Plasma and target-site subcutaneous tissue population pharmacokinetics and dosing simulations of cefazolin in post-trauma critically ill patients

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Objectives: The objective of this study was to describe the population pharmacokinetics of cefazolin in plasma and the interstitial fluid of subcutaneous tissue of post-trauma critically ill patients and provide clinically relevant dosing recommendations that result in optimal concentrations at the target site.

Patients and methods: This was a pharmacokinetic study in a tertiary referral ICU. We recruited 30 post-trauma critically ill adult patients and collected serial total and unbound plasma cefazolin concentrations. Interstitial fluid concentrations were determined using in vivo microdialysis. Population pharmacokinetic analysis and Monte Carlo simulations were undertaken with Pmetrics®. Fractional target attainment against an MIC distribution for Staphylococcus aureus isolates was calculated.

Results: The mean (SD) age, weight, APACHE II score and CLCR were 37.0 (14.1) years, 86.8 (22.7) kg, 16.9 (5.3) and 163 (44) mL/min, respectively. A three-compartment linear population pharmacokinetic model was most appropriate. Covariates included in the model were CLCR on drug clearance and serum albumin concentration and body weight on the volume of the central compartment. The fractional target attainment for a 1 g intravenous 8-hourly dose for a CLCR of 50 mL/min was 88%, whereas for a patient with a CLCR of 215 mL/min, a dose of 2 g 6-hourly achieved 84% fractional target attainment.

Conclusions: Clinicians should be mindful of the effects of elevated CLCR and serum albumin concentrations on dosing requirements for post-trauma critically ill patients.

Keywords: PK, pharmacodynamics, antibiotics, microdialysis, Monte Carlo simulations

Introduction

Effective antibiotic therapy is crucial for improving outcomes in critically ill patients.1–3 Whilst much research has been devoted to optimizing antibiotic therapy for infected patients, the ideal use of antibiotics administered for prophylaxis remains poorly investigated. Given that the EPIC II study demonstrated that approximately one-third of critically ill patients receive antibiotics for prophylaxis,4 prophylaxis is an area where strong data supporting dosing are required. It is likely that sub-optimal administration for this indication could result in failure of prophylaxis or the emergence of resistant pathogens4 that make later antibiotic treatment highly problematic.

Use of first-generation cephalosporins for prophylaxis in critically ill patients with serious skin and soft tissue injury after major trauma is common. Cefazolin is typically administered at 1 or 2 g intravenously 8-hourly for 24–72 h. The package insert dose recommendation for antibiotics is based on plasma pharmacokinetic data from non-critically ill patients. Such an approach may be inappropriate given the pharmacokinetic changes that are likely
to occur in critically ill patients.16,20,23 Indeed, post-trauma critically ill patients are unlikely to have renal dysfunction, and are in fact at risk of augmented renal clearance,8–13 due to their hyperdynamic circulatory state and significant fluid requirements. Dramatically decreased serum albumin concentrations are also common in these patients.15 For a renally cleared antibiotic like cefazolin, which has high protein binding (~90%), these changes can severely alter plasma concentrations.3,15 The effects of these changes on cefazolin concentrations in the interstitial fluid (ISF) of subcutaneous tissues, which is the site of infection for serious skin and soft tissue injury, are also unknown, but crucial to successful prescription.

Microdialysis is an in vivo sampling technique that has been successfully applied to measure the distribution of antibiotics in the ISF of various tissue sites.16 In the presence of sepsis and septic shock, antibiotic-specific effects have been described whereby, for piperacillin and meropenem, concentrations in ISF that are 2- to 10-fold lower than plasma concentrations have been observed.17–21 For other antibiotics little difference has been demonstrated between plasma and ISF concentrations.22 Unfortunately, these previous studies have rarely evaluated concentrations at the site of infection.20,23

The aim of this study was to describe the population pharmacokinetics of cefazolin in plasma and subcutaneous ISF of critically ill patients with serious skin and soft tissue injuries after major trauma. We then sought to use this model to perform Monte Carlo dosing simulations to determine doses necessary for optimal cefazolin concentrations in ISF.

Patients and methods

Institution where this work was carried out

Department of Intensive Care Medicine, Royal Brisbane and Womens’ Hospital, Butterfield Street, Herston, Queensland, Australia 4029.

Setting

This was an observational pharmacokinetic study using convenient sampling at a tertiary referral ICU. Ethics approval was obtained from the local institutional Human Research Ethics Committee (HREC 2007/188). Written informed consent was obtained from either the patient or their nominated substitute decision-maker.

Study population

The inclusion criteria for this study were: (i) age 18–80 years; and (ii) receiving cefazolin as prophylaxis for skin and soft tissue and bone infections after major trauma. The exclusion criteria were: (i) absence of intra-arterial catheter; (ii) pre-existing renal impairment (defined as a plasma creatinine concentration >171 μmol/L or the need for renal replacement therapy); or (iii) a history of allergy to cephalosporin antibiotics or iodine.

Study protocol

The protocol pertaining to this study has been published in detail elsewhere.24 In brief, 1 g of cefazolin (DBL Australia, NSW, Australia) diluted in 20 mL of 0.9% sodium chloride, was administered intravenously over 5 min as part of the patient’s prescribed therapy. Blood samples to determine plasma cefazolin concentrations were taken pre-dose, at 5 min (end of infusion) and 20, 60, 210 and 360 min. All urine was collected via an indwelling catheter over the dosing interval, following which urine volume and urinary creatinine concentration were determined by laboratory analysis. Plasma creatinine concentrations on the day of investigation were used to calculate the measured CLcr.

Additional clinical and demographic data were collected, including the requirement for mechanical ventilation, vasopressor support, modified SOFA score (excluding the neurological component) and 24 h fluid balance, on the day of drug administration. APACHE II score, body surface area, BMI and ICU and in-hospital mortality were also recorded.

Microdialysis

A microdialysis catheter (CMA 60, 20 kDa dialysis window, Global Scientific, Sweden) was inserted into subcutaneous tissue by an experienced clinician. The catheter was perfused at 1.5 μL/min with a solution of 0.9% sodium chloride and cefalotin (10 mg/L). After a 30 min equilibration period, the first microdialysis sample was taken 1 min prior to the start of the antibiotic infusion with repeat measurements taken at 20, 40, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330 and 360 min. The recovery of cefazolin in the microdialysate solution was interpolated from the loss of internal standard (cefalotin) across the microdialysis membrane.18,19,25

\[ \text{Percentage cefazolin recovery} = 100 \times \left( \frac{C_{\text{in}} - \text{mean} C_{\text{out}}}{C_{\text{in}}} \right) \]

where \( C_{\text{in}} = 10 \text{ mg/L} \) cefalotin (perfusate) and \( C_{\text{out}} \) is the measured cefalotin concentration in the microdialysate.

Sample handling, storage and measurement

Blood samples were immediately placed on ice and centrifuged within 60 min at 3000 rpm for 10 min. Plasma and microdialysis samples were stored at −80 °C until analysis. HPLC was used to measure cefazolin concentrations in plasma and LC–tandem MS to measure concentrations in microdialysate (including cefalotin) as previously described.23 All bioanalysis techniques were validated and conducted in accordance with the criteria of the US FDA’s guidance for industry on bioanalysis (available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070107). To isolate the unbound fraction for analysis, protein-bound cefazolin was removed from the plasma sample with centrifugal filter devices (Centrifree–30K, Merck Millipore, Tullagreen, Ireland).

Population pharmacokinetic modelling

Two- and three-compartment models were developed with the non-parametric adaptive grid (nPAG) algorithm within the Pmetrics package for R (Los Angeles, CA, USA).26,27 Elimination from the central compartment and intercompartmental distribution into the ISF compartment and other compartments were modelled as first-order processes using differential equations. Estimates of assay error were included in the modelling process as a polynomial, SD = \( C_0 + C_1 Y + C_2 Y^2 + C_3 Y^3 \), with values of 0.02, 0.09, 0 and 0 for plasma data and 0.08, 0.1, 0 and 0 for the ISF data. AUC from 0 to 6 h (AUC0–6) in plasma and ISF was also calculated. Demographic and clinical characteristics that were considered biologically plausible for affecting cefazolin pharmacokinetics were tested for inclusion as covariates. If inclusion of the covariate resulted in a statistically significant improvement in the log likelihood (P < 0.05) and/or improved the goodness-of-fit plots, it was supported for inclusion.

Model diagnostics

The goodness of fit was assessed by visual inspection of the observed–predicted plot, the coefficient of determination of the linear regression
of the observed–predicted values and the log-likelihood values from each run. Predictive performance evaluation was based on mean prediction error (bias) and the mean bias-adjusted squared prediction error (imprecision) of the population and individual prediction models in both plasma and ISF compartments.

**Probability of target attainment (PTA) for subcutaneous ISF concentrations**

Monte Carlo simulations (n = 1000) of subcutaneous ISF concentrations were performed using Pmetrics to determine the PTA with varying MIC for a standard patient with a CLCR of 130 mL/min, serum albumin concentration of 22 g/L and weight of 60 kg. Intravenous doses of 1 g 6-hourly, 1 g 8-hourly, 1 g 12-hourly, 2 g 6-hourly, 2 g 8-hourly and 2 g 12-hourly were simulated. Four different levels of renal function were tested that reflected the broad distribution of values observed in this patient population (ClCR 50, 90, 130 and 215 mL/min). Four different serum albumin concentrations (15, 22, 30 and 44 g/L) were also simulated for a 60 kg patient with a ClCR of 130 mL/min. The PTA for achieving 50% T >MIC (maintaining concentrations above the MIC for at least 50% of the dosing interval) in plasma and separately in ISF were calculated.28,29

**Fractional target attainment calculation**

MIC data for Staphylococcus aureus (a common skin pathogen) from the EUCAST database (available at www.eucast.org; date accessed 14 July 2014) were used to determine fractional target attainment. The fractional target attainment identifies the achievement of target antibiotic exposures by comparing the pharmacodynamic exposure (PTA) against an MIC distribution. The fractional target attainment was calculated using 50% T >MIC. The PTA for achieving 50% T >MIC was calculated from the Monte Carlo simulations (n = 1000) for 1 and 2 g doses at 6-hourly, 8-hourly and 12-hourly frequencies for patients with ClCR of 50, 90, 130 and 215 mL/min at MIC values from 0.06 mg/L to 32 mg/L per the EUCAST database. A dosing regimen was considered successful if the fractional target attainment was >85%.

Continuous data are presented as the mean (SD) or median (IQR). Categorical data are presented as counts (%).

**Results**

**Demographic data**

Thirty patients were recruited into the study per protocol.16 Demographic and clinical data are presented in Table 1. Sampling occurred within 48 h of commencement of therapy for all patients. The cohort was relatively young, with low to moderate illness severity. The vast majority required invasive mechanical ventilation (90%), with 40% requiring vasopressor therapy. No patients died in the ICU; three patients (10%) died in hospital.

**Pharmacokinetic model building**

The time course of total plasma and unbound ISF concentrations of cefazolin was best described by a three-compartment linear model (Figure 2). This model included zero-order input of drug into the central compartment. The only covariates that improved the fit of the model were, for cefazolin clearance, ClCR normalized to 100 mL/min and, for Vc, serum albumin concentration normalized to 24 g/L and total body weight normalized by 80 kg (to the power of 0.75). When these covariates were added sequentially, each resulted in a statistically significant improvement in the log likelihood from the previous model (ClCR, P < 0.01; serum albumin

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### Table 1. Demographic, anthropometric, illness severity and outcome data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD), n (%) or median (IQR)</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>37 (14)</td>
<td>19–65</td>
</tr>
<tr>
<td>Male gender</td>
<td>25 (83%)</td>
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</tr>
<tr>
<td>Height (m)</td>
<td>1.76 (0.08)</td>
<td>1.60–1.93</td>
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<td>Weight (kg)</td>
<td>87 (23)</td>
<td>60–175</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>28.1 (6.5)</td>
<td>20.2–47.5</td>
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<tr>
<td>Body surface area (m²)</td>
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<td>1.64–2.90</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>17 (5)</td>
<td>5–34</td>
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<tr>
<td>Modified SOFA score</td>
<td>4 (2)</td>
<td>0–7</td>
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<tr>
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<tr>
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<td>NA</td>
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<tr>
<td>24 h fluid balance (mL)</td>
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<tr>
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</tr>
<tr>
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**Figure 1.** Observed cefazolin concentration–time profile in critically ill post-trauma patients. Data are presented as median (IQR). The grey broken line represents the MIC₉₀ of cefazolin for S. aureus (EUCAST).

respectively. Using comparative mean AUC₀–₆ values, the median percentage penetration of unbound cefazolin from plasma to ISF was 74% (34%–86%).

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**Pharmacokinetic model building**

The time course of total plasma and unbound ISF concentrations of cefazolin was best described by a three-compartment linear model (Figure 2). This model included zero-order input of drug into the central compartment. The only covariates that improved the fit of the model were, for cefazolin clearance, ClCR normalized to 100 mL/min and, for Vc, serum albumin concentration normalized to 24 g/L and total body weight normalized by 80 kg (to the power of 0.75). When these covariates were added sequentially, each resulted in a statistically significant improvement in the log likelihood from the previous model (ClCR, P < 0.01; serum albumin
concentration, $P < 0.01$; and body weight, $P = 0.01$). The final model was as follows:

$$TVCL = \frac{CL \times CLCR}{100}$$

$$TVV_c = \frac{V_c \times alb}{24} \times \left[ \left( \frac{wt}{80} \right)^{0.75} \right]$$

where $TVCL$ is the typical value of cefazolin clearance, $TVV_c$ is the typical value of $V_c$, $CL$ is the population parameter estimate of cefazolin clearance, $CLCR$ is measured creatinine clearance, $V_c$ is the population parameter estimate of the volume of the central compartment, $alb$ is serum albumin concentration and $wt$ is total body weight.

The mean (SD) population pharmacokinetic parameter estimates from the final covariate model are shown in Table 2. The diagnostic plots to confirm the goodness of fit of the model were considered acceptable and are shown in Figure 3. The final covariate model was then used for dosing simulations.

### Dosing simulations

The Monte Carlo simulations and PTA for achieving 50% $fT_{\geq MIC}$ in unbound subcutaneous ISF for various cefazolin doses are described in Figure 4. These simulations generally showed that increasing $CLCR$ was associated with a reduced PTA for the same MIC. Increasing dose and increasing dose frequency resulted in increased PTA. Figure 5 describes the effects of altered serum albumin concentrations on PTA and shows that a greater level of hypoalbuminaemia was associated with a reduced PTA.

### Fractional target attainment

The fractional target attainment for the simulated PTAs in subcutaneous ISF for a range of cefazolin doses, dose frequencies and $CLCR$ values against the MIC distribution for $S. aureus$ is shown in Table 3. These data show that, for a $CLCR$ of 50 mL/min, a 1 g 12-hourly dose is acceptable, covering 88% of isolates, whereas for a patient with a $CLCR$ of 215 mL/min a dose of 2 g 6-hourly is necessary to achieve target cefazolin concentrations for 84% of isolates.

### Discussion

To the best of our knowledge, this is the first study that has modelled and simulated target site exposures of an antibiotic in critically ill post-trauma patients. This analysis has demonstrated that increasing $CLCR$ or decreasing serum albumin concentrations reduce the likelihood of achieving optimal cefazolin exposures in ISF. For patients without an elevated $CLCR$ ($50–90$ mL/min), a standard dosing regimen of 1 g intravenously 8-hourly commonly results in adequate cefazolin concentrations in ISF for an MIC distribution of a common skin pathogen like $S. aureus$. In the presence of augmented renal clearance ($CLCR >130$ mL/min), a much higher dose of 2 g intravenously 6-hourly is required to get similar relative drug exposures in subcutaneous ISF.

Cefazolin is a widely used prophylaxis and treatment option for severe wound infections in post-trauma critically ill patients. It is highly bound to albumin (≏90%), suggesting that in critical illness and/or the presence of hypoalbuminaemia, altered pharmacokinetics are likely. Such effects are likely to be common in critically ill patients, given that ~40% will have serum albumin concentrations <25 g/L. The increased unbound
Figure 3. Diagnostic plots for the final covariate model. Observed versus population predicted concentrations (left-hand panels) and individual predicted concentrations (right-hand panels) in plasma (a) and subcutaneous ISF (b). Visual predictive checks of plasma data (c) and subcutaneous ISF data (d). Data are presented in mg/L.
plasma concentration that results from such pathophysiological changes should lead to higher pharmacologically active concentrations but also capacity for increased drug clearance. The simulations shown in Figure 5 support the contention that a higher albumin concentration results in better cefazolin exposures in ISF. Without the reservoir of cefazolin bound to albumin to supplement unbound drug that is cleared from the body, patients with lower albumin concentrations are more likely to have reduced pharmacokinetic/pharmacodynamic target attainment. Although plausible, a statistically significant relationship between clearance and serum albumin concentration was not observed in this study.

Using microdialysis to measure ISF concentrations, we also observed remarkably similar unbound plasma and unbound ISF concentrations in the drug’s elimination phase (Figure 1). This result contrasts previous antibiotic studies in critically ill patients, where much lower concentrations in ISF compared with plasma have been described. In one study of critically ill patients with septic shock, Joukhadar et al. demonstrated that subcutaneous ISF concentrations of piperacillin could be 5- to 10-fold lower than the concentrations measured in plasma. In the current sample of patients, however, the hyperdynamic physiological response to trauma appears to have resulted in relatively good tissue perfusion and, consequently, antibiotic distribution into ISF. We observed a median 74% (34%–86%) penetration of unbound cefazolin from the plasma into ISF, which is slightly less than that demonstrated in a recent study by Douglas et al., who observed a median 85% (78%–106%) penetration in a cohort of patients undergoing open abdominal aortic aneurysm repair surgery. Other studies using microdialysis to measure subcutaneous ISF penetration of cefazolin have described a mean of (SD) 106% (78%) penetration in patients with lower limb infections and a mean (range) of 70% (68%–103%) to 102% (85%–141%) for morbidly obese versus non-obese patients who were not critically ill.

A consequence of the higher unbound concentration in plasma is that it is available for renal elimination from the body and

Figure 4. Monte Carlo simulations and PTA in subcutaneous ISF for 1 and 2 g doses for a CLCR of 50 (a), 90 (b), 130 (c) and 215 mL/min (d).

Figure 5. Monte Carlo simulations and PTA in subcutaneous ISF for various serum albumin concentrations for a 1 g intravenous 8-hourly cefazolin dose administered to a 60 kg patient with a CLCR of 130 mL/min.
increased drug clearance is likely to result in increased CLCR. Indeed, CLCR was a strong covariate in our model, which is in keeping with its renal elimination characteristics. The higher drug clearance was particularly prominent in patients with elevated renal function, with many patients having very low cefazolin concentrations towards the end of the dosing interval. Indeed, this elevated renal function, also described as augmented renal clearance, is an increasingly described phenomenon in the critically ill, with an incidence of >60% reported in some studies.8

As a time-dependent antibiotic, for which it is desirable to maintain concentrations above the MIC, these altered pharmacokinetics in the presence of augmented renal clearance are highly problematic for cefazolin. The Monte Carlo simulations provided above highlight this effect. From a comparative perspective, a dose of 1 g intravenously 8-hourly in a patient with a CLCR of 50 mL/min will achieve optimal exposures against 89% of S. aureus, whereas in a patient with augmented renal clearance and a CLCR of 215 mL/min, this will reduce to 65%. Such elevated renal function is being increasingly described in critically ill patients.9,10,34 Risk factors for augmented renal clearance include post-trauma admission, young age and male sex.8 Indeed, these were all common features of this sample, highlighting that clinicians need to be aware of the need for altered antibiotic dosing requirements in these patients.

We wish to acknowledge the following limitations. These data are from a single centre and therefore may not be representative of the patients admitted to other institutions. Our inclusion criteria were designed to select patients without major renal impairment, as optimal antibiotic dosing in such patients remains problematic.6,35 Finally, although this is a large sample size for a pharmacokinetic study, it would be considered small for a clinical study and therefore no conclusions about the clinical implications of these data are possible.

In conclusion, our results indicate that standard dosing of cefazolin is appropriate for achieving optimal concentrations at the target site of infection for post-trauma critically ill patients with normal renal function. However, in the presence of elevated renal function, which is common in this group of patients, or in the presence of severe hypoalbuminaemia, the likelihood of achieving optimal antibiotic exposure decreases significantly, suggesting that higher antibiotic dosing is required for these patients.

### Table 3. Fractional target attainment for the various cefazolin doses and CLCR values for an S. aureus MIC distribution

<table>
<thead>
<tr>
<th>CLCR (mL/min)</th>
<th>1 g 6-hourly</th>
<th>1 g 8-hourly</th>
<th>1 g 12-hourly</th>
<th>2 g 6-hourly</th>
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<tr>
<td>50</td>
<td>89.2%</td>
<td>89.2%</td>
<td>88.3%</td>
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<td>89.7%</td>
<td>89.4%</td>
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<tr>
<td>90</td>
<td>88.6%</td>
<td>86.8%</td>
<td>79.8%</td>
<td>89.6%</td>
<td>89.2%</td>
<td>86.0%</td>
</tr>
<tr>
<td>130</td>
<td>86.1%</td>
<td>80.8%</td>
<td>66.8%</td>
<td>89.0%</td>
<td>86.6%</td>
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<td>215</td>
<td>77.2%</td>
<td>64.5%</td>
<td>40.1%</td>
<td>84.2%</td>
<td>76.8%</td>
<td>56.3%</td>
</tr>
</tbody>
</table>

Doses and CLCR values achieving the a priori target of PTA against at least 85% of isolates indicated by bold percentages.

### References
27 Neely MN, van Guilder MG, Yamada WM et al. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Ther Drug Monit 2012; 34: 467–76.