The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients

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The aim of this study was to determine the pharmacokinetic profile of the normal recommended dose of ceftriaxone in critically ill patients and to establish whether the current daily dosing recommendation maintains plasma concentrations adequate for antibacterial efficacy. Ceftriaxone at a recommended dose of 2 g iv was administered od to 12 critically ill patients with severe sepsis and normal serum creatinine concentrations. Blood samples were taken at predetermined intervals over the first 24 h and on day 3 for measurement of ceftriaxone concentrations. There was wide variability in drug disposition, explained by the presence of variable renal function and identified by the measurement of creatinine clearance. In nine patients with normal renal function, there was a high level of creatinine clearance (mean ± s.d., 41 ± 12 mL/min) and volume of distribution (20 ± 3.3 L), which resulted in an elimination half-life of 6.4 ± 1.1 h. In comparison with normal subjects, ceftriaxone clearance was increased 100%, volume of distribution increased 90% and the elimination half-life was similar. Three patients had substantially suboptimal plasma ceftriaxone concentrations. We confirm previous findings that ceftriaxone clearance in critically ill patients correlates with renal clearance by glomerular filtration. The elimination half-life is prolonged (21.4 ± 9.8 h) in critically ill patients with renal failure when compared with previously published data in non-critically ill patients with renal failure. We conclude that in critically ill patients with normal renal function, inadequate plasma concentrations may result following od bolus dosing of ceftriaxone. Drug accumulation may occur in critically ill patients with renal failure.

Introduction

Dosage regimens for drugs used in critically ill patients are frequently based on pharmacokinetic data obtained from healthy or less severely ill patients. Drug disposition in critically ill patients may be greatly altered for various reasons, including variations in vascular permeability, intravascular volume, and in the composition and distribution of plasma proteins. Renal and hepatic dysfunction is frequent. Altered pharmacokinetic variables have been demonstrated for various drugs in critically ill patients. These drugs include sedatives anticonvulsants and antibiotics such as the aminoglycosides, vancomycin, aztreonam, imipenem and cephalosporins. The altered pharmacokinetics of these agents may result in drug accumulation and toxicity, or in loss of efficacy due to drug concentrations that are too low.

Although ceftriaxone is commonly used in intensive care units, there are few data on the pharmacokinetics of ceftriaxone in critically ill patients. The severity of critical illness was not documented in either of the two studies that have reported data on the disposition of ceftriaxone in critically ill patients. Neither were individual patient data and trough antibiotic levels. Adequate data on the pharmacokinetics of od administration of ceftriaxone in critically ill patients are therefore lacking and it is unclear whether the current daily dosing recommendation, based on pharmacokinetic data from non-critically ill patients, is appropriate in the critically ill.

We measured plasma concentrations of ceftriaxone in critically ill patients with severe sepsis to determine the pharmacokinetic profile of the normal recommended dose of ceftriaxone for severe infections and to determine whether the current daily dosing recommendation main-
tains adequate plasma concentrations for antibacterial efficacy.

Materials and methods

The study was performed in a 22 bed mixed medical and surgical intensive care unit (ICU) of a university teaching hospital. Approval was obtained from the Clinical Research Ethics Committee of the Chinese University of Hong Kong. Written informed consent was obtained from the patient or most senior relative when appropriate.

Twelve adult patients in the ICU with severe sepsis and who received ceftriaxone according to usual clinical practice were entered into the study. Patients with suspected allergy or renal impairment (plasma creatinine >120 μmol/L at enrolment) were excluded. Clinical indications for ceftriaxone included nosocomial pneumonia, intra-abdominal sepsis, urinary sepsis and empirical therapy for clinical sepsis without proven source. In accordance with usual clinical practice, all patients had an indwelling arterial cannula. All patients met recognized criteria for severe sepsis: clinical evidence of acute infection, temperature >38.3°C or <35.6°C, heart rate >90 beats per minute and tachypnoea >20 breaths per minute, as well as evidence of organ dysfunction or inadequate organ perfusion. Evidence of organ hypoperfusion included shock (defined as a systolic blood pressure of <90 mmHg or a decrease in baseline blood pressure of >40 mmHg after adequate fluid resuscitation), systemic acidosis, high blood lactate concentrations, oliguria and acute alteration of mental status. Blood pressure was measured continuously using an indwelling arterial catheter and recorded hourly for the duration of the study. The presence of shock and the need for inotropes during the study period were recorded.

The patients were prescribed an od dose of ceftriaxone (2 g) administered as an infusion over 30 min. Samples of arterial blood were collected at 0, 5, 10, 20 and 30 min during the first infusion and then, after completion of the infusion, at 1, 2, 5, 10, 20, 30, 60, 120, 210, 450, 690, 930, 1170 and 1410 min. Single specimens of blood for trough concentrations were taken on day 3. Specimens were centrifuged and plasma stored at –70°C for later analysis. Patient demographic data, clinical details and APACHE II scores were collected at the time of entry into the study and was therefore excluded. Patient demographic data and clinical details of the remaining 11 patients are shown in Table I. Seven patients met the study entry criteria for shock. Of these seven patients, six received inotrope infusions (Table I). The other shocked patient (patient 6) was managed during the study period with aggressive fluid resuscitation (5.1 L of fluid was infused over the first 24 h to achieve a central venous pressure of >20 mmHg). All patients had serum creatinine concentrations within the normal range at the time of entry into the study and no patient’s creatinine exceeded 120 μmol/L during the study period. However, impaired renal function was subsequently confirmed by a creatinine clearance <50 mL/min in two patients (Table I). Because we intended to study patients with normal renal function, these patients’ pharmacokinetic parameters were separated from those with normal renal function in a secondary analysis. The total (free and bound) ceftriaxone concentration–time curves for individual patients are shown in Figure 1. Pharmacokinetic variables for the 11 patients are shown in Table II. The day 3 trough concentration for patient 8 is missing because of a sampling error. Mean pharmacokinetic variables for patients separated on the basis of renal function are shown in Table III, along with previously published pharmacokinetic data for ceftriaxone. The 95% CIs for all 11 patients were 18.1–26.6 L for Vss, 29–45 mL/min for CL and 5.1–13.2 h for t1/2. The 95% CIs for patients with normal renal function were 17.6–22.4 L for Vss, 33–50 mL/min for CL and 5.5–7.1 h for t1/2.

There was no correlation between the pharmacokinetic variables of total ceftriaxone clearance, Vss and Vss and serum bilirubin or plasma albumin (Tables I and II). There was a moderate direct correlation between total ceftriaxone clearance and creatinine clearance (r = 0.67; P = 0.03). Because of inadequate sample volume in one patient, protein binding data were available for only 10 patients. The mean non-protein-bound or free fraction of ceftriaxone was 27% (range 1–59%). Protein binding was concent-

The non-protein-bound fraction of ceftriaxone was determined by equilibrium dialysis as described previously. The free fraction was determined after equilibrium dialysis at pH 7.4 for 3.5 h at 37°C.

Ceftriaxone data were fitted to a two-compartment model using Kinetica (Simed SA, Creteil, France). Ninety-five percent confidence intervals (95% CIs) were calculated for elimination half-life (t1/2), volume of distribution at steady state (Vss) and total body clearance (CL), to enable comparison with published data. The association between pharmacokinetic variables and serum bilirubin, albumin and creatinine clearance was determined by linear regression analysis. P values of <0.05 were considered significant.

Results

Twelve patients were enrolled. One patient died 9 h after entry into the study and was therefore excluded. Patient demographic data and clinical details of the remaining 11 patients are shown in Table I. Seven patients met the study entry criteria for shock. Of these seven patients, six received inotrope infusions (Table I). The other shocked patient (patient 6) was managed during the study period with aggressive fluid resuscitation (5.1 L of fluid was infused over the first 24 h to achieve a central venous pressure of >20 mmHg). All patients had serum creatinine concentrations within the normal range at the time of entry into the study and no patient’s creatinine exceeded 120 μmol/L during the study period. However, impaired renal function was subsequently confirmed by a creatinine clearance <50 mL/min in two patients (Table I). Because we intended to study patients with normal renal function, these patients’ pharmacokinetic parameters were separated from those with normal renal function in a secondary analysis. The total (free and bound) ceftriaxone concentration–time curves for individual patients are shown in Figure 1. Pharmacokinetic variables for the 11 patients are shown in Table II. The day 3 trough concentration for patient 8 is missing because of a sampling error. Mean pharmacokinetic variables for patients separated on the basis of renal function are shown in Table III, along with previously published pharmacokinetic data for ceftriaxone. The 95% CIs for all 11 patients were 18.1–26.6 L for Vss, 29–45 mL/min for CL and 5.1–13.2 h for t1/2. The 95% CIs for patients with normal renal function were 17.6–22.4 L for Vss, 33–50 mL/min for CL and 5.5–7.1 h for t1/2.

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In patients with normal renal function ($n = 8$), the mean free fraction was 23% (range 1–50%), and in those with abnormal renal function ($n = 2$), it was 40% (range 1–59%). The free (unbound) ceftriaxone concentration–time curves for individual patients are shown in Figure 3. The limits of the ceftriaxone assay used were such that ceftriaxone concentrations $<0.5$ mg/L were not detectable. Reported concentrations $<5$ mg/L may be less accurate and should be interpreted with caution.

Discussion

This study demonstrates that the pharmacokinetics of ceftriaxone in critically ill patients are different from previously reported data in healthy volunteers (Tables II and III). The summary of total (bound and unbound) ceftriaxone data of all 11 patients demonstrates a prolonged $t_{1/2}$, and an increase in CL and $V_{ss}$. There is, however, wide inter-patient pharmacokinetic variability and a wide range of trough plasma concentrations (range 2–27 mg/L). Much of this variability results from the heterogeneity of the study sample. While intending to select patients with normal renal function, two patients with abnormal renal function (creatinine CL $<50$ mL/min) were included in the study sample. If these patients are separated into those with normal and abnormal renal function (Table III), this variability is markedly attenuated and the results are more easily explained. In critically ill patients with normal renal function, there is a 100% increase in CL and a 90% increase in the $V_{ss}$ compared with normal patients.\(^{16,17}\) This is consistent with our finding that the range of trough concentrations (2–14 mg/L) was lower than expected from studies in normal adults (7–22 mg/L).\(^{17}\) Ceftriaxone is excreted largely unchanged and is dealt with in approximately equal proportions by the liver (in bile) and the kidneys, where it is eliminated by glomerular filtration.\(^{16,17}\) Although the high $V_{ss}$ value contributes to the lower trough concentrations in our patients, the contribution of glomerular filtration to the high clearance of ceftriaxone is demonstrated by three patients in whom plasma ceftriaxone concentrations were below the desired threshold for a substantial proportion of the dosing interval (patients 5, 6 and 9). All three patients had a high creatinine clearance. It is possible that the use of inotropes and aggressive fluid resuscitation, commonly required in severely ill patients, contributed to the high clearances seen in these patients.

Few data on ceftriaxone pharmacokinetics and plasma concentrations in critically ill patients have been published previously. Comparison of pharmacokinetic data obtained in different studies is complicated by the fact that ceftriaxone CL is dose dependent as a result of concentration-dependent plasma protein binding of ceftriaxone.\(^{18}\) In comparison with the results of the three intensive care patients reported by van Dalen \& Vree,\(^{10}\) our eight patients had a 130% higher CL, a 50% increase in $V_{ss}$, and a shorter...
The higher ceftriaxone dose (van Dalen & Vree used 1.5 g daily) and possible differences in albumin levels and illness severity may explain the differences seen (disease severity was not reported in van Dalen & Vree’s study). The β-lactam antibiotic ceftriaxone is unique because it is 90% protein-bound at clinically relevant doses in non-critically ill patients. In patients with severe sepsis, plasma albumin often falls rapidly. This hypoalbuminaemia is marked in our patient group (mean albumin level, 22 ± 6.1) and would be expected to increase the free fraction of ceftriaxone; this is confirmed by our data (Figure 2). In comparison with normal patients, protein binding was decreased by 20–30%. Elimination of ceftriaxone by the kidneys is by glomerular filtration, and it is well known that plasma protein binding will reduce the rate of drug elimination by glomerular filtration. The higher free fraction of ceftriaxone would therefore result in increased ceftriaxone CL in the presence of normal or increased creatinine clearance (Tables I and II), thereby contributing to the observed low trough concentrations.

**Figure 1.** Total plasma ceftriaxone concentrations of individual patients (logarithmic scale) over 24 h following iv administration. The curves drawn with a short-dashed (−−−) line represent the patients with renal failure. The long-dashed (———) line, representing the desired MIC, is at 8 mg/L.

**Figure 2.** Scatter graph showing the relationship between blood concentration and percentage free fraction of ceftriaxone in patients with normal renal function (●) and patients with renal failure (○).
### Table II. Selected total (free and bound) ceftriaxone concentrations and pharmacokinetic parameters for each patient

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<th>Vss (L)</th>
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<th>k12 (per min)</th>
<th>k21 (per min)</th>
<th>t1/2alpha (min)</th>
<th>t1/2beta (h)</th>
<th>CL (mL/min)</th>
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Abbreviations: Vc, volume of the central compartment; Vss, volume of distribution at steady state; Kd, elimination rate constant; k12, k21, rate constant between the two compartments; t1/2alpha, distribution half-life; t1/2beta, elimination half-life; CL, total clearance; Cmax, maximum modelled concentration.

*aMeasured trough concentrations at 24 h and on day 3.

**Figure 3.** Free plasma ceftriaxone concentrations of individual patients (logarithmic scale) over 24 h following iv administration. The curves drawn with a short-dashed (---) line represent the patients with renal failure. The long-dashed (——) line, representing the desired MIC, is at 8 mg/L. Concentration–time curves are not complete as a result of the detection limit of the ceftriaxone assay (see text).
Our results are also different from those published by Heinemeyer et al.11 Our patients had an increased CL, increased Vss and a 50% shorter $t_{1/2}$ (Table III). The differences in the patient populations investigated in these two studies are the most likely cause of discrepancies between the findings. Our patients have clearly defined severe disease as confirmed by APACHE II scores and presence of severe sepsis, whereas the patients in the Heinemeyer study were described only as post-operative surgical patients with bacterial bronchial tract infection—the severity of disease was not reported. The reported mean albumin concentration from their series (mean 38 ± 6.6 g/L) is close to normal values. Low albumin has been associated with severity of illness and decreased survival in critically ill patients,22,23 and the lower albumin levels in our patients (mean 22 ± 6.1 g/L compared with 38 ± 6.6 g/L) suggest that our patients were more severely ill. For the reasons discussed previously the low albumin levels would contribute to the higher Vss and ceftriaxone CL seen in our patients.

The occurrence of low ceftriaxone concentrations for a substantial part of the dosing interval has potential clinical implications. The bactericidal activity of β-lactam antibiotics on Gram-negative bacilli is related to the time that concentrations in tissue and plasma exceed a certain threshold. The effect is maximal at a relatively low antibiotic concentration, approximately four to five times the MIC, and there is no added benefit at higher concentrations.24,25 If antibiotic concentration in vitro falls below the threshold level, breakthrough bacterial growth will occur.26,27 In addition, there is no significant post-antibiotic effect, as seen with the aminoglycosides, and re-growth occurs as soon as concentrations fall below the MIC.28 It has also recently been demonstrated that resistance to β-lactam antibiotics is associated with antibiotic concentrations that fall below the MIC for more than half the dosing interval.29 Thus, it seems to be necessary for the efficacy of β-lactams that clinical dosing regimens maintain adequate plasma levels for a substantial part of the course of therapy. Common Gram-negative organisms found in ICU patients include Escherichia coli, Enterobacter spp., Klebsiella spp., Proteus spp., Morganella morganii, Citrobacter spp. and Pseudomonas aeruginosa.30 With the exception of P. aeruginosa, the average MIC$_{90}$ of ceftriaxone for these organisms is in the region of 2 mg/L (range of averages, <1–8 mg/L).31–34 The National Committee for Clinical Laboratory Standards (NCCLS) recommended MIC breakpoint for ceftriaxone susceptibility is 8 mg/L.35 We therefore conservatively determined the appropriate desired minimum threshold concentration for ceftriaxone to be 8 mg/L—four times the MIC of most susceptible organisms and at least greater than the NCCLS MIC breakpoint. Four of eight patients with normal renal function failed to maintain total (bound and unbound) ceftriaxone concentrations above the desired threshold for the entire dosing interval and three for a substantial part of the dosing interval.
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(Figure 1). Total trough ceftriaxone concentrations on day 3 continued to be low in all four of these patients (Table II). Despite the higher percentage of free to total plasma ceftriaxone in our patients, actual free concentrations fall rapidly. Free ceftriaxone concentrations were below the desired MIC in five of eight patients with normal renal function by 4 h, and were undetectable in all patients with normal renal function by 8 h (Figure 3).

The clinical importance of this observation is not yet clear; however, in intensive care patients, optimal efficacy of antibiotics is particularly important. Patients frequently have underlying disease, are shocked and have severe infections. These categories of patients have altered immune responses and there is evidence that they require markedly increased doses of cephalosporins to ensure efficacy. Therefore, although not clinically proven, it would seem prudent to choose a dose and dosing interval that would maintain optimal antibiotic concentrations in these patients. It may not be possible to estimate tissue antibiotic concentrations and subsequent clinical efficacy directly from blood concentrations; however, it is likely that altered antibiotic disposition and blood concentrations will have effects on tissue concentrations. This is particularly relevant at low concentrations towards the end of the dosing interval. If it is assumed that it is the free fraction of ceftriaxone that is pharmacodynamically active, and that plasma concentrations are in approximate equilibrium with extracellular concentrations, then free concentrations fall below the desired MIC (in plasma and tissue) in the majority of patients with normal renal function within 4 h.

In a simulated model based on normal subjects and a dose of 2 g iv, the time taken for free ceftriaxone levels to fall below the threshold concentration was approximately double (8 h), and total ceftriaxone levels remained above the threshold level for the entire dosing interval.

As can be seen from our data, total and free plasma ceftriaxone concentrations are frequently lower than threshold, and lower than those measured in non-critically ill patients. It is therefore likely that tissue concentrations will be low for a substantial part of the dosing interval. In the absence of data describing tissue levels of ceftriaxone in critically ill patients, it would seem appropriate to aim first for adequate total ceftriaxone concentrations in blood, which equate with efficacy in non-critically ill patients.

Our observations suggest that the same daily dose, given at either a shorter dosing interval or with administration by infusion, would be required to ensure adequate ceftriaxone concentrations over the full dosing interval in patients with severe sepsis and normal renal function. To ensure adequate total ceftriaxone concentrations for the entire dosing interval in most patients with normal renal function, we utilized the mean $+2$ S.D. of our pharmacokinetic data to calculate the loading and infusion dosage required. A loading dose of 300 mg followed by a continuous infusion at 1000 mg over 24 h should ensure antibiotic concentrations $>10$ mg/L for the entire dosing interval in at least 95% of patients. The potential extra cost of infusion is expected to be small because infusion pumps, a high nursing staff density and pharmacy personnel are already present in ICUs. As the total antibiotic dose required is less than the current recommended dose, cost savings could even be expected if continuous infusion is used.

The consequences of moderate or severe renal failure are an approximately three-fold increase in $t_{1/2}$, a 50% increase in $V_{ss}$, and halved CL, in comparison with baseline values in intensive care patients. The magnitude of these changes is similar to that reported in two previous studies of critically ill patients. The markedly prolonged $t_{1/2}$ in critically ill patients with renal failure differs from that reported in other acute renal failure patients, in whom the $t_{1/2}$ is only mildly prolonged. In non-critically ill patients, the increased proportion of free ceftriaxone that accompanies renal failure results in an increase in hepatic clearance and a consistent or only slightly increased $t_{1/2}$. It has been demonstrated previously that although the free fraction of ceftriaxone does increase, there is a decrease in hepatic clearance in critically ill patients, the cause of which has not been clearly delineated. The results in our critically ill patients confirm this important previous finding that ceftriaxone CL in critically ill patients is primarily dependent on renal CL, and the increased $V_{ss}$ and decreased CL result in a markedly prolonged $t_{1/2}$. This finding is clinically important as renal dysfunction may result in unsuspected accumulation in critically ill patients. The determination of creatinine clearance, preferably by direct measurement, and not simply observation of blood creatinine concentrations is needed. A dose reduction of one-third in patients with $>50\%$ reduction in creatinine CL, and a reduction of two-thirds in patients who are anuric has been suggested.

In conclusion, the pharmacokinetic parameters of ceftriaxone (2 g iv daily) in critically ill patients with severe sepsis are different from those described in normal patients. In critically ill patients with normal renal function, there is an increase in CL and the $V_{ss}$, which results in a similar $t_{1/2}$. Resulting ceftriaxone concentrations, however, are frequently below the desired threshold concentration as a result of the larger volume of distribution. In critically ill patients, it is even more important to optimize factors that could reduce treatment failure and emergence of antibiotic resistance. While not yet supporting a change in clinical practice, we recommend that a decrease in dosing interval or continuous infusion be evaluated further in critically ill patients with normal renal function.

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