83 (54–100)	1 (0–4)
2 g daily			
CL _{cr} = 30 ml min ⁻¹	2.28 (3.62–5.17)	100 (100–100)	21 (10–50)
CL _{cr} = 120 ml min ⁻¹	2.10 (1.09–3.36)	100 (100–100)	16 (8–29)
CL _{cr} = 180 ml min ⁻¹	1.51 (0.68–2.65)	100 (87–100)	12.5 (8–25)

Figure 4

Simulation of ceftriaxone pharmacokinetics (total [top] and free [bottom] concentrations) following a 1 g (A) or 2 g (B) injection in a patient with a creatinine clearance of 120 ml min⁻¹ (median, 25 and 75 centiles). The dotted line represents the desired threshold concentrations (1 and 8 mg l⁻¹, respectively)

was not affected by the degree of renal insufficiency. Most importantly, our results reveal an increased clearance of ceftriaxone in patients with an increased GFR. This correlation between cephalosporin clearance and CL_{cr} confirms

previous findings [4,5,16]. Joynt *et al.* studied 12 critically ill patients with severe sepsis or septic shock using a standard pharmacokinetic analysis [4]. The authors found that in the nine patients with no renal insufficiency, ceftriaxone

clearance was increased by 100% in comparison with normal subjects. In their study, four of the nine patients had a $CL_{cr} > 140 \text{ ml min}^{-1}$, suggesting that the increase in ceftriaxone clearance may be due to increased GFR, as was the case in our study. As the renal clearance operates on the free drug in plasma, decreased binding due to hypoalbuminaemia may have contributed to this observation. The mean total ceftriaxone clearance found in our patients was 0.88 l h^{-1} , i.e. 14 ml min^{-1} . As glomerular clearance is obtained by multiplying the free fraction (about 10% in our patients) by the GFR, it represents 12 ml min^{-1} in a patient with a GFR of 120 ml min^{-1} . Thus, an increase in the free fraction may have a significant impact on total ceftriaxone clearance. On the other hand, an increase in GFR, without any change in protein binding, would have exactly the same consequence. As covariate analysis found no direct relationship between ceftriaxone total clearance and albuminaemia in our patients, our hypothesis was that an increased GFR *per se* rather than decreased protein binding was likely to be responsible for the increased ceftriaxone clearance in patients with a $CL_{cr} > 180 \text{ ml min}^{-1}$. The significant fluid resuscitation used in our patients is thought to contribute to increased renal perfusion.

Joynt *et al.* found that the volume of distribution increased by 90% as compared with normal subjects. In our study, the volume of distribution was also higher when compared with values reported in normal subjects [17], increasing with the severity of sepsis. From a theoretical point of view, an increase in the free fraction due to hypoalbuminaemia is accompanied by an increased volume of distribution [18]. The mean serum albumin in our patients (25 g l^{-1}) was low as compared with normal subjects, which could explain the differences. However, in our patients, decreased protein binding did not contribute to interindividual variability of V_d to a great extent, as albuminaemia was not correlated with V_d .

Patients undergoing HF are a particular group for which dosing recommendations are often lacking. Kroh *et al.* [19] showed that the pharmacokinetic parameters of six patients undergoing HF were similar to those of eight patients with normal renal function. In our study, which included 12 patients undergoing HF, ceftriaxone parameter values were similar to those obtained in non-HF patients. Our data confirms that no specific dosing recommendations are necessary in critically ill HF patients as compared with other ICU patients.

Ceftriaxone is a well-tolerated antibiotic of the β -lactam class. Data derived from *in vitro* and animal studies suggest that the time above the MIC is the most relevant pharmacodynamic outcome predictor [7, 20]. Nonetheless, the length of time in which concentrations must exceed the MIC is still debated, and possibly depends on the pathogen. Some authors suggest that this should be the case for 60% of the dosing interval. Yet, others maintain that maximum killing can only be achieved when this figure approaches 90–100% [20, 21]. According to the rec-

ommendations of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), a clinically inferior MIC breakpoint of ceftriaxone should not exceed 1 mg l^{-1} [22]. We therefore determined the appropriate threshold concentration for ceftriaxone to be 1 mg l^{-1} . In all of our patients, observed trough concentrations of ceftriaxone (based on total concentrations) were above the MIC of the pathogen involved. The estimated free concentration (from experimental trough concentrations observed in our patients) was below 1 mg l^{-1} in 4% and 10% of patients at the dose of 1 g and 2 g, respectively.

No clinical MIC breakpoints for *S. aureus* are defined. The MIC measured for the five *S. aureus* isolates in our study ranged from 4 mg l^{-1} to 8 mg l^{-1} in accordance with the ESCMID survey data [22]. Even if all our patients infected with *S. aureus* had total trough ceftriaxone concentrations exceeding the MIC, failure to maintain ceftriaxone concentrations above this level for a sufficient length of time could theoretically occur. Of note is that the five *S. aureus* isolates in our study were susceptible to oxacillin.

Several dosing simulations were derived from the final model. We thus obtained simulated total and free concentrations for various dosing regimens and renal functions. When considering total concentrations, the risk of concentrations dropping below the MIC at trough concentration was very low for pathogens commonly treated with ceftriaxone, even at a dose of 1 g once a day. This risk appears evident only in patients with a high GFR ($CL_{cr} > 120 \text{ ml min}^{-1}$ and especially $\geq 180 \text{ ml min}^{-1}$) receiving 1 g or in patients infected by high MIC pathogens (e.g. *S. aureus*).

On the contrary, the time when simulated free concentrations exceeded the MIC ($T > \text{MIC}$) was clearly dependent on dose, renal function and the MIC considered. For pathogens with a low MIC (1 mg l^{-1}), free concentrations were above the MIC for all patients except those with a high GFR. Indeed, 25% of patients with $CL_{cr} = 180 \text{ ml min}^{-1}$ receiving 1 g had a $T > \text{MIC}$ of less than 50% (Table 4). When considering pathogens with high MIC (8 mg l^{-1}), the target was never reached, with median $T > \text{MIC}$ always below 21%, even in patients with impaired renal function receiving 2 g day⁻¹.

Our simulations were based on a saturable model of protein binding with published *in vivo* binding parameters [13]. The equation takes into account the number of binding sites (nP), in which P refers to albuminaemia and $n = 0.7$. Therefore, in our patients, nP was set at $295 \mu\text{mol l}^{-1}$ in place of the theoretical value of $517 \mu\text{mol l}^{-1}$ found in subjects with normal albuminaemia. Consequently, this correction predicts higher free concentrations than those the original model would have given. Despite this, simulated free concentrations were inferior to the pharmacodynamic target in some patients. Although it is commonly recognized that it is the free fraction of an antibiotic with a high degree of protein binding that essentially acts on bacteria, the bound fraction may also contribute to the drug's activ-

ity. This has been previously proven for teicoplanin [23] and ceftriaxone [24]. Elkhallil *et al.* found that the bound fraction of ceftriaxone is implicated in the bactericidal action on *Streptococcus pneumoniae*. It is acknowledged that the protein-bound fraction acts as a reservoir, as it is progressively released along with the elimination of the free part of the antibiotic. The role of the bound fraction of ceftriaxone on the calculation of pharmacokinetic–pharmacodynamic parameters must thus be considered. This is reinforced by the observation that most of our patients were cured despite very low free drug concentrations over time.

Our data revealed a weak increase in V_d but no increase in ceftriaxone clearance as compared with normal patients. Thus, total concentrations were similar to those observed in normal patients. Conversely, simulated free concentrations were higher, indicating that the risk of having ineffective concentrations was even lower in critically ill as compared with normal patients. Our results confirm that ceftriaxone should not be used in critically ill patients infected by *S. aureus*, in agreement with what was previously recommended for the general population [25].

In summary, we used population pharmacokinetic modelling and Monte Carlo simulation to characterize the pharmacokinetic profile of ceftriaxone in critically ill patients. Despite the wide inter-patient variability, our results showed that the only parameter that influenced ceftriaxone pharmacokinetics was CL_{cr} . Assuming that only the free fraction is microbiologically active, our results indicate that the risk of being under the threshold concentration exists only in patients with a high GFR (CL_{cr} above 120 ml min^{-1}), provided that the pathogen is sensitive to the drug used.

Competing Interests

There are no competing interests to declare.

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Author Contributions

Study concept and design: D. Garot, P.F. Dequin and C. Le Guellec

Acquisition of clinical data: D. Garot, E. Mercier and S. Ehrmann

Drug assay: N. Simon

Bacteriological study: P. Lanotte

Pharmacokinetic analysis and dosing simulation: R. Respaud, N. Simon and C. Le Guellec

Analysis and interpretation of data: D. Garot, N. Simon and C. Le Guellec.

Drafting of the manuscript: D. Garot and C. Le Guellec.

Critical revision of the manuscript for important intellectual content: D. Garot, P.F. Dequin and C. Le Guellec

Obtained funding: D. Perrotin and P.F. Dequin

Administrative, technical or material support: E. Mercier, S. Ehrmann and D. Perrotin

Study supervision: D. Garot, P.F. Dequin and C. Le Guellec

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