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First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis

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ABSTRACT

The objectives of this study were (i) to compare the plasma concentration–time profiles for first-dose and steady-state piperacillin administered by intermittent or continuous dosing to critically ill patients with sepsis and (ii) to use population pharmacokinetics to perform Monte Carlo dosing simulations in order to assess the probability of target attainment (PTA) by minimum inhibitory concentration (MIC) for different piperacillin dosing regimens against bacterial pathogens commonly encountered in critical care units. Plasma samples were collected on Days 1 and 2 of therapy in 16 critically ill patients, with 8 patients receiving intermittent bolus dosing and 8 patients receiving continuous infusion of piperacillin (administered with tazobactam). A population pharmacokinetic model was developed using NONMEM®, which found that a two-compartment population pharmacokinetic model best described the data. Total body weight was found to be correlated with drug clearance and was included in the final model. In addition, 2000 critically ill patients were simulated for pharmacodynamic evaluation of PTA by MIC [free (unbound) concentration maintained above the MIC for 50% of the dosing interval (50% $f_{T>MIC}$)] and it was found that continuous infusion maintained superior free piperacillin concentrations compared with bolus administration across the dosing interval. Dosing simulations showed that administration of 16 g/day by continuous infusion vs. bolus dosing (4 g every 6 h) provided superior achievement of the pharmacodynamic endpoint (PTA by MIC) at 93% and 53%, respectively. These data suggest that administration of piperacillin by continuous infusion, with a loading dose, both for first dose and for subsequent dosing achieves superior pharmacodynamic targets compared with conventional bolus dosing.

1. Introduction

Piperacillin is an extended-spectrum penicillin frequently prescribed for empirical treatment of hospital-acquired infections in critically ill patients with sepsis or septic shock. Given the importance of early and appropriate antibiotic therapy for reducing mortality in these patients [1–6], optimised dosing for piperacillin in the initial phase of treatment is essential in order to maximise its clinical efficacy.

Piperacillin is a time-dependent antibiotic, where antibacterial activity is related to the time for which the free (unbound) concentration is maintained above the minimum inhibitory concentration (MIC) during a dosing interval ($f_{T>MIC}$) [7]. Data on the $f_{T>MIC}$ required for optimal activity of penicillins have been obtained from in vitro and in vivo animal models and suggest that $f_{T>MIC}$ of 50% is necessary [8]. Other in vitro data report that β-lactam concentrations four to five times the MIC may maximise bactericidal activity [9]. Recent retrospective human data from critically ill patients reported by McKinnon et al. [10] suggested that an $_{T>MIC}$ of 100% is associated with superior bacteriological and clinical outcomes for broad-spectrum cephalosporin antibiotics. It follows that to maximise the efficacy of penicillins such as piperacillin, $f_{T>MIC}$ >50% is essential and 100% $f_{T>MIC}$ is preferable.

Achieving target concentrations in critically ill patients with sepsis remains a challenging issue for clinicians. Pathophysiological changes associated with the disease process can increase

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the drug volume of distribution (V_d) and drug clearance leading to low plasma concentrations [5,11]. For time-dependent antibiotics, dosing by extended infusion [12] or continuous infusion has been suggested to maximise drug exposure and to minimise the consequences of pharmacokinetic changes in critically ill patients [13–17]. Whilst piperacillin has been studied in other patient populations [18–22], little data exist comparing intermittent and continuous administration in critically ill patients [23,24], particularly potential variations in day-to-day pharmacokinetics. Importantly, very little data describing the potentially different pharmacokinetics/pharmacodynamics of the first dose of piperacillin for critically ill patients with sepsis exist. Knowledge of pharmacokinetics/pharmacodynamics at this time, when obtaining maximal antibiotic activity can define outcomes, is essential.

The current data set has, in part, been previously published and analysed using a standard pharmacokinetic two-stage approach [25]. This form of pharmacokinetic analysis has some limitations [26] and it is now preferred that population pharmacokinetic analysis is utilised to provide a more accurate estimation of between-subject variability and this has become the basis for dosing simulations that can compare different dosing strategies in this difficult patient population [27].

The objectives of this study were: (i) to compare the observed plasma concentration–time profiles for piperacillin administered by intermittent or continuous dosing to critically ill patients with sepsis at first dose and at steady state; (ii) to describe the pharmacokinetic variability of piperacillin in these patients with a population pharmacokinetic model; and (iii) to assess the pharmacokinetic/pharmacodynamic profile of various piperacillin dosing regimens and to assess the expected probability of target attainment (PTA) by MIC against bacterial pathogens commonly encountered in critical care units.

2. Methods

2.1. Patients

This study was performed in an 18-bed tertiary referral Critical Care Unit. Consent to participate was obtained from the patient's legally authorised representative. Inclusion criteria were patients admitted to the Critical Care Unit with known or suspected sepsis as defined previously [28] and with normal renal function (defined as plasma creatinine <120 μmol/L). Patients were randomised to receive different doses of piperacillin by intermittent bolus (16 g/day) or continuous infusion (12 g/day) using random numbers selected from an opaque sealed envelope.

2.2. Drug administration and dosage

All patients received piperacillin/tazobactam (Tazocin®; Wyeth, Sydney, Australia). Patients in the continuous infusion group ($n = 8$) were administered 12 g/day. A lower piperacillin dosage was selected for the continuous infusion group in line with previous comparative studies with β-lactam antibiotics [18,24,29–31]. Patients received an initial loading dose of 4/0.5 g piperacillin/tazobactam in 50 mL of 0.9% sodium chloride over 20 min via the central line, followed immediately by a continuous 24-h infusion (333 mg/h) of piperacillin, i.e. 8 g piperacillin/1 g tazobactam in 500 mL of 0.9% sodium chloride. From Day 2 onwards the patients were given 12/1.5 g piperacillin/tazobactam administered by 24-h infusion in 500 mL of 0.9% sodium chloride (piperacillin 500 mg/h). Patients in the intermittent bolus group ($n = 8$) received 4/0.5 g piperacillin/tazobactam as a 20-min infusion via the central line every 6 h (q6h) or every 8 h (q8h) as prescribed by the treating critical care physician. In both groups, piperacillin/tazobactam was administered using a volumetric infusion pump controller (iMed Gemini PC-2®; Alaris Medical Systems, San Diego, CA).

2.3. Blood sampling

For each sample, 5 mL of blood was collected using the indwelling arterial catheter for determination of plasma piperacillin concentrations. For both groups, samples were collected on Day 1 at ca. 0, 3, 6, 15 and 20 min during the bolus infusion. Additional samples were collected for both groups after the bolus infusion at 3, 6, 15, 20, 30, 45, 60, 90, 120, 210, 360 and 480 min. On Day 2 (fifth piperacillin/tazobactam bolus dose or change of 24-h continuous infusion bag), steady-state blood samples were taken immediately prior to (0 min) and at 5, 10, 20, 30, 60, 120, 180, 240 and 480 min after commencement of the new infusion (continuous infusion bag replacement or bolus infusion dose). Specimens were centrifuged at 3000 rpm for 10 min and then frozen at −20 °C for subsequent analysis. As piperacillin is less stable at −20 °C than at −70 °C (i.e. it undergoes 10% degradation within 16 days at −20 °C) [32,33] (data on file), samples were assayed within 7 days of collection. In line with these data, no allowance for possible sample degradation was included in the data analysis as any degradation would be insignificant.

2.4. Drug assay

Plasma piperacillin concentrations were measured using high-performance liquid chromatography (HPLC) with ultraviolet detection (Waters HPLC system with 510 pump, 717 autosampler and 486 Tunable Absorbance Detector set at 218 nm λ) using an acetonitrile phosphate buffer gradient based on a method by Ocampo et al. [34]. The limit of quantification for piperacillin was 0.25 mg/L. The coefficient of correlation for the assay was 0.994 over the range of the standard curve of 0.25–400 mg/L. Linearity was also demonstrated over this concentration range. The assay had intraday and interday reproducibility of 2.2% and 6.4%, respectively.

2.5. Determination of the unbound piperacillin fraction in plasma

Five hundred microlitres of 100 μg/mL piperacillin in plasma from patients was ultracentrifuged (12 000 rpm for 20 min) through 3 kDa nominal cut-off membrane devices (Amicon® YM30; Millipore Corp., Billerica, MA), giving an approximate filtrate yield of 25% original volume. One hundred microlitres of filtrate plus 20 μL of 500 μg/mL penicillin G (internal standard) were analysed by HPLC.

2.6. Statistical analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, IL). Mann–Whitney *U*-test or Fisher's exact test were used to compare demographic and clinical characteristics between the intermittent and continuous treatment groups, which were all considered non-normal distributions. *P*-values of <0.05 were considered significant.

2.7. Pharmacokinetic/pharmacodynamic analysis

The concentration–time data for piperacillin in plasma were analysed by a non-linear mixed-effects modelling approach [35] using NONMEM version 6.1 (GloboMax LLC, Hanover, MD) with double precision with the COMPAQ VISUAL FORTRAN compiler. The NONMEM runs were executed using Wings for NONMEM (WFN 6.1.3). Data were analysed using the first-order conditional estimation (FOCE) method with INTERACTION.

For the population pharmacokinetic analysis, plasma piperacillin concentrations were fitted to one-, two- or three-compartment models using subroutines from the NONMEM library [35]. The concentration–time profile can be described by the equation:

$$y_{ij} = f_{ij}(\theta_i, x_{ij})\varepsilon^{\varepsilon 1ij} + \varepsilon_{2ij}, \quad (1)$$

where y_{ij} is the jth observed concentration at time points x_{ij} for the ith subject, θ_i represents a fixed-effects parameter of the structural model to be estimated, f_{ij} is the function for the prediction of the jth response for the ith subject, and ε_{ij} denotes the jth measurement error for the ith subject. In other words, ε_{ij} is the difference in the observed concentration from the predicted concentration. It is assumed to be independent and identically distributed with a normal distribution around the mean zero and variance σ^2.

2.7.1. Between-subject variability (BSV) and between-occasion variability (BOV)

BSV was modelled using an exponential variability model:

$$\theta_i = \theta e^{\eta i}, \quad (2)$$

where θ_i is the value of the parameter for the ith subject, θ is the typical value of the parameter in the population, and finally ηi is a random vector with normal distribution, zero mean and variance-covariance matrix of BSV Ω to be estimated.

BOV is the variability of a parameter within a subject during treatment and includes between-occasion variability and within-occasion variability. BOV was assumed to be log normally distributed and modelled over the two pharmacokinetic study occasions:

$$\theta_{i,k} = \theta e^{\eta i + \eta i,k}, \quad (3)$$

where $\theta_{i,k}$ is the value of the parameter for the ith subject on the kth occasion.

2.7.2. Model diagnostics

Statistical comparison of nested models was based on a χ^2 test of the difference in the objective function. A decrease in the objective function of 3.84 units ($P < 0.05$) was considered significant. Goodness of fit was evaluated by visual inspection.

2.7.3. Bootstrap

A non-parametric bootstrap method [36] ($n = 2000$) was used to study the uncertainty of all pharmacokinetic parameter estimates. From the bootstrap empirical posterior distribution we were able to obtain the 95% confidence interval (2.5–97.5% percentile) for the parameters, as described previously [37].

2.7.4. Covariate screening

Various covariates were considered for analysis of lean body weight and total body weight (TBW) as well as creatinine clearance (CL_{Cr}) measured by 8-h urine collection or via the Cockroft–Gault equation [38]. The individual covariates were centred by the median values. Individual empirical Bayesian (POSTHOC) parameters were plotted against covariate values to assess relationships. If a trend between covariates and a pharmacokinetic parameter was observed, then it was considered for inclusion in the population model.

2.7.5. Visual predictive checks

Using the final covariate model, a visual predictive check was performed by simulating 2000 subjects to assess the predictive performance of the model. The visual predictive checks were generated using a Perl Script (version 1e) [39]. The visual checks and representative percentiles [25th, 50th (median) and 75th percentile] were visually assessed using Prism® 2005 version 4.03 (GraphPad Software Inc., La Jolla, CA).

2.7.6. Dosing simulations

Four intermittent administration (IA), two extended infusion (EI) and three continuous infusion (CI) dosing regimens were simulated using Monte Carlo simulations. The four IA bolus dose regimens (infusion over 20 min) evaluated were 4 g q6h, 4 g q8h, 3 g q6h and 3 g every 4 h. The two EI regimens were 4 g q6h (infusion over 3 h) and 4 g q8h (infusion over 4 h). The three CI regimens evaluated were 8, 12 and 16 g piperacillin every 24 h including a loading dose of 4 g on Day 1. Each Monte Carlo simulation generated free concentration–time profiles for 2000 subjects per dosing regimen. A constant value of 30% protein binding was used in all simulations [25]. From these data the $f_{T>MIC}$ for the first dose (0 to 6 h or 8 h) was calculated for each simulated subject using linear interpolation. The PTA was obtained by counting the subjects who achieved free piperacillin concentrations greater than the MIC for 50% of the dosing interval [40].

2.8. Minimum inhibitory concentration distributions

MIC distributions of various nosocomial pathogens against piperacillin/tazobactam from the 2003 US MYSTIC database previously reported by Sun et al. [41] were used to determine the cumulative fraction of response (see below). The MYSTIC programme is a global, multicentre surveillance study containing data for nosocomial pathogens worldwide.

2.9. Probability of target attainment by minimum inhibitory concentration

The PTA by MIC identifies the likely success of treatment by comparing the pharmacodynamic exposure (PTA) against a MIC distribution of likely pathogens. The PTA by MIC is calculated by multiplying the PTA at each MIC by the fraction of organisms susceptible at that concentration of the respective MIC distribution. The sum of those individual products is the PTA by MIC for the respective MIC distribution. The PTA by MIC can be interpreted as the probability of successful treatment of infections caused by bacteria with a specific susceptibility pattern (MIC distribution) in the studied patient population.

3. Results

3.1. Patient demographics

Sixteen patients were enrolled, with eight patients randomised to intermittent dosing and the eight patients randomised to continuous dosing. All patients except one in the intermittent group received 6-hourly antibiotic dosing. All patients were ventilated and fulfilled the criteria for sepsis, with four patients also receiving vasopressor therapy (two in the bolus group and two in the infusion group). No significant pharmacokinetic differences were observed between patients receiving vasopressors and those not. Patients were evenly matched with regard to demographic data and level of sickness severity (see Table 1).

3.2. Drug concentrations

Observed plasma concentration–time profiles for piperacillin at first dose and at steady state are depicted in Fig. 1. The comparative peak concentrations (C_{max}) and trough concentrations (C_{min}) in a dosing period are described in Table 1. Protein binding of piperacillin was measured at 30% in this cohort of patients.

Table 1
Demographic and clinical data.[a].

	Bolus infusion ($N = 8$)	Continuous infusion ($N = 8$)	P-value[b]
Gender (male/female) (n)	5/3	6/2	0.5
Age (years)	41 (22–65)	30 (23–40)	0.38
Height (cm)	174 (172–180)	176 (171–177)	0.88
TBW (kg)	80 (74–86)	73 (64–83)	0.44
BMI (kg/m^2)	26.3 (24.9–28.8)	25.4 (24.4–26.7)	0.33
Day 1 APACHE II score	24 (18–26)	20 (16–22)	0.28
Day 2 APACHE II score	23 (18–25)	19 (16–26)	0.72
Day 1 SOFA score	3 (3–3)	4 (3–6)	0.33
Day 2 SOFA score	3 (3–4)	3 (2–5)	0.88
CL_{Cr} (L/h)[c]	5.3 (3.2–6.06)	5.8 (1.9–8.9)	0.72
Piperacillin dose (mg day/kg)	229 (204–254)	168 (160–188)	0.03
Outcome (no. of survivors/no. of non-survivors)	8/0	8/0	1.00
C_{max} (mg/L)	266.6 (208.2–292.3)	144 (118–224)	0.04
Day 1 C_{min}/C_{ss} (mg/L)	7.2 (3.2–12.5)	7.1 (3.8–26.4)	0.51
Day 2 C_{min}/C_{ss} (mg/L)	6.2 (2.7–10.7)	21.2 (15.9–30.6)	0.001

TBW, total body weight; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sepsis Organ Failure Assessment; CL_{Cr}, creatinine clearance; C_{max}, observed peak concentration; C_{min}, observed lowest concentration in bolus dosing period; C_{ss}, observed lowest steady-state concentration during continuous infusion sampling period.

[a] Data are presented as median (interquartile range) (except gender and outcome); all distributions were non-normal.

[b] P-values were calculated using Mann–Whitney U-test, except for gender which used the Fisher's exact test.

[c] CL_{Cr} calculated using Cockroft–Gault equation [38].

3.3. Model building

The best base model consisted of a two-compartment linear model and a combined residual unknown variability with a lag time to account for the time between when the infusion started and when the drug reached the patient. No difference in drug clearance could be supported between the intermittent and continuous treatment groups. Correlation between parameters was evaluated using the OMEGA BLOCK functionality in NONMEM for all parameters. However, correlation could only be supported between clearance (CL) and intercompartmental clearance (Q). BOV could only be supported on CL, Q and central volume of distribution (V1). The final objective function for this model was 2477.653.

Table 2 shows the mean and 95% confidence interval for the parameters computed from all the bootstrap runs. The only covariate that could be justified for inclusion in the covariate model to describe piperacillin clearance was total body weight (TBW), normalised to 70 kg. Addition of this parameter did not reduce the objective function by a statistically significant 3.84 (reduced by 2.35), however we elected to include this in the final covariate model as it reduced the BSV for clearance (6.2%) and is biologically plausible. The final model was represented by Eq. (4):

$$\mathrm{TVCL} = \theta_1 \left(\frac{\mathrm{TBW}}{70}\right) \quad (4)$$

where TVCL is the typical value of clearance.

Goodness of fit plots were generated for the final model. The weighted residual graphs showed no apparent visual or statistical bias for the prediction. The visual predictive check with the final covariate model for occasion 1 and occasion 2 confirmed the goodness of fit of the model to the observed data (Supplementary Figs. 1 and 2). All subsequent piperacillin Monte Carlo simulations were then based on this model.

3.4. Dosing simulations

PTA vs. MIC profiles for dosing simulations for different intermittent, extended and continuous infusions are depicted below for piperacillin dosing of 12 g/day (Fig. 2a) and 16 g/day (Fig. 2b). The manufacturer's product information [42] recommends a dosing regimen for patients with no renal dysfunction of 4 g q6h or q8h. When piperacillin is given 6-hourly the PTA is 79.2% for an

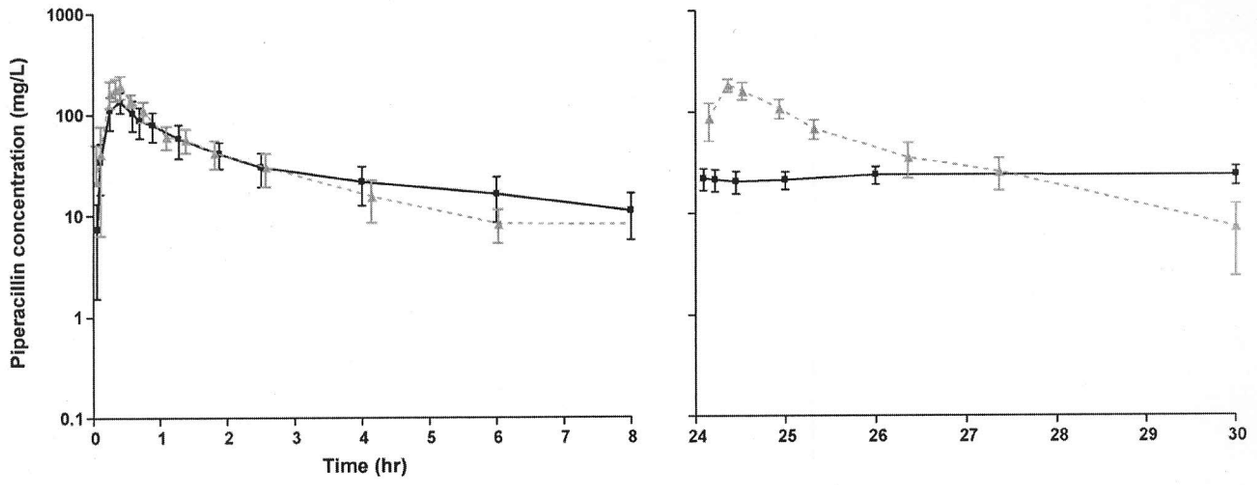

Fig. 1. Observed (mean ± standard deviation) concentrations of piperacillin administered to critically ill patients with sepsis by intermittent infusion over 20 min (▲) and by continuous infusion (–■–) on Day 1 (first dose) and at steady state (fifth dose).

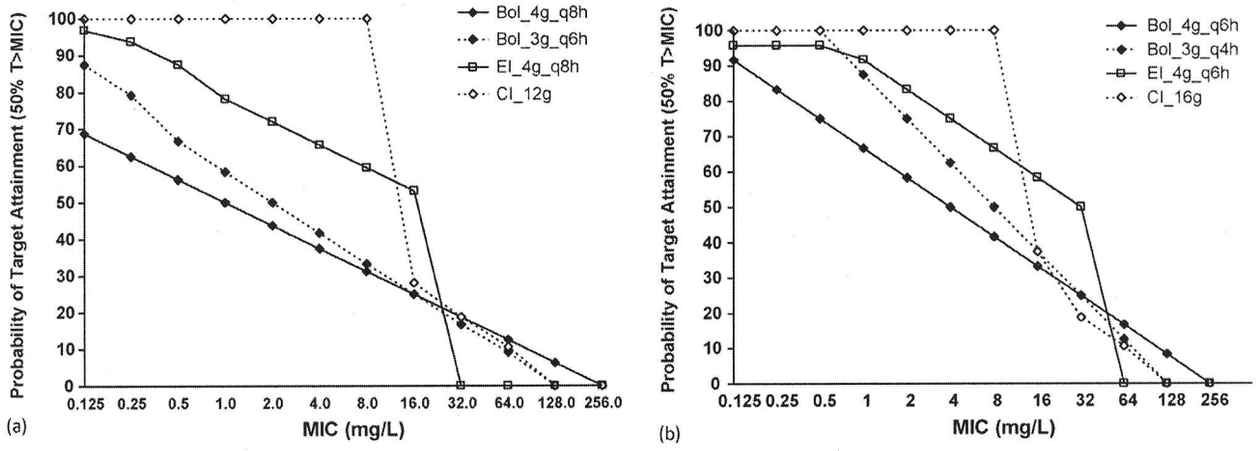

Fig. 2. Probability of target attainment (PTA) for piperacillin administered by bolus, extended or continuous dosing as (a) 12 g/day and (b) 16 g/day or 18 g/day. The chosen target for analysis was 50% of the dosing interval for piperacillin plasma concentrations to be in excess of the minimum inhibitory concentration (MIC). Bol, bolus; q8h, administered every 8 h; q6h, administered every 6 h; EI, extended infusion; CI, continuous infusion.

MIC of 0.25 mg/L, and when given 8-hourly the PTA is 59.4% during first dose, which is below the accepted 90% target. Administration of smaller and more frequent doses or administration by extended or continuous infusion achieves a superior PTA. For example, when 16 g/day is dosed via extended or continuous infusions it achieves at least 90% PTA at a MIC of 1 mg/L after the first dose.

3.5. Probability of target attainment by minimum inhibitory concentration

The assessment of PTA by MIC for various dosing simulations that achieved more than 50% $f_{T>MIC}$ for the first dose is described in Table 3. These data support the $\%f_{T>MIC}$ data from above that continuous infusion is superior to extended infusion and bolus dosing at achieving 50% $f_{T>MIC}$ for various MICs. This is evident even for smaller continuous infusion doses.

Table 2
Bootstrap parameter final estimates of the final base model.

Parameter	Mean	95% CI	
Fixed effects			
CL (L/h)	17.1	14.4	20.6
V1 (L)	7.2	5.4	9.9
V2 (L)	17.8	13.8	24.5
Q (L/h)	52.0	36.8	70.5
ALAG (h^{-1})	0.07	0.06	0.09
Random effects			
Between-subject variability Ω_{BSV} (CV%)			
BSV_{CL}	29.8	10.0	45.4
BSV_{V1}	26.4	0.1	55.2
BSV_{Q}	50.2	16.7	78.8
BSV_{V2}	73.2	28.0	105.8
BSV_{ALAG}	43.7	26.1	61.7
Between-occasion variability Ω_{BOV} (CV%)			
BOV_{CL}	46.2	27.3	59.5
BOV_{V1}	24.4	0.1	64.1
Random error			
Residual unexplained variability (CV%)	25.3	22.0	29.1
S.D. (mg/L)	3.2	1.5	4.4

CI, confidence interval; CL, clearance; V1, central volume of distribution; V2, peripheral volume of distribution; Q, intercompartmental clearance; ALAG, time lag from dose infuser to patient; BSV, between-subject variability; BOV, between-occasion variability; CV, coefficient of variation; S.D., standard deviation.

4. Discussion

This paper demonstrates that continuous infusion of piperacillin maintains superior target concentrations compared with intermittent bolus dosing in critically ill patients with sepsis at first dose and at steady state. Using these data we have developed a population pharmacokinetic model for piperacillin to identify the large pharmacokinetic variability of piperacillin in this population. Importantly, the dosing simulations undertaken demonstrate that suboptimal piperacillin exposures can occur with standard bolus dosing regimens and that other dosing strategies may be clinically advantageous for critically ill patients with sepsis because of the different pharmacokinetic parameters evident in this population. In this cohort of critically ill patients with sepsis we identified different values of volume of distribution (V_d) and clearance (CL) compared with previous studies for piperacillin in other patient populations.

The piperacillin V_d was significantly larger in the present patient group with a calculated total V_d of 25.0 L (0.33 L/kg) compared with other studies in healthy volunteers (10.4 L [19] and 7.4 L [43]), in patients with intra-abdominal infections (22.3 L [21]) and in cystic fibrosis patients administered piperacillin by bolus dosing (9.5 L [19] and 13.1 L [22]). The concept of increased V_d in sepsis is likely to be related to the level of sickness severity [5] and has been described previously for other antibiotics [44].

Drug clearance was also noticeably higher in this cohort of critically ill patients with sepsis (17.2 L/h) compared with other studies in healthy volunteers (11.3 L/h [19] and 8.1 L/h [43]), in patients with intra-abdominal infections (13.8 L/h [21]) and in cystic fibrosis patients administered piperacillin by bolus dosing (11.3 L/h [19] and 13.1 L/h [22]). Vinks et al. [22] found very high clearances (24.4 L/h) of piperacillin administered by continuous infusion in patients with cystic fibrosis, but this is likely to be due to increased systemic metabolism common to this population potentially leading to increased renal tubular secretion. The increased clearance that we observed in critically ill patients with sepsis and no renal dysfunction is likely to be due to increased cardiac output and consequent increased renal perfusion that results from this disease process [11]. Such physiological changes support suggestions for increased doses of renally cleared antibiotics in this patient population [5,13,45]. Despite this, the only covariate that we could statistically support in our model was TBW (normalised to 70 kg), which we found reduced the BSV of piperacillin clearance.

Table 3
Probability of target attainment by minimum inhibitory concentration (%) for various bolus, extended and continuous dosing strategies of piperacillin in critically ill patients with sepsis.

MIC (mg/L)	% frequency from MYSTIC database [41]	Bolus dosing				Extended infusion		Continuous Infusion		
		3 g q4h	3 g q6h	4 g q8h	4 g q6h	4 g q8h	4 g q6h	8 g/day	12 g/day	16 g/day
0.125	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.25	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	54.58	47.76	31.82	25.58	34.11	42.63	50.05	54.58	54.58	54.58
2	21.84	16.38	10.92	8.87	11.83	15.70	18.19	21.84	21.84	21.84
4	9.51	5.94	3.97	3.27	4.36	6.24	7.13	9.51	9.51	9.51
8	5.48	2.74	1.82	1.54	2.06	3.26	3.66	1.89	5.48	5.48
16	1.75	0.66	0.44	0.38	0.51	0.93	1.02	0.44	0.49	0.66
32	2.05	0.51	0.34	0.32	0.43	0.00	1.03	0.32	0.39	0.39
64	0.63	0.08	0.06	0.06	0.08	0.00	0.00	0.06	0.07	0.07
128	4.16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
CFR		74.07	49.37	40.03	53.38	68.75	81.08	88.64	92.35	92.52

The target chosen was 50% $f_{T>MIC}$. Data for piperacillin susceptibility includes various pathogens isolated. MIC, minimum inhibitory concentration; q4h, every 4 h; q6h, every 6 h; q8h, every 8 h; CFR, cumulative fraction of response.

Unlike other studies, our population model was not able to statistically support CL_{Cr} as a covariate to predict likely piperacillin clearance. However, given the narrow range of renal function in the group, the likelihood of estimating a renal covariate would be low. Another contributing reason for the higher effect of TBW (normalised to 70 kg) on clearance, compared with CL_{Cr}, may be the significant effect of rapid drug distribution into tissues resulting from the capillary leak syndrome in these patients with sepsis. It is likely that further pharmacokinetic sampling beyond the time period of this study would have also shown an effect of CL_{Cr} on piperacillin clearance. These data suggest that in the initial phase of dosing (Days 1–3), dosing regimens that account for body weight should also be a primary consideration for the clinician.

Most pharmacodynamic data on optimal β-lactam activity have been generated in in vitro and animal in vivo studies [7–9,40]. A recent retrospective analysis of the cephalosporin antibiotics cefepime and ceftazidime is the first data correlating pharmacokinetic/pharmacodynamic data with clinical and bacteriological outcome for patients [10]. The authors found significantly improved clinical and bacteriological cure when 100% $T>$ MIC was maintained. Although cephalosporins are thought to require a higher % $f_{T>MIC}$ for optimal bactericidal activity than penicillins (60–70% vs. 50–60%), a similar advantage could be argued for maintaining 100% $T>$ MIC is likely to exist for penicillins such as piperacillin in critically ill patients. From our research and that of others, it is clear that continuous infusions are far more likely to enable achievement of 100% $f_{T>MIC}$ whilst minimising drug costs [46,47]. However, the lack of robust data supporting the essential requirement of 100% $f_{T>MIC}$ meant that we used 50% $f_{T>MIC}$ as the pharmacodynamic target for piperacillin dosing.

Our data show that current suggested dosing regimens (4 g q6h or q8h) are less likely to achieve pharmacodynamic targets than alternate dosing regimens in this patient group. Dosing simulations suggest that dosing by extended or continuous infusion will achieve pharmacodynamic targets more successfully in critically ill patients with sepsis. The apparent advantages in favour of administration by continuous infusion (with a loading dose) were evident for the first dose. Given the association between early and appropriate antibiotic therapy and improved clinical outcomes for critically ill patients [1–6], these data support the use of continuous infusions early in the course of treatment. The wide pharmacokinetic variability observed in this sample also supports the possible use of therapeutic drug monitoring of β-lactam antibiotics such as piperacillin in critically ill patients should administration be either by bolus, extended or continuous infusion.

A small number of prospective randomised controlled clinical trials have been conducted in critically ill patients comparing continuous and bolus administration. Each of these has demonstrated equivalence of effect between both modes of dosing [17,24,29,30,48,49], although the lack of difference may be due to the small sample sizes of each study. Two large retrospective cohort studies using extended or continuous infusion of a β-lactam antibiotic have provided data of superior clinical and bacteriological outcomes compared with bolus administration [12,50]. Our dose simulations support these conclusions by showing that extended and continuous infusion both obtain superior PTAs, particularly after the first administered dose.

Given the variable pharmacokinetics likely to be observed with different levels of patient sickness severity that can affect patient pharmacokinetics, a limitation of this study may be the small cohort size ($n = 16$). This may have prevented other covariates from being shown to be significant.

5. Conclusion

This paper represents the first known data examining the population pharmacokinetics of piperacillin in critically ill patients with sepsis during first dose and at steady state. The data describe significantly different pharmacokinetic parameters than those observed in other patient populations, including critically ill patients without sepsis. The results of the Monte Carlo simulations suggest that the likelihood of achieving pharmacodynamic targets improves with an increased length of infusion. Dosing by extended or continuous infusion would appear necessary for optimising first-dose pharmacokinetics, probably due to the increased V_d of piperacillin observed in critically ill patients with sepsis.

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Competing interests: None declared.

Ethical approval: This study was approved by the Royal Brisbane & Women's Hospital (protocol 2005/028) and The University of Queensland (protocol 2005000288) Ethics Committees. The study was conducted following the guidelines of the Declaration of Helsinki.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2009.10.008.

References

[1] Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Crit Care Med 2003;31:2742–51.

[2] Garnacho-Montero J, Aldabo-Pallas T, Garnacho-Montero C, Cayuela A, Jiménez R, Barroso S, et al. Timing of adequate antibiotic therapy is a greater determinant of outcome than are TNF and IL-10 polymorphisms in patients with sepsis. Crit Care 2006;10:R111.

[3] Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am J Med 2003;115:529–35.

[4] Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462–74.

[5] Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1589–96.

[6] MacArthur RD, Miller M, Albertson T, Panacek E, Johnson D, Teoh L, et al. Adequacy of early empiric antibiotic treatment and survival in severe sepsis: experience from the MONARCS trial. Clin Infect Dis 2004;38:284–8.

[7] Mouton JW, Dudley MN, Cars O, Derendorf H, Drusano GL. Standardization of pharmacokinetic/pharmacodynamic (PK/PD) terminology for anti-infective drugs: an update. J Antimicrob Chemother 2005;55:601–7.

[8] Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol 2004;2:289–300.

[9] Mouton JW, den Hollander JG. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an in vitro pharmacokinetic model. Antimicrob Agents Chemother 1994;38:931–6.

[10] McKinnon PS, Paladino JA, Schentag JJ. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration ($T>$MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int J Antimicrob Agents 2008;31:345–51.

[11] Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit Care Med 2009;37:840–51.

[12] Lodise Jr TP, Lomaestro B, Drusano GL. Piperacillin–tazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. Clin Infect Dis 2007;44:357–63.

[13] Dalley AJ, Lipman J, Venkatesh B, Rudd M, Roberts MS, Cross SE. Inadequate antimicrobial prophylaxis during surgery: a study of β-lactam levels during burn debridement. J Antimicrob Chemother 2007;60:166–9.

[14] Angus BJ, Smith MD, Suputtamongkol Y, Mattie H, Walsh AL, Wuthiekanun V, et al. Pharmacokinetic–pharmacodynamic evaluation of ceftazidime continuous infusion vs intermittent bolus injection in septicaemic melioidosis. Br J Clin Pharmacol 2000;50:184–91.

[15] Benko AS, Cappelletty DM, Kruse JA, Rybak MJ. Continuous infusion versus intermittent administration of ceftazidime in critically ill patients with suspected Gram-negative infections. Antimicrob Agents Chemother 1996;40:691–5.

[16] Buijk SL, Gyssens IC, Mouton JW, Van Vliet A, Verbrugh HA, Bruining HA. Pharmacokinetics of ceftazidime in serum and peritoneal exudate during continuous versus intermittent administration to patients with severe intra-abdominal infections. J Antimicrob Chemother 2002;49:121–8.

[17] Hanes SD, Wood GC, Herring V, Croce MA, Fabian TC, Pritchard E, et al. Intermittent and continuous ceftazidime infusion for critically ill trauma patients. Am J Surg 2000;179:436–40.

[18] Buck C, Bertram N, Ackermann T, Sauerbruch T, Derendorf H, Paar WD. Pharmacokinetics of piperacillin–tazobactam: intermittent dosing versus continuous infusion. Int J Antimicrob Agents 2005;25:62–7.

[19] Bulitta JB, Duffull SB, Kinzig-Schippers M, Holzgrabe U, Stephan U, Drusano GL, et al. Systematic comparison of the population pharmacokinetics and pharmacodynamics of piperacillin in cystic fibrosis patients and healthy volunteers. Antimicrob Agents Chemother 2007;51:2497–507.

[20] Lau WK, Mercer D, Itani KM, Nicolau DP, Kuti JL, Mansfield D, et al. Randomized, open-label, comparative study of piperacillin–tazobactam administered by continuous infusion versus intermittent infusion for treatment of hospitalized patients with complicated intra-abdominal infection. Antimicrob Agents Chemother 2006;50:3556–61.

[21] Li C, Kuti JL, Nightingale CH, Mansfield DL, Dana A, Nicolau DP. Population pharmacokinetics and pharmacodynamics of piperacillin/tazobactam in patients with complicated intra-abdominal infection. J Antimicrob Chemother 2005;56:388–95.

[22] Vinks AA, Den Hollander JG, Overbeek SE, Jelliffe RW, Mouton JW. Population pharmacokinetic analysis of nonlinear behavior of piperacillin during intermittent or continuous infusion in patients with cystic fibrosis. Antimicrob Agents Chemother 2003;47:541–7.

[23] Boselli E, Breilh D, Rimmelé T, Guillaume C, Xuereb F, Saux MC, et al. Alveolar concentrations of piperacillin/tazobactam administered in continuous infusion to patients with ventilator-associated pneumonia. Crit Care Med 2008;36:1500–6.

[24] Rafati MR, Rouini MR, Mojtahedzadeh M, Najafi A, Tavakoli H, Gholami K, et al. Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients. Int J Antimicrob Agents 2006;28:122–7.

[25] Roberts JA, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Piperacillin penetration into tissue of critically ill patients with sepsis—bolus versus continuous administration? Crit Care Med 2009;37:926–33.

[26] Steimer JL, Mallet A, Golmard JL, Boisvieux JF. Alternative approaches to estimation of population pharmacokinetic parameters: comparison with the nonlinear mixed-effect model. Drug Metab Rev 1984;15:265–92.

[27] Roos JF, Lipman J, Kirkpatrick CM. Population pharmacokinetics and pharmacodynamics of cefpirome in critically ill patients against Gram-negative bacteria. Intensive Care Med 2007;33:781–8.

[28] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101: 1644–55.

[29] Nicolau DP, McNabb J, Lacy MK, Quintiliani R, Nightingale CH. Continuous versus intermittent administration of ceftazidime in intensive care unit patients with nosocomial pneumonia. Int J Antimicrob Agents 2001;17:497–504.

[30] Sakka SG, Glauner AK, Bulitta JB, Kinzig-Schippers M, Pfister W, Drusano GL, et al. Population pharmacokinetics and pharmacodynamics of continuous versus short-term infusion of imipenem–cilastatin in critically ill patients in a randomized, controlled trial. Antimicrob Agents Chemother 2007;51: 3304–10.

[31] van Zanten AR, Oudijk M, Nohlmans-Paulssen MK, van der Meer YG, Girbes AR, Polderman KH. Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: pharmacokinetics/pharmacodynamics, bacterial susceptibility and clinical efficacy. Br J Clin Pharmacol 2007;63:100–9.

[32] Arzuaga A, Isla A, Gascón AR, Maynar J, Martín A, Solinís MA, et al. Quantitation and stability of piperacillin and tazobactam in plasma and ultrafiltrate from patients undergoing continuous venovenous hemofiltration by HPLC. Biomed Chromatogr 2005;19:570–8.

[33] Riegel MA, Ellis PP. High-performance liquid chromatographic assay for piperacillin in aqueous humor of the eye. J Chromatogr 1988;424:177–81.

[34] Ocampo AP, Hoyt KD, Wadgaonkar N, Carver AH, Puglisi CV. Determination of tazobactam and piperacillin in human plasma, serum, bile and urine by gradient elution reversed-phase high-performance liquid chromatography. J Chromatogr 1989;496:167–79.

[35] Beal SL, Sheiner LB. NONMEM user guides (I–VIII). San Francisco, CA: University of California at San Francisco; 1998.

[36] Parke J, Holford NH, Charles BG. A procedure for generating bootstrap samples for the validation of nonlinear mixed-effects population models. Comput Methods Programs Biomed 1999;59:19–29.

[37] Matthews I, Kirkpatrick C, Holford N. Quantitative justification for target concentration intervention—parameter variability and predictive performance using population pharmacokinetic models for aminoglycosides. Br J Clin Pharmacol 2004;58:8–19.

[38] Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.

[39] Bulitta J, Holford NH. Assessment of predictive performance of pharmacokinetic models based on plasma and urine data. Brisbane, Australia: PAGANZ Population Approach Group in Australia & New Zealand; 2005.

[40] Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1–10.

[41] Sun HK, Kuti JL, Nicolau DP. Pharmacodynamics of antimicrobials for the empirical treatment of nosocomial pneumonia: a report from the OPTAMA Program. Crit Care Med 2005;33:2222–7.

[42] MIMS Australia. Tazocin® product information. In: Donohoo E, editor. MIMS online. St Leonards, NSW: CMPMedica Australia Pty Ltd.; 2005.

[43] Landersdorfer C. Modern pharmacokinetic–pharmacodynamic techniques to study physiological mechanisms of pharmacokinetic drug–drug interactions and disposition of antibiotics and to assess clinical relevance. Julius-Maximilians-Universität Würzburg; 2006, p. 255.

[44] Marik PE. Aminoglycoside volume of distribution and illness severity in critically ill septic patients. Anaesth Intensive Care 1993;21:172–3.

[45] Roberts JA, Paratz JD, Lipman J. Continuous infusion of β-lactams in the intensive care unit—best way to hit the target? Crit Care Med 2008;36: 1663–4.

[46] McNabb JJ, Nightingale CH, Quintiliani R, Nicolau DP. Cost-effectiveness of ceftazidime by continuous infusion versus intermittent infusion for nosocomial pneumonia. Pharmacotherapy 2001;21:549–55.

[47] Roberts JA, Paratz JD, Paratz E, Krueger WA, Lipman J. Continuous infusion of β-lactam antibiotics in severe infections: a review of its role. Int J Antimicrob Agents 2007;30:11–8.
[48] Georges B, Conil JM, Cougot P, Decun JF, Archambaud M, Seguin T, et al. Cefepime in critically ill patients: continuous infusion vs. an intermittent dosing regimen. Int J Clin Pharmacol Ther 2005;43:360–9.
[49] Roberts JA, Boots R, Rickard CM, Thomas P, Quinn J, Roberts DM, et al. Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomized controlled pilot study. J Antimicrob Chemother 2007;59:285–91.
[50] Lorente L, Lorenzo L, Martín MM, Jiménez A, Mora ML. Meropenem by continuous versus intermittent infusion in ventilator-associated pneumonia due to Gram-negative bacilli. Ann Pharmacother 2006;40:219–23.