**Comparison of piperacillin exposure in the lung of critically ill patients and healthy volunteers.**

Short title: Pulmonary piperacillin penetration

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Abstract

**Backgound:** Severe infections of the respiratory tract of critically ill patients are common and associated with excess morbidity and mortality. Piperacillin is commonly used to treat pulmonary infections in critically ill patients. Adequate antibiotic concentration in the epithelial lining fluid (ELF) of the lung is essential for successful treatment of pulmonary infection.

**Objectives:** To compare piperacillin pharmacokinetic-pharmacodynamics in the serum and ELF of healthy volunteers and critically ill patients.

**Methods:** Piperacillin concentrations in serum and ELF healthy volunteers and critically ill patients were compared using population methodologies.

**Results:** Median piperacillin exposure was significantly higher in the serum and the ELF of critically ill patients compared with healthy volunteers. The interquartile range for serum piperacillin exposure in critically ill patients was six times greater than for healthy volunteers. The interquartile range for piperacillin exposure in the ELF of critically ill patients was four times greater than for healthy volunteers. The median pulmonary piperacillin penetration ratio was 0.31 in healthy volunteers and 0.54 in critically ill patients.

**Conclusions:** Greater variability in serum and ELF piperacillin concentrations is observed in critically ill patients compared to healthy adult subjects and must to be considered in the development of dosage regimens. Pulmonary penetration of antimicrobial agents should be studied in critically ill patients, as well as healthy volunteers, during drug development to ensure appropriate dosing of patients with pneumonia.

Introduction

Pulmonary infections in critically ill patients are associated with an unacceptable high morbidity and mortality, which results in an increase in length of ICU stay and excess treatment costs.1, 2 The lung is a common site of infection with approximately 16% of critically ill patients presenting with pulmonary infections (1). The lung is also the primary site of infection in 60% of healthcare associated infections developing in the ICU.3 Community-acquired pneumonia (CAP) resulting in ICU admission has a mortality of 14–26% while the attributable mortality from ventilator-associated pneumonia (VAP) is estimated to be 13%.4, 5 Timely administration of appropriate antimicrobial agent is associated with improved clinical outcomes.6, 7 Administration of currently licensed regimens to critically ill patients results in sub-optimal drug exposures due to pharmacokinetic variability in this patient cohort.8 Marked pharmacokinetic variability is seen in critically ill patients due to changes in cardiac output, tissue perfusion and end-organ failure often supported by extracorporeal circuits.8 Low exposures of antimicrobial agents are associated with treatment failure and emergence of antimicrobial resistance while high exposures may result in drug-induced toxicity.8

Piperacillin is an extended spectrum β-lactam antibiotic that is commonly administered in combination with the β-lactamase inhibitor tazobactam. Piperacillin/tazobactam has a broad-spectrum of action with activity against both gram-positive and gram-negative bacteria. Piperacillin is a common treatment choice for critically ill patients and is recommended, first-line therapy in the management of VAP.9 The pharmacodynamic index that best links piperacillin concentrations with antimicrobial effect is the fraction of the dosing interval that unbound piperacillin concentrations are above the MIC.10 Near-maximal antimicrobial effect is generally observed when free piperacillin concentrations exceed the MIC for at least 50% of the dosing interval (50% fT>MIC).8

To be effective, an antimicrobial agent must reach efficacious concentrations at the site of infection.11, 12 The alveolus is the site of infection for respiratory tract infections, such as CAP and VAP. Epithelial lining fluid (ELF) of the alveolus is accessible to sampling and represents a clinically relevant compartment to measure antimicrobial agent concentration in patients with pneumonia. Penetration of antimicrobial agents into ELF and the exposure-response relationship in the lung is poorly understood even for commonly used antimicrobial agents such as piperacillin.13 In healthy volunteers the AUC for piperacillin in ELF is approximately 25% of the serum piperacillin AUC.14 Pharmacokinetic alterations in critically ill patients result in an increase in piperacillin penetration into ELF with a much greater degree of variability.15 The difference in pulmonary penetration between healthy volunteers (in phase I clinical trials) and critically ill patients (in phase II/III clinical trials and in clinical practice) makes identifying the optimal regimen to treat pneumonia complex.

Clinical drug development pathways typically begin in healthy subjects before progressing into patients. Here, we use a population pharmacokinetic modelling approach to investigate if piperacillin exposures in serum and ELF in healthy volunteers predict serum and ELF exposures in critically ill patients.

Methods

**Pharmacokinetics studies of healthy volunteers**. Pharmacokinetic data from 25 healthy volunteers from a previously published study was used.14 A total of 150 serum piperacillin concentrations and 25 ELF piperacillin concentrations were available. Each patient contributed 6 serum piperacillin concentrations and 1 ELF piperacillin concentration. Participants were administered 4 g of piperacillin by 30 minute infusions every 6 hours for three doses. Serum samples were obtained at 0, 0.5, 1, 2, 4, and 6 hours after the third dose. ELF samples were collected at random at one of the serum sampling time points.

**Pharmacokinetics studies of critically ill patients**. Pharmacokinetic data from 53 critically ill patients from two previously published studies was used.15, 16 A total of 202 serum piperacillin concentrations and 63 ELF piperacillin concentrations were available. Felton *et al*15 contributed 13 critically ill, mechanically ventilated patients (4 patients were excluded from the analysis as they were receiving renal replacement therapy). Patients were administered 4 g of piperacillin by either 5 minute or 30 minute infusions every 8 hours. Serum samples were collected at 0.25, 0.75, 2, 3.5, and 4.5 h after initiation of the infusion at steady state in all 13 patients. Additionally, 2 of the 13 patients had serum samples collected at 0.5, 1.5, 2.5, 3.75, 5, and 6 h after initiation of the first dose. ELF samples were collected at 0.75 and 2 h or at 0.75 and 3.5 h after initiation of the infusion at steady state. Patients had between 4 and 12 serum and either 1 or 2 ELF samples collected. Boselli *et al*16 contributed 40 critically ill patients with VAP. Patients were administered either 12 g or 16 g of piperacillin by continuous infusion. Three serum samples and 1 ELF sample were collected during the second 24 hours of treatment.

**Piperacillin and urea assays.** Piperacillin was quantified using either high-performance liquid chromatography or liquid chromatography–tandem mass spectrometry assays.14-16 Urea was quantified using a colorimetric technique (QuantiChromTM Urea Assay, Bioxys. Belgium).14-16 Piperacillin concentration in ELF was corrected for dilution introduced by lavage sampling using the urea dilution method.17

**Population pharmacokinetic analysis.** Data from the healthy volunteers and critically ill patients were analysed independently using a population pharmacokinetic methodology with the non-parametric adaptive grid program Pmetrics 1.4.18 A three-compartment structural, mathematical model was assumed to be most appropriate for population analysis.15

The differential equations for the three-compartment structural mathematical model used are shown above. X1, X2 and X3 are the amounts (in mg) of piperacillin in the central, peripheral and ELF compartments, respectively. R(1) represents the infusion of piperacillin. Cl (L/hr) is the clearance, and Vc is the volume of the central compartment (L). Kcp, Kpc, Kcl and Klc are the first-order inter-compartmental rate constants between the central and peripheral and central and ELF compartments. For the analysis of the critically ill patients, creatinine clearance (estimated by Cockcroft-Gault) (CG) was included as a covariate for piperacillin clearance in the structural model. Clr (L/hr) and Clnr (L/hr) are the renal and non-renal piperacillin clearance. A linear total clearance term was used for healthy volunteers as there was an insufficient range of creatinine clearances to define renal and non-renal piperacillin clearance

The pharmacokinetic data were weighted by the inverse of the measured piperacillin assay variance at that concentration. The polynomial describing the assay variance used in Felton *et al* was used.15 The means, medians, and standard deviations of the population parameters were estimated. Bayesian posterior estimates for each parameter were also obtained for each patient (using the “population of one” utility in Pmetrics). Scatter plots of observed versus predicted piperacillin concentrations were examined for the population as a whole and for individual patients. The fit of the structural model to the data were assessed in the following way: (a) the log-likelihood value; (b) the coefficients of determination (*r2*), slope and y-intercept from regression of the observed-predicted plots before and after the Bayesian step; and (c) the Akaike information criterion (AIC).

**Simulation to estimate piperacillin exposure in serum and ELF and Fractional Target Attainment.** Monte Carlo simulation was performed using 5,000 subject simulations in Pmetrics 1.4.18 The “semi-parametric” simulation method was used for both the healthy volunteers and critically ill patients. The observed distribution of creatinine clearance from the population of critically ill patients was used in the simulations with covariates for critically ill patients. A regimen of 4 g of piperacillin administered over 30 minutes every 8 hours was used. Generation of the serum and ELF piperacillin AUCs and for the fractional target attainment analysis was performed for the third dosing interval. The ratio of serum to ELF piperacillin AUC was calculated for each of the 5,000 simulated patients. From the simulation the geometric mean, median, 5th-percentile, 25th–percentile, 75th–percentile, and 95th–percentile serum piperacillin AUC, ELF piperacillin AUC and serum:ELF piperacillin AUC ratio was identified. Comparison between AUC distributions in healthy volunteers and critically ill patients was made using Mann-Whitney U test in GraphPad Prism version 7 for Windows.

The fraction of simulated subjects who achieved (i) an unbound serum piperacillin concentration above the MIC for 50% of the third dosing interval (50% fT>MIC) and (ii) an ELF piperacillin concentration above the MIC for 50% of the third dosing interval was identified for a range of MICs. A range of MICs from 0.5 to 128 mg/L was investigated. Serum protein binding for piperacillin was assumed to be 30%.19

Results

**Pharmacokinetic studies.** The mean age of the healthy volunteers and critically ill patients was 34 and 60 years, respectively (Table 1). Fifty-six percent of the healthy volunteers and 58% of the critically ill patients were male. Creatinine clearance ranged from 78.9 to 170.3 mL/min in the healthy volunteers compared with a range of 14.0 to 245.7 mL/min in the critically ill patients.

**Population pharmacokinetic analysis.** The fit of the mathematical model to the observed data for both the healthy volunteers and the critically ill patients was acceptable (Figure 1). Linear regression of the predicted-versus-observed piperacillin concentrations in the healthy volunteers were: observed piperacillin serum concentration = 0.97 x predicted piperacillin serum concentration + 2.74; r2 = 0.99 and observed piperacillin ELF concentration = 1.00 x predicted piperacillin ELF concentration – 0.03; r2 = 1. For critically ill patients the observed piperacillin serum concentration = 1.02 x predicted piperacillin serum concentration + 2.30; r2 = 0.93 and observed piperacillin ELF concentration = 1.2 x predicted piperacillin ELF concentration – 0.86; r2 = 0.87. For serum piperacillin concentration for the healthy volunteers and critically ill patients the mean weighted biases were -0.09 and -0.05, respectively, and the bias-adjusted mean weighted precision values were 1.19 and 0.74, respectively. For ELF piperacillin concentration for the healthy volunteers and critically ill patients the mean weighted biases were 0.36 and -1.28, respectively, and the bias-adjusted mean weighted precision values were 1.41 and 30.4, respectively. The parameter estimates from both the population analyses are summarised in Table 2.

**Piperacillin concentration in the serum and the lung of healthy volunteers and critically ill patients.** Simulated piperacillin concentration-time profiles in serum and ELF in healthy volunteers and critically ill patients are shown in Figure 2. Each simulation shows the median, 5th and 95th percentile piperacillin concentration following administration of 3 doses of 4 g of piperacillin as a 30-minute infusion every 8 hours. The median AUCserum18-24 for the healthy volunteers was 238.4 mg.hr.L-1 (interquartile range (IQR) 48.3 mg.hr.L-1) compared with median AUCserum18-24 of 304.2 mg.hr.L-1 (IQR 331.7 mg.hr.L-1) for critically ill patients (Table 3 and Figure 3). While the median AUCELF18-24 for the healthy volunteers was 78.8 mg.hr.L-1 (IQR 51.3 mg.hr.L-1) compared with median AUCELF18-24 of 173.3 mg.hr.L-1 (IQR 218.7 mg.hr.L-1) for critically ill patients. The AUCserum18-24 was higher in patients with reduced creatinine clearance but the median AUCELF18-24–to-AUCserum18-24 ratio was unaffected by creatinine clearance (Figure 4). The median AUCELF18-24–to-AUCserum18-24 ratio for the healthy volunteers was 0.33 (IQR 0.18) compared with median AUCELF18-24–to-AUCserum18-24 ratio of 0.54 (IQR 0.51) for critically ill patients (Table 3 and Figure 5). Comparison of each of the AUCserum18-24, AUCELF18-24 and AUCELF18-24–to-AUCserum18-24 in healthy volunteers to critically ill patients was shown to be significantly different for each of the 3 comparisons (P < 0.0001).

**Fractional Target Attainment analysis.** The results of the target attainment analysis are shown in Figure 6. Administration of 4 g of piperacillin three times daily as a 30-minute infusion to treat an organism with an MIC of 1 mg/L results in >95% of healthy volunteers and critically ill patients achieving an adequate exposure in serum and the ELF. Simulation suggests that administration of 4 g piperacillin three times daily as a 30-minute infusion would be insufficient to achieve an effective piperacillin exposure in either the serum or ELF of healthy volunteers to treat an organism with an MIC of 16 mg/L (the current recommended breakpoint for *Pseudomonas aeruginosa*).20, 21 However, approximately 50% of critically ill patients will achieve a sufficient serum and ELF piperacillin exposure to treat an organism with an MIC of 16 mg/L following administration of 4 g piperacillin three times daily as a 30-minute infusion as a result of increased penetration into ELF.

Discussion

Pharmacokinetic variability is a common finding with hydrophilic antimicrobial agents, such as piperacillin, in critically ill patients.8, 22 Variability occurs due to pathophysiological changes associated with critical illness and includes alterations in renal function, both acute kidney injury and augmented renal clearance, and variation in a drug’s volume of distribution. The concentration-time profiles in Figure 2 illustrate the marked pharmacokinetic variability in critically ill patients compared with healthy volunteers. The median serum piperacillin AUC in critically ill patients (304.2 mg.hr.L-1) was significantly higher compared with healthy volunteers (238.4 mg.hr.L-1). What is more striking is the difference in the interquartile range which is more than 6 times higher in critically ill patients (331.7 mg.hr.L-1) compared with healthy volunteers (48.3 mg.hr.L-1). The extent of the variability is also illustrated in the histogram plots of AUC in Figure 3.

Marked variability is also demonstrated with piperacillin exposures seen in the lung. The median ELF piperacillin AUC in critically ill patients (173.5 mg.hr.L-1) is more than double the median ELF piperacillin AUC in healthy volunteers (78.8 mg.hr.L-1). The interquartile range is more than four times higher in critically ill patients (218.7 mg.hr.L-1) compared with healthy volunteers (51.3 mg.hr.L-1). The penetration ratio for piperacillin into the lung of healthy volunteers is 0.33 (IQR 0.18) compared with the penetration ratio for piperacillin into the lung of critically ill patients which was 0.54 (IQR 0.51). Previous analysis of ELF pharmacokinetics has demonstrated that serum pharmacokinetic variability alone is insufficient to explain ELF variability.15 The only previous study of piperacillin penetration into ELF of critically ill patients, whose data is not included in this analysis, demonstrated a similar penetration ratio of 0.54.23 Renal function does not appear to have an effect on the penetration ratio of piperacillin into the lung. Increasing evidence suggests that drugs cross the blood-alveolar barrier using carrier-mediated active transport rather than by passive diffusion as previously thought.24, 25 Here, pulmonary infection and inflammation, associated with critical illness, may increase pulmonary permeability to antimicrobial agents increasing lung exposures. Additionally, these changes to pulmonary penetration are likely to change during the course of critical illness as the injured lung recovers.

During the past 25 years, there have been numerous intrapulmonary penetration studies performed to compare serum and ELF concentrations of anti-infective agents.13 The majority of these intrapulmonary penetration studies were conducted in healthy adult subjects participating in a Phase 1 clinical pharmacokinetic and safety trial or outpatients undergoing diagnostic bronchoscopy.13 The results of these studies are useful for assessing if an antimicrobial agent penetrates to the potential site of infection and investigating the time course and magnitude of extracellular concentrations in the ELF. Determining these initial pharmacokinetic data has become important during the early phase of drug development programs for investigational antimicrobial agents being considered for the treatment of lower respiratory tract infections.11 Here we have illustrated, for the first time (Figure 3), the variability and/or magnitude of serum and ELF drug concentrations observed in healthy subjects may not be reflective of those observed in severely ill patients. Simulation using a population pharmacokinetic model of an antimicrobial agent from a healthy volunteer study but with a broader, that observed, range of drug clearance may help predict serum pharmacokinetics in critically ill patents. However we recommend investigation, early in a development programme, of the pulmonary penetration in critically ill patients for antimicrobial agents being developed for the treatment of severe respiratory infections. We also suggest that pulmonary penetrations sub-studies are incorporated into phase 2 and phase 3 clinical trials for antimicrobial agents being developed for the treatment of severe respiratory infections to determine the magnitude of serum and ELF drug concentrations. The intrapulmonary penetration results from this targeted patient population along with the appropriate application of mathematical modelling and evaluation of target attainment can subsequently be used to guide and confirm the selected dosage regimen designs of patients with severe pneumonia.

Pharmacodynamic analysis using fractional target attainment illustrated the impact of the differences between healthy volunteers and critically ill patients (Figure 6). The higher exposures seen in critically ill patients results in higher target attainments for less susceptible MICs. The target attainment analysis shows how exposures calculated/predicted from pharmacokinetic analysis derived from healthy volunteers do not predict treatment success in the ELF. Although the fractional target attainment in the serum and ELF of critically ill patients is almost identical it has previously been demonstrated that serum exposure does not correlate well with lung exposure for piperacillin.15 Therefore, estimating the piperacillin regimen for critically ill patients from healthy volunteers would result in “overdosing” of critically ill patients. Therapeutic drug monitoring and dose adaption is increasingly being recommended for the optimal treatment of critically ill patients.8 However therapeutic drug monitoring based on serum drug concentration may be ineffective to optimise ELF drug concentrations and require an alternative strategy with sampling of ELF in high risk patients.

The aim of this manuscript was to explore the differences in PK-PD between healthy volunteers and critically ill patients. As such the target attainment analysis was only performed for a single regimen (4 g piperacillin administered over 30 minutes every 8 hours). Using this regimen suggests the breakpoint for piperacillin in critically ill patients is an MIC ≤ 4 mg/L. It is well established that the administration of β-lactams, including piperacillin, as continuous or extended infusions results in improved target attainment even when using a lower total daily dose.26, 27 However, recent clinical trials have failed to demonstrate a survival advantage for delivery of β-lactams by continuous or extended infusions.28

In conclusion, this study demonstrates significant differences in serum and ELF piperacillin exposures between healthy volunteers and critically ill patients. Both the median piperacillin exposure and variance was greater in critically ill patients, not only in serum but also in ELF, the site of extracellular respiratory tract infections. This further supports the importance of identifying the optimal dosage regimen to effectively reach the site of infection in critically ill patients.11

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Transparency declarations

None to declare

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Table 1.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Healthy volunteers | Critically ill patients |  |  |  |
| Number of patients | 25 | 53 |  |  |  |
|  | Mean (median) [minimum to maximum] | |  |  |  |
| Age (years) | 34.2 (32.0) [22.0-50.0] | 59.7 (56.4) [31.4-88.0] |  |  |  |
| Weight (kg) | 80.4 (81.0) [62.0-100.0] | 74.0 (70.0) [49.0-113.0] |  |  |  |
| Creatinine clearance (mL/min) | 111.4 (108.5) [78.9-170.3] | 83.4 (77.4) [14.0-245.7] |  |  |  |
| Sex (no of males:no of females) | 14:11 | 31:22 |  |  |  |

Table 2.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Cl | Clnr | Clr | Vc | Vl | Kcl | Klc | Kcp | Kpc |
| Healthy volunteers | Mean | 11.45 | - | - | 6.85 | 15.25 | 2.02 | 2.97 | 0.71 | 3.67 |
| S.D. | 1.94 | - | - | 2.27 | 3.81 | 1.62 | 1.87 | 1.15 | 1.97 |
| Median | 11.57 | - | - | 6.86 | 14.62 | 2.16 | 3.63 | 0.14 | 5.00 |
| Critically ill patients | Mean | - | 3.52 | 6.92 | 7.54 | 14.37 | 4.78 | 4.89 | 4.84 | 5.49 |
| S.D. | - | 1.72 | 4.81 | 3.78 | 3.05 | 3.12 | 3.23 | 3.63 | 3.36 |
| Median | - | 3.33 | 6.69 | 7.68 | 13.78 | 5.58 | 4.77 | 4.41 | 5.85 |

Table 3.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | Geometric mean | Median | 25%-75% Percentile | Interquartile range |
| Healthy volunteers | AUCserum 18-24 (mg.hr.L-1) | 239.4 | 238.4 | 213.4 - 261.7 | 48.3 |
| AUCELF18-24 (mg.hr.L-1) | 73.54 | 78.8 | 55.87-107.2 | 51.3 |
| AUCELF18-24–to-AUCserum18-24 | 0.31 | 0.33 | 0.24 – 0.43 | 0.18 |
| Critically ill patients | AUCserum 18-24 (mg.hr.L-1) | 322.3 | 304.2 | 184.6 - 516.3 | 331.7 |
| AUCELF 18-24 (mg.hr.L-1) | 176.0 | 173.3 | 95.6 - 314.3 | 218.7 |
| AUCELF18-24–to-AUCserum18-24 | 0.54 | 0.54 | 0.34 – 0.85 | 0.51 |



Figure 1. Observed-predicted piperacillin concentrations in the serum of healthy volunteers (top left); epithelial lining fluid of healthy volunteers (top right); serum of critically ill patients (bottom left) and epithelial lining fluid of critically ill patients (bottom right).



Figure 2. Median piperacillin concentration-time profiles (Grey area represents the 5-to-95 percentile) in the serum of healthy volunteers (top left), serum of critically ill patients (top right), ELF of healthy volunteers (bottom left) and ELF of critically ill patients (bottom right).

Figure 3. Frequency of area-under-the-piperacillin-concertation curves for 5,000 simulated healthy volunteers (0-1000) and critically ill patients (0-200). The panels show the AUC in the serum of healthy volunteers (top left), serum of critically ill patients (top right), ELF of healthy volunteers (bottom left) and ELF of critically ill patients (bottom right).



Figure 4. Relationship between the observed (A) area under the serum piperacillin concentration time curve; (B) area under the ELF piperacillin concentration time curve and (C) ratio of piperacillin serum-to-ELF exposures and estimated creatinine clearance.



Figure 5. Comparison of the ratio of simulated piperacillin exposure in serum-to-ELF in healthy volunteers and critically ill patients.



Figure 6. Results of the Monte Carlo simulation with the fraction of target attainments for unbound plasma and ELF piperacillin in healthy volunteers and critically ill patients against a range of MICs.