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Population pharmacokinetics and pharmacodynamics of piperacillin/tazobactam in patients with complicated intra-abdominal infection

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***Objectives*: We investigated the population pharmacokinetics and pharmacodynamics of piperacillin and tazobactam in hospitalized patients.**

***Patients and methods*: A multicentre, randomized clinical trial was conducted in hospitalized patients with complicated intra-abdominal infection. Patients received piperacillin/tazobactam administered by either continuous infusion (13.5 g over 24 h, $n = 130$) or intermittent infusion (3.375 g every 6 h, $n = 132$). NONMEM was used to perform population pharmacokinetic analysis in a subset of patients ($n = 56$) who had serum samples obtained at steady-state for drug concentration analyses. Classification and regression tree analysis was used to identify the breakpoints of piperacillin PK-PD indexes in 94 patients with causative pathogen's MIC.**

***Results*: A one-compartment model was applied to fit the data. Creatinine clearance and body weight were the most significant variables to explain patient variability in piperacillin and tazobactam clearance and volume of distribution. The infusion method had no influence on PK parameters. For patients ($n = 30$) receiving intermittent infusion in the pharmacokinetic study, mean C_{max} and half-life were 122.22 mg/L and 1.17 h for piperacillin, and 15.74 mg/L and 1.81 h for tazobactam. For patients ($n = 26$) receiving continuous infusion in the pharmacokinetic study, mean steady-state concentration was 35.31 ± 12.15 mg/L for piperacillin and 7.29 ± 3.28 mg/L for tazobactam. As a result of a low rate of failures (<11%) observed in the trial and the low MICs for infecting pathogens, no association could be established between clinical/microbiological outcome and drug exposure.**

***Conclusions*: Intermittent infusion and continuous infusion of piperacillin and tazobactam provided sufficient drug exposure to treat those pathogens commonly implicated in intra-abdominal infections.**

Keywords: intermittent infusion, continuous infusion, β-lactams, $t >$ MIC

Introduction

The combination of piperacillin and tazobactam has been shown to be efficacious for the treatment of intra-abdominal infections, skin and soft tissue infections, moderately severe community-acquired pneumonia, and bacteraemia in neutropenic patients.[1] The pharmacokinetics of piperacillin and tazobactam has been extensively investigated in human subjects.[2–6] Most of these studies were limited to a small number of healthy volunteers or patients. There are four published studies focused on the population pharmacokinetics of piperacillin.[7–10] Only one of these, in which patients received piperacillin/tazobactam via continuous infusion, developed a patient covariate model to estimate piperacillin clearance.[8] None of the studies attempted to link the drug exposure to clinical or microbiological response. To date, there is no published description of tazobactam pharmacokinetics using population-based techniques.

Like other β-lactams, piperacillin/tazobactam displays concentration-independent pharmacodynamics, whereby the duration of time that concentrations remain above the MIC correlate

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best with bacterial kill. The protein bindings of piperacillin and tazobactam in human plasma are 20–30% and 20–23%, respectively.[11] Whereas free drug concentrations above the MIC for 50% of the dosing interval are required for bactericidal effects, administering this agent as a 24 h continuous infusion can achieve 100% time above MIC and result in pharmacodynamic and pharmacoeconomic advantages compared with intermittent infusion.[12] As a result, a large, multicentre, randomized clinical trial in hospitalized patients with complicated intra-abdominal infections was designed to determine whether continuous infusion results in equivalent clinical and microbiological responses to intermittent infusion.

The primary objective of this study was to explore the population pharmacokinetics of piperacillin and tazobactam in hospitalized patients with complicated intra-abdominal infections, evaluate their interindividual and intraindividual variability, and determine the influence of patient characteristics on pharmacokinetic parameters. The secondary objective was to use the developed models to predict free piperacillin/tazobactam concentrations at steady-state in patients receiving the continuous infusion regimen. Lastly, we sought to determine whether a relationship could be described between the pharmacodynamic profile of the test agent and clinical and microbiological response.

Materials and methods

Study design

Pharmacokinetic data were collected as part of a Phase IV, multicentre, prospective, randomized, open-label clinical trial of hospitalized patients with complicated intra-abdominal infection. The study procedures and methods were reviewed and approved by the participating investigators' local Institutional Review Committee. Informed consent was obtained from all subjects at the time of study enrolment. Patients aged 18 years or older were known or suspected to have at least one of the following intra-abdominal infections of less than 1 week duration: intra-abdominal abscess; periappendiceal abscess; complicated perforated diverticulitis requiring surgical intervention within 24 h of diagnosis; peritonitis due to perforation of a hollow viscus; or post-traumatic peritonitis occurring more than 12 h after the traumatic event. Patients must have had exploration via laparotomy or laparoscopy indicated by the presence or suspicion of an intra-abdominal infection within one calendar day prior to, or after, the first dose of piperacillin/tazobactam. The minimal clinical criteria included the presence of fever or leucocytosis, plus at least two of the following signs and symptoms: localized or diffuse abdominal wall rigidity and/or involuntary guarding; abdominal tenderness or abdominal pain; nausea, vomiting or ileus; radiographic, scintigraphic, sonographic, computerized tomographic (CT), or magnetic resonance imaging studies suggesting a perforated viscus, an intra-abdominal abscess, or other focus of intra-abdominal infection.

Patients were excluded if they had any of the following: concurrent haemodialysis, peritoneal dialysis, indwelling peritoneal catheters or shunts, plasmapheresis, haemoperfusion, or severe organ failure; known or suspected hypersensitivity or adverse reaction to penicillins or β-lactamase inhibitors; creatinine clearance <20 mL/min; presence of sustained shock, defined as systolic blood pressure <90 mmHg for more than 2 h with evidence of hypoperfusion despite adequate fluid resuscitation, or the need for sympathomimetic agents to maintain blood pressure.

Patients who met inclusion/exclusion criteria were randomly assigned to receive piperacillin/tazobactam either by continuous infusion or intermittent infusion for a minimum of 4 days and not more than 14 days. Patients with normal renal function who were randomized to intermittent infusion dosing received 3 g/0.375 g piperacillin/tazobactam infused over 30 min every 6 h. Patients assigned to continuous infusion received a single loading dose of 2 g/0.25 g piperacillin/tazobactam administered over 30 min followed immediately by administration of 12 g/1.5 g piperacillin/tazobactam infused continuously over 24 h and repeated daily. Dose adjustment for both test regimens was required for patients with an estimated creatinine clearance of 20–40 mL/min. Creatinine clearance (CL_{CR}) was estimated using the equation proposed by Cockcroft and Gault.[13] For intermittent infusion, patients requiring a dose adjustment received 2 g/0.25 g piperacillin/tazobactam every 6 h according to the package insert. The continuous infusion regimen consisted of the same loading dose followed by 8 g/1 g piperacillin/tazobactam over 24 h, so as to provide the same daily dose as the intermittent infusion.

Sampling procedure

Blood samples (5 mL) for pharmacokinetic assessments were obtained after subjects reached the steady-state in both dose regimens. For continuous infusion, steady-state was defined as at least 24 h, and three blood samples at least 2 h apart were drawn over the following 24 h period. For patients receiving intermittent infusion, blood samples were collected around the 4th, 5th or 6th dose at the following sampling time points: 0 (prior to the next dose), 0.5, 2, 4 and 6 h. Blood samples were centrifuged, separated and frozen at –70°C until the time of analysis.

HPLC analysis

Piperacillin and tazobactam were simultaneously assayed by validated high-pressure liquid chromatography with gradient elution.[14] The concentration ranges of the standard curves were 2–100 mg/L for piperacillin and 1–50 mg/L for tazobactam. There were three quality controls for each standard curve to ensure assay accuracy. The relative standard deviations and relative errors of the inter- and intra-assay of these HPLC methods were less than 5.8%. The concentrations of the unknown samples above the quantification limits were prediluted with tested drug-free human serum.

Pharmacokinetic analysis

Population pharmacokinetics of piperacillin and tazobactam were analysed with the non-linear mixed-effect modelling program NONMEM (version V, level 1.1, double precision).[15] The first-order conditional maximum likelihood estimation (FOCE) method was used throughout the model-building process.

One- and two-compartment models with zero-order input and first-order elimination were evaluated as the potential pharmacokinetic structure model. Interindividual variability of population pharmacokinetic parameter was assumed to be log-normally distributed with a mean of zero and variance of ω^2. To maximize the model flexibility, the residual error (intraindividual variability) was modelled as a combination of additive and proportional error. The selection of the base model was determined by the Akaike information criteria (AIC) and diagnostic scatter plots. AIC was calculated as AIC = OFV + 2*p*, where OFV is the minimum objective function value for a given model and *p* is the number of parameters used in the model. The model with the smaller AIC was chosen as the superior model.

Bayesian estimates of the pharmacokinetic parameters and patient covariates were explored to build the covariate model. A preliminary graphical exploratory assessment of all covariates was performed to identify any linear/non-linear related covariates, including continuous covariates (body weight, height, age, creatinine clearance, serum creatinine concentration and APACHE II score) and categorical

covariates (gender, race and infusion method). Continuous covariates were normalized on the median of that covariate, and the influence of categorical covariates on the pharmacokinetic parameter was entered as a linear proportional change.

During the covariate model-building process, the stepwise forward inclusion procedure was applied to build the full model. The likelihood ratio test was applied to discriminate the alternative nested models using the model selection criteria with a significance level of 0.05, i.e. the difference of the objective function value is larger than 3.84 with 1 degree of freedom. A stepwise deletion procedure was applied to breakdown the full model to the final model with a stringent statistical criterion ($\alpha > 0.01$), i.e. the difference of the objective function value is larger than 6.63 with 1 degree of freedom. Diagnostic scatter plots were used to evaluate the goodness of fit throughout the model-building procedure. The plots were as follows: weighted residual versus time, weighted residual versus prediction, observed concentration versus prediction, and observed concentration versus individual prediction. The first-order conditional maximum likelihood estimation method with interaction η–ε option (FOCEI) was used to re-evaluate the final model. The final population pharmacokinetic covariate model was used to estimate individual patient pharmacokinetic parameters; the results were summarized using descriptive statistics.

The predictive ability of the final model was evaluated via Monte Carlo simulation in NONMEM. The simulation of piperacillin/tazobactam concentrations of all patients was performed based on the final model and point estimates, and 100 simulated data sets (5200 patients with 18 400 piperacillin concentrations and 4700 patients with 14 300 tazobactam concentrations) were obtained based on the final models with fixed and random effects. The simulated piperacillin/tazobactam concentrations were compared with the observed concentrations to determine the predictive performance of the final model by quantile–quantile (Q–Q) plot (S-Plus 2000, Mathsoft, Inc., Seattle, WA, USA).

After the final models were validated, piperacillin and tazobactam concentrations at steady-state were predicted for the entire study population receiving continuous infusion. The free drug concentrations at the steady-state (C_{ss}) were calculated using the following equation: $C_{ss} = f \times R/\mathrm{CL}$, where f is the percentage of unbound drug; CL is clearance; and R is the continuous infusion rate. Based on protein binding, the unbound drug concentrations were adjusted with 70% for piperacillin and 77% for tazobactam.

Pharmacodynamic analysis

Pharmacodynamic analysis was conducted on clinically evaluable subjects who had a baseline pathogen identified and had a piperacillin/tazobactam MIC available. MICs were measured by the Epsilometer test (Etest, AB Biodisk, Solna, Sweden) at each participating site for pathogens isolated from the peritoneum and blood during the intra-abdominal infection process. Estimates of clearance (CL) and volume of distribution (V) of piperacillin were generated using each patient's demographic data and the final population PK model. For patients with polymicrobial infections, the highest MIC for isolated organisms was integrated with free drug exposure to calculate $t >$ MIC, $C_{max\ (free)}$/MIC, $C_{min\ (free)}$/MIC for the intermittent infusion and $t >$ MIC and $C_{ss\ (free)}$/MIC for the continuous infusion. Clinical success was defined as cure or improvement of all signs and symptoms caused by the infection and no additional antibiotic therapy required. Clinical failure was defined as persistent or worsening of any one of the clinical symptoms, new clinical signs and symptoms of infection, or other systemic antimicrobial therapy required. Microbiological outcome was classified as eradication, presumed eradication, persistence, or presumed persistence. In order to simplify the data analysis, bacteriological response was categorized as success (including eradication and presumed eradication) and failure (including persistence and presumed persistence). Classification and regression tree (CART) analysis was applied to determine PD breakpoints with clinical and microbiological response. Statistical significances were validated by Fisher's exact test.

Results

The entire intent-to-treat study population included 262 patients, with 130 assigned to the continuous infusion regimen and 132 assigned to the intermittent infusion regimen. Of the enrolled patients, only 56 patients had blood samples obtained for the population pharmacokinetic analyses including 26 in the continuous infusion regimen and 30 in the intermittent infusion regimen. Therefore, these 56 patients were used for the pharmacokinetic analysis. The demographics of the total study population were similar to the pharmacokinetic study population, and patient characteristics in the continuous infusion regimen were similar to those in the intermittent infusion regimen (Table 1). Some samples were excluded from the pharmacokinetic analyses due to concentrations below the detection limit, interference from other concomitant medications, defrosting during shipment, or outlying concentrations (5-fold higher than the average). The final pharmacokinetic database consisted of 184 piperacillin concentrations from 52 patients including 24 patients receiving continuous infusion and 28 patients receiving intermittent infusion, and 143 tazobactam concentrations from 47 patients including 23 patients receiving continuous infusion and 24 patients receiving intermittent infusion.

Preliminary analysis of the pharmacokinetic base model showed that AIC values of one- and two-compartment models were 1053.08 and 1058.61 for piperacillin, and 356.50 and 357.88 for tazobactam. Thus, a one-compartment model resulted in a better fit to describe piperacillin and tazobactam serum concentration data.

Table 1. Demographics of patients included in the population pharmacokinetic study

	Continuous infusion	Intermittent infusion	Overall
Categorical variables, number of patients (percentage)			
gender			
male	20 (77%)	21 (70%)	41 (73%)
female	6 (23%)	9 (30%)	15 (27%)
race			
black	4 (15%)	4 (13.3%)	8 (14%)
Caucasian	17 (65%)	16 (53.3%)	33 (59%)
Hispanic	5 (20%)	9 (30%)	14 (25%)
other	0 (0%)	1 (3.3%)	1 (2%)
Continuous variables, median (range)			
age (years)	52 (18–82)	47.5 (18–85)	48 (18–85)
CL_{CR} (mL/min)	93 (22–150)	84 (36–136)	89 (22–150)
body weight (kg)	80 (55.5–115)	82.6 (55–136)	81.8 (55–136)
height (inches)	68 (51–78)	67 (60–78)	67 (51–78)
S_{CR} (mg/dL)	1 (0.5–1.8)	0.9 (0.5–2)	1 (0.5–2)
APACHE II score	7 (0–29)	8 (3–20)	8 (0–29)

CL_{CR}, creatinine clearance; S_{CR}, serum creatinine concentration.

Table 2. Piperacillin final population model parameter estimates

Parameter	Pharmacokinetic structural model[a] Population estimate	SE[b]	RSE (%)[c]
Clearance (L/h)	$CL = \theta_1 + \theta_2 \times CL_{CR}/89$		
θ_1	5.05	1.24	24.55
θ_2	9.60	1.67	17.40
interindividual variability	27.7%	0.0169	21.98
Volume of distribution (L)	$V = \theta_3 \times WT/81.8$		
θ_3	22.3	1.57	7.04
interindividual variability	25.2%	0.0329	51.65
Residual error model			
proportional	18.5%	0.0126	36.73
additive	1.77 mg/L	3.01	96.17

[a]AIC value of the final model was 993.04.
[b]SE, standard error of θ_1, θ_2 and θ_3; and standard error of the variance of the interindividual variability and residual errors.
[c]RSE, relative standard error.

Table 3. Tazobactam final population model parameter estimates

Parameter	Pharmacokinetic structural model[a] Population estimate	SE[b]	RSE (%)[c]
Clearance (L/h)	$CL = \theta_1 + \theta_2 \times CL_{CR}/89$		
θ_1	4.92	1.07	21.74
θ_2	5.44	1.52	27.94
interindividual variability	40.2%	0.0320	19.26
Volume of distribution (L)	$V = \theta_3 \times WT/81.8$		
θ_3	23.0	1.93	8.39
interindividual variability	32.1%	0.0782	75.92
Residual error model			
proportional	13.5%	0.00461	25.19
additive	0.40 mg/L	0.0945	59.06

[a]AIC value of the final model was 318.31.
[b]SE, standard error of θ_1, θ_2 and θ_3; and standard error of the variance of the interindividual variability and residual errors.
[c]RSE, relative standard error.

The population estimates of piperacillin pharmacokinetic parameters in complicated intra-abdominal infection patients were 13.8 L/h for CL and 19.4 L for *V* the interindividual variability was 34.6% for CL and 40.0% for *V*, and the combinational additive and proportional error of intraindividual variability were 3.55 mg/L and 14.4%, respectively. The population estimates of tazobactam pharmacokinetic parameters in the patients analysed were 9.80 L/h for CL and 21.2 L for *V*, the interindividual variability was 42.8% for CL and 38.1% for *V*, and the combinational additive and proportional error of intraindividual variability were 0.65 mg/L and 13.7%, respectively.

In the procedure for finding the final model, inclusion of creatinine clearance to clearance of piperacillin/tazobactam, and body weight to volume of distribution of piperacillin/tazobactam produced the most significant decrease in objective function and interindividual variances of pharmacokinetic parameters. Based on the diagnostic scatter plots, the combinational additive and proportional error model was selected for modelling intraindividual variability. Tables 2 and 3 summarize the final population pharmacokinetic parameter estimates for piperacillin and tazobactam. Figures 1 and 2 present the weighted residual versus the predicted concentration, the population predicted versus observed concentration, and the individual predicted versus observed concentration. These diagnostic plots indicated a good fit of the model to piperacillin and tazobactam in the target population.

Bayesian estimates of individual clearance and volume of distribution of the study population were obtained based on the final models. Individual estimates of half-life ($t_{1/2}$), maximum concentration for intermittent infusion (C_{max}), and concentration at the steady-state for continuous infusion (C_{ss}) were calculated according to their clearance and volume of distribution. Table 4 summarizes the calculated parameters, and there were no statistical differences in CL and *V* of piperacillin/tazobactam between patients in the intermittent infusion regimen and the continuous infusion regimen ($P > 0.11$).

In the Monte Carlo simulation process, 100 sets of simulated concentration data were created. The data appear to approximate the line of unity (Figure 3). These plots indicated that the final models adequately characterized the pharmacokinetic profile of piperacillin and tazobactam in hospitalized intra-abdominal infected patients.

According to the final models, the predicted free piperacillin and tazobactam steady-state concentrations (mean ± standard deviation) administered by continuous infusion for the 130 patients in the clinical trial were 27.1 ± 6.8 mg/L (range: 14.5–47.3 mg/L) and 5.1 ± 1.0 mg/L (range: 3.1–7.7 mg/L), respectively.

Of the total enrolled patients, 45 patients in the continuous infusion regimen and 49 patients in the intermittent infusion regimen had available MIC data, ranging from 0.016 to 16 mg/L. For continuous infusion, the $t >$ MIC for unbound piperacillin in all 45 patients was 100%, and the median (range) of $C_{ss\ (free)}$/MIC was 5.04 (1.04–1767.64). There were four failures in 38 bacteriologically evaluable patients, and five failures in 45 clinically evaluable patients. For the intermittent infusion, the median (range) of $t >$ MIC of unbound piperacillin was 95.01% (43.41–100%), the median (range) of $C_{max\ (free)}$/MIC was 15.34 (3.38–779.51), and the median (range) of $C_{min\ (free)}$/MIC was 0.47 (0.02–45.12). Two failures were found among 39 bacteriologically evaluable patients, and five failures were found among 49 clinically evaluable patients. CART analysis could not identify a significant breakpoint for any PD exposure to predict clinical or bacteriological response.

Discussion

This Phase IV, multicentre, randomized clinical trial was conducted in hospitalized patients with complicated intra-abdominal infection who received piperacillin/tazobactam via continuous infusion or intermittent infusion. Serum samples were collected in about one-fifth of the enrolled patients to perform the population pharmacokinetic study. Clearances of piperacillin/tazobactam

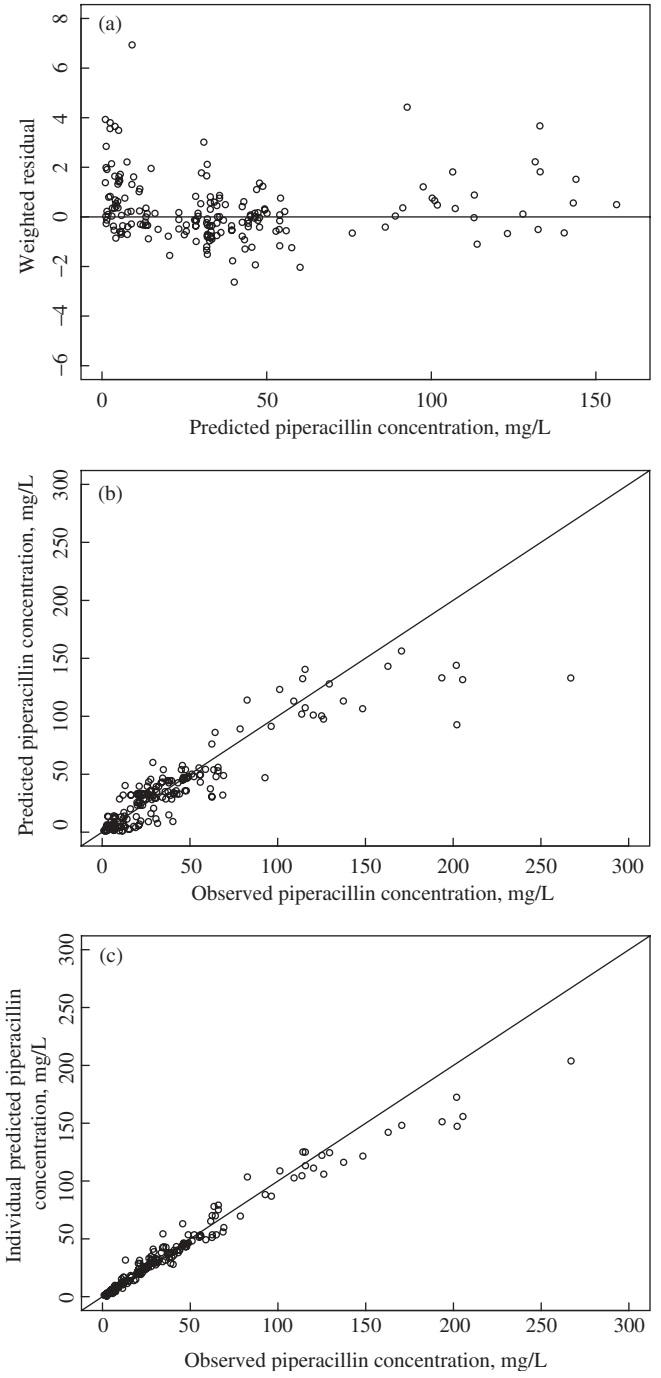

Figure 1. Diagnostic scatter plots for piperacillin population final model. (a) Predicted concentration versus weighted residual, (b) population-predicted piperacillin concentration versus observed concentration, and (c) individual predicted piperacillin concentration versus observed concentration for the final model. The line of unity is included.

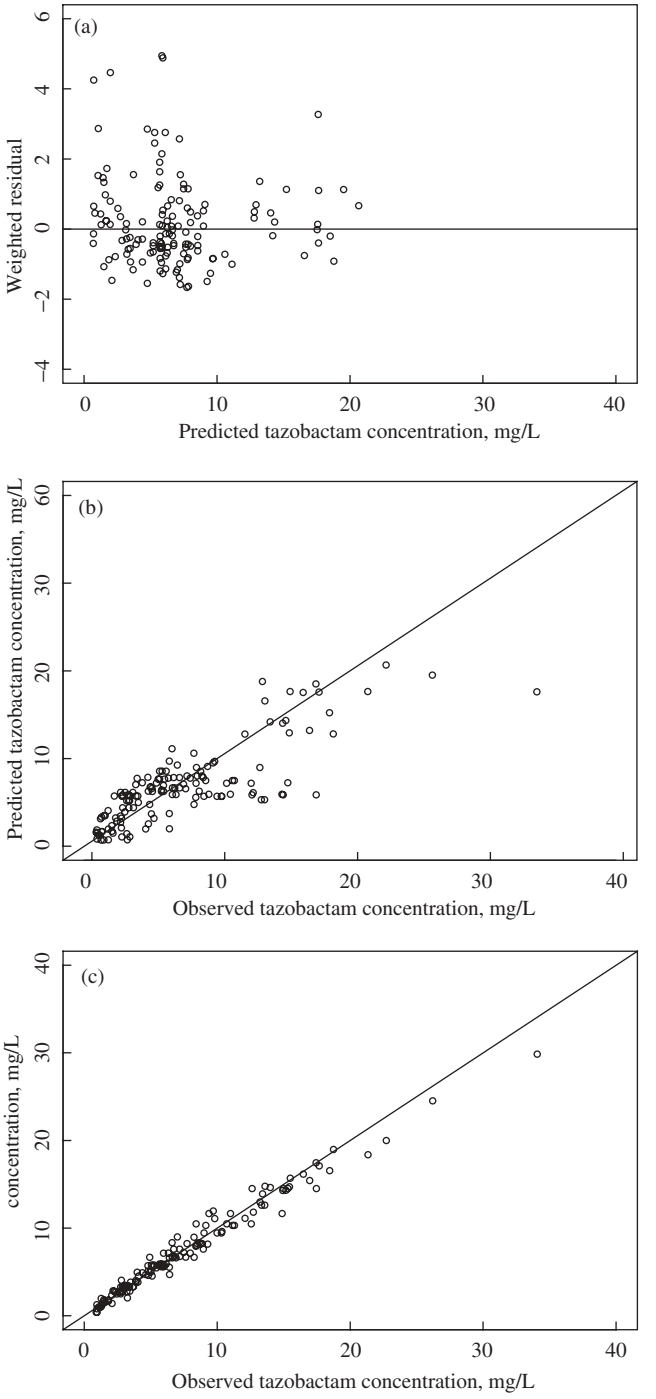

Figure 2. Diagnostic scatter plots for tazobactam population final model. (a) Predicted concentration versus weighted residual, (b) population-predicted tazobactam concentration versus observed concentration, and (c) individual predicted tazobactam concentration versus observed concentration for the final model. The line of unity is included.

were similar between patients receiving continuous infusion and intermittent infusion, suggesting that the infusion method had no influence on the pharmacokinetics of piperacillin and tazobactam. For patients receiving intermittent infusion (3.375 g every 6 h), the mean volume of distribution was 22.43 L for piperacillin and 23.19 L for tazobactam, and the mean clearance was 13.72 L/h for piperacillin and 11.04 L/h for tazobactam. In a previously reported pharmacokinetic study, Jhee *et al.*[3] investigated 18 intra-abdominal patients receiving 4.5 g piperacillin/tazobactam by intermittent infusion every 8 h. The estimated non-compartmental pharmacokinetic parameters (mean ± SD) were as follows: mean volume of distribution of 21.00 ± 4.18 L for piperacillin and 22.47 ± 8.27 L for tazobactam; mean clearance of 14.75 ± 3.93 L/h for piperacillin and 14.78 ± 4.39 L/h for tazobactam. Except for

Table 4. Bayesian estimates of individual pharmacokinetic parameters

	Continuous infusion	Intermittent infusion
Piperacillin		
CL (L/h)	15.96 ± 5.71	13.72 ± 4.31
V (L)	22.25 ± 4.54	22.43 ± 6.18
$t_{1/2}$ (h)	1.08 ± 0.45	1.24 ± 0.64
C_{max} (mg/L)	NA	122.22 ± 30.37
C_{ss} (mg/L)	35.31 ± 12.15	NA
Tazobactam		
CL (L/h)	10.70 ± 5.42	11.04 ± 3.82
V (L)	22.82 ± 4.69	23.19 ± 8.87
$t_{1/2}$ (h)	1.88 ± 1.04	1.73 ± 1.34
C_{max} (mg/L)	NA	15.75 ± 4.84
C_{ss} (mg/L)	7.29 ± 3.28	NA

Numbers represent means ± standard deviations; NA, not available.

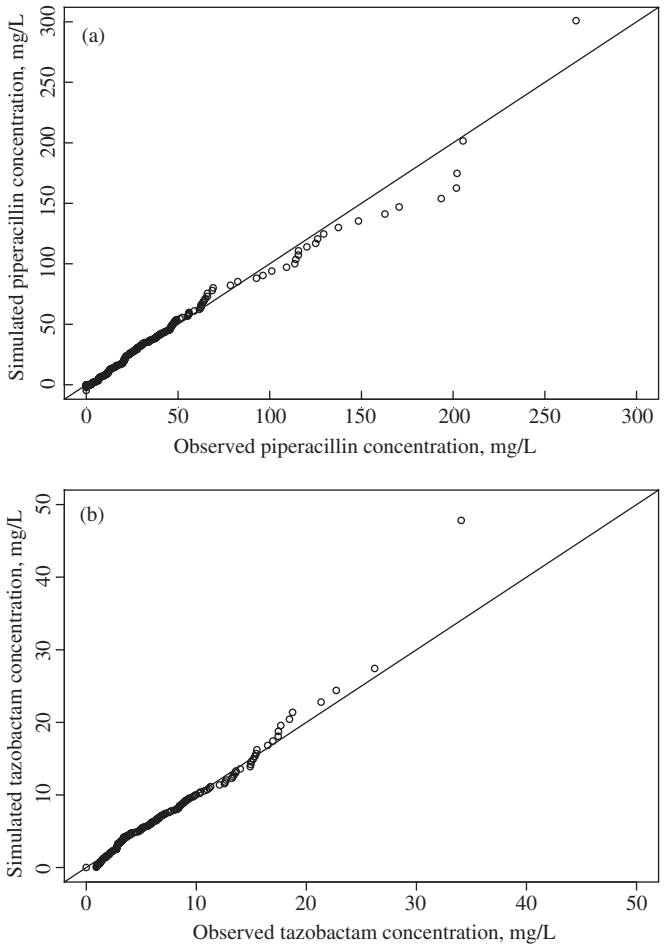

Figure 3. Quantile–quantile plot of (a) piperacillin and (b) tazobactam observed concentration versus simulated concentration. The line of unity is included.

a lower clearance found for tazobactam, our results for the pharmacokinetic parameters were very similar to the study by Jhee *et al.*[3]

The mean steady-state concentration of piperacillin by continuous infusion in our study was 35.31 mg/L in the pharmacokinetic sample population. These results were very similar to those reported by Burgess and Waldrep,[16] in which healthy volunteers received the same dose regimen as our study (i.e. 12 g/1.5 g piperacillin/tazobactam via continuous infusion over 24 h). Our results, however, are lower than the study by Facca *et al.*,[8] in which 55 patients with various infection types (respiratory tract, urinary tract, intra-abdominal, skin structure infection and septicaemia) received piperacillin/tazobactam by continuous infusion over 24 h. The mean steady-state concentration in this study was 53 mg/L. It is difficult to compare these findings with ours because the total daily dose of piperacillin/tazobactam administered was not specified in their study. Additionally, these investigators proposed a population pharmacokinetic model to estimate piperacillin clearance using the patient's body weight, age and serum creatinine concentration. In their proposed model, the non-renal clearance of piperacillin was 2.10 L/h, much less than the reported values (3.4–9.8 L/h) in healthy subjects or renal failure patients.[17] Finally, the volume of distribution could not be estimated since blood samples were only collected at steady-state for those patients receiving continuous infusion. As a result, when their model was applied to fit our data (not shown), different parameter estimates were obtained and there was a discrepancy between the predicted concentration and our observed concentrations.

In addition to the study by Facca *et al.*, there are three other published population pharmacokinetic studies of piperacillin and tazobactam. One study by Auclair and Ducharme[7] pointed out that piperacillin and tazobactam exhibited linear pharmacokinetics with the usual clinical dosing regimens. Lodise *et al.*[10] characterized piperacillin pharmacokinetics with a linear model. In contrast, Vinks *et al.*[9] applied the population pharmacokinetic approach to analyse the data from eight patients with cystic fibrosis, and used a two-compartment Michaelis–Menten model to describe the non-linear pharmacokinetics of piperacillin. However, none of these three studies assessed the influence of patient covariates on pharmacokinetic profiles, and no covariate model was proposed.

It is controversial whether piperacillin exhibits linear or non-linear pharmacokinetics. In previous studies, investigators claimed that the pharmacokinetics of piperacillin was non-linear based on non-compartmental pharmacokinetic analysis, but they also reported good fittings using linear one- and two-compartment models.[18–21] Even with the population pharmacokinetic approaches, linear and non-linear models were proposed by different investigators.[7,9,10] With the sparse sampling schedule in our study, there were not enough samples collected in the distribution phase to characterize a two-compartment model, and blood samples were only collected at the steady-state for the continuous infusion regimen. In this case, a one-compartment model better described piperacillin/tazobactam pharmacokinetics for our data. In spite of the variation seen in the study population, the majority of data were fairly predicted with the exception of the underestimation of five patients' peak levels (Figure 1b). In Figures 1(c) and 2(c), the individual predicted concentrations matched well with the observed concentrations, except for a very slight underestimation of these five patients' peak concentrations. In other words, piperacillin and tazobactam concentrations in the terminal elimination phase were fitted well with the proposed models. As a result, $t >$ MIC for piperacillin can be calculated accurately for such time-dependent antibiotics. Furthermore, the model validations indicated that the models were accurate (Figure 3).

As an extended-spectrum antimicrobial agent, piperacillin/tazobactam has demonstrated efficacy against most organisms

involved in intra-abdominal infection and is widely used for this indication. Piperacillin displays concentration-independent pharmacodynamic activity, whereby maintaining concentrations above the MIC during the dosing interval correlates best with bacterial killing. Compared with intermittent infusion, the use of continuous infusion may be a more efficient means to maximize the time above MIC and to improve efficacy. The predicted free piperacillin concentration (mean ± standard deviation) administered by continuous infusion for all patients (n = 130) who received this regimen in the clinical trial was 27.1 ± 6.8 mg/L (range: 14.5–47.3 mg/L). Piperacillin penetration into abdominal tissues is excellent, and the absolute concentration of piperacillin in the appendix can reach 26.5 μg/g.[22] The current breakpoints of piperacillin/tazobactam for susceptible *Staphylococcus*, *Bacteroides*, Enterobacteriaceae and *Pseudomonas aeruginosa* are ≤8/4, ≤16/4, ≤16/4 and ≤64/4 mg/L according to NCCLS guidelines.[23] Although the breakpoint for *Pseudomonas* is 64/4 mg/L for piperacillin/tazobactam, the majority of isolates nationally have lower MICs, in the range of 4/4–8/4 mg/L.[24,25] Under these circumstances, piperacillin/tazobactam (12/1.5 g) by 24 h continuous infusion appears to provide sufficient drug exposure to ensure clinical success with this dosing technique. Moreover, successful clinical outcome via continuous infusion of piperacillin/tazobactam was observed by our previously published study, in which a 94% clinical success rate and 89% microbiological success rate were achieved in patients with a variety of infections including respiratory traction infections, intra-abdominal infections, and skin and soft tissue infections.[12]

During the pharmacodynamic evaluation, we could not identify any significant breakpoint of PK-PD exposure indexes to predict the clinical or bacteriological outcomes. This was probably due to the small number of failures (<11%) in our study population and the low MICs for causative pathogens that were collected. For time-dependent β-lactams, t > MIC is the most important pharmacodynamic parameter to predict antimicrobial efficacy. It has been demonstrated in animal studies that bacterial killing can reach the maximum plateau as t > MIC is larger than 50%.[26] For continuous infusion, the t > MIC values for unbound piperacillin in all 45 patients were 100%. For intermittent infusion, the median t > MIC for unbound piperacillin was 95.01%; and with the exception of one patient, all achieved greater that 50% t > MIC. Further evaluation of piperacillin/tazobactam concentration–effect relationships in the clinical setting is needed and this population model should be useful in predicting exposures for larger numbers of patients who have evaluable MIC data.

In summary, population pharmacokinetic models were developed for piperacillin and tazobactam administered via continuous infusion and intermittent infusion to hospitalized patients with complicated intra-abdominal infection. Creatinine clearance and body weight were identified as significant covariates influencing the pharmacokinetics of piperacillin and tazobactam. The infusion type did not change the pharmacokinetics of piperacillin and tazobactam. The final models were validated via Monte Carlo simulation and showed accurate predictive performance. In addition, the predicted unbound piperacillin concentrations for patients receiving continuous infusion in the clinical trial indicate that continuous infusion provides sufficient drug exposure to treat those pathogens commonly implicated in intra-abdominal infections. As a result of a small number of clinical or bacteriological failures along with high drug exposures, no significant PD breakpoint could be identified to predict clinical or bacteriological outcome. We conclude that intermittent and continuous infusion of piperacillin and tazobactam provide sufficient drug exposures to treat those pathogens commonly implicated in intra-abdominal infections.

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