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CLINICAL TRIAL

Population pharmacokinetics of piperacillin/tazobactam in neonates and young infants

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Abstract
Objectives To develop population pharmacokinetic (PK) models for piperacillin/tazobactam in neonates and infants of less than 2 months of age in order to determine the appropriate dosing regimen and provide a rational basis for the development of preliminary dosing guidelines suitable for this population.
Methods A two-stage, open-label study was conducted in neonates and infants less than 2 months of age in the neonatal intensive care unit (NICU). A total of 207 piperacillin and 204 tazobactam concentration–time data sets from 71 patients were analyzed using a nonlinear mixed-effect modeling approach (NONMEM VII). PK models were developed for piperacillin and tazobactam. The final models were evaluated using both bootstrap and visual predictive checks. External model evaluations were made in 20 additional patients.
Results For neonates and young infants less than 2 months of age, the median central clearance was 0.133 and 0.149 L/h/kg for piperacillin and tazobactam, respectively. Postmenstrual age (PMA) was identified as the most significant covariate on central clearance of piperacillin and tazobactam. However, the combination of current bodyweight (BW) and postnatal age proved to be superior to PMA alone. BW was the most important covariate for apparent central volume of distribution. Both internal and external evaluations supported the prediction of the final piperacillin and tazobactam PK models. The dosing strategy 44.44/5.56 mg/kg/dose piperacillin/tazobactam every 8 or 12 h evaluated in this study achieved the pharmacodynamic target (free piperacillin concentrations >4 mg/L for more than 50 % of the dosing interval) in about 67 % of infants.
Conclusions Population PK models accurately described the PK profiles of piperacillin/tazobactam in infants less than 2 months of age. The results indicated that higher doses or more frequent dosing regimens may be required for controlling infection in this population in NICU.

Keywords Piperacillin/tazobactam · Population pharmacokinetics · Neonate · t > MIC

Introduction

Piperacillin/tazobactam, an injectable antibacterial combination consisting of the semisynthetic piperacillin sodium and the β-lactamase inhibitor tazobactam sodium, has been indicated for the treatment of moderate to severe infections, including *Pseudomonas aeruginosa* infections [1], complicated urinary tract infections [2], complicated skin and soft tissue infections [3], complicated intra-abdominal infection [4], and severe sepsis and septic shock [5]. Piperacillin/tazobactam has been approved for the treatment of pediatric patients (age 2 months to 17 years) in the USA [6]. Tornøe et al. conducted a pharmacometric analysis to evaluate appropriate dosing regimens for pediatric patients as young as

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2 months [7], but to date there are no data on which to base additional recommendations for pediatric patients younger than 2 months. In addition, there is no published description of piperacillin/tazobactam pharmacokinetics (PK) in neonates and young infants less than 2 months of age using population-based techniques. Previous data suggest that the protein-binding capacities of piperacillin and tazobactam are approximately 20 to30 % and 20 to23 %, respectively. Both piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion [8]. The antibacterial activity of piperacillin is related to the time that the free drug concentration exceeds the minimal inhibitory concentration (MIC) of the infecting pathogen (f%T >MIC%, where f is the the free drug fraction and T is time) during a dosing interval. Data on the T >MIC% required for optimal activity for β-lactams has been obtained from dynamic in vitro and in vivo animal models and suggest that an f%T >MIC% of approximately 50 % of the dosing interval for Gram-negative bacteria is necessary [9–11]. Piperacillin MIC_{50} values of extended-spectrum beta-lactamase (ESBL) *Escherichia coli* and *Pseudomonas aeruginosa* in the Asia-Pacific region are 4 and 8 mg/L, respectively [12]; the MIC_{50} value of ESBL-producing *Klebsiella pneumoniae* is 32 mg/L global [13].

Children differ significantly from adults in the way they dispose of and respond to drugs. Pharmacodynamic and PK parameters also vary as children grow from neonates through to adolescence. The importance of medication efficacy and safety in neonates and young infants has been gaining increasing attention in the past decades with the realization that neonates and young infants are not “little adults.” Postnatal anatomical, physiological, and psychological developments make it hard to these patients by just scaling adult doses on the basis of their age, weight, or body surface area [14]. Atypical or indirect responses may occur in newborns [15], and premature birth can complicate treatment even more. A knowledge of PK and PD parameters in neonates and young infants is significantly important to maximize the clinical utility and reduce antimicrobial resistance.

We therefore designed and conducted a two-stage, open-label clinical trial in the neonatal intensive care unit (NICU) with the objective of developing population PK models for piperacillin/tazobactam to provide the appropriate dosing regimen and a rational basis for the development of preliminary dosing guidelines suitable for use in neonates and infants younger than 2 months.

Methods

Study design

At stage 1, a total of 71 patients receiving antimicrobial therapy for suspected or confirmed bacterial infection were enrolled in the study, including 46 newborns and 25 young infants. Newborns were stratified into 4-week periods based on gestational age at birth (GA) between 24 and 43 weeks, and the target recruitment was approximately 8–12 patients per 4-week period. Each patient was enrolled to receive piperacillin/tazobactam (Bangda®; Qilu Pharmaceutical, Jinan, China; each glass vial contains 1.0 g of piperacillin sodium and 0.125 g of tazobactam sodium) 44.44/5.56 mg/kg/dose, every 12 h. For neonates and infants with severe infection, the dosing interval could be decreased to 8 h based on the decision of the attending physician. A small number of samples (n=3) were drawn for each patient on day 1 (first dose) or the day when steady state concentrations were reached. A population PK model was established to investigate piperacillin/tazobactam PK parameters and their variability estimates in this population.

At stage 2, according to the preliminary population PK model, a simulation was conducted to determine the optimal dosing regimen in this population with similar characteristics. The simulated optimal dosing regimen was evaluated in an additional 20 neonates and young infants.

Patients and data collection

Data were collected from neonates and young infants in the NICU at Children’s Hospital of Fudan University. Inclusion criteria included an age of <61 days, sufficient intravascular access (either peripheral or central) to receive the study drug, suspected or confirmed bacterial infection that necessitated treatment with piperacillin/tazobactam as part of the standard of care following the decision of the attending physician. Participants were excluded for the following conditions: (1) so severely ill that they were not likely to survive the duration of the trial (at least 8 days), (2) history of allergic reactions to any penicillin, cephalosporin, or beta-lactamase inhibitor, (3) hepatic dysfunction, as evidenced by aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels of ≥90th percentile for corrected postmenstrual age (PMA) [16], (4) renal dysfunction, as evidenced by a serum creatinine (Scr) level of ≥90th percentile for infants with PMA of <28 weeks [17] and ≥28 weeks [mean+3 standard deviations (SD)] for other gestational ages [18, 19], (5) having received a systemic investigational drug or (6) having any condition which in the opinion of the investigator made the subject unsuitable for enrollment. The study protocol was approved by the Ethics Committee of Children's Hospital of Fudan University. All study participants were enrolled after obtaining written permission (informed consent) from each child’s parents or legal guardians.

The following demographic factors were collected for all patients on enrollment: gender (SEX), gestational age (GA), postnatal age (PNA),PMA, birth body weight (BBW), body weight (BW), height (HT), body surface area [BSA: BW

$(kg)^{0.5378} \times HT(m)^{0.3964} \times 0.024265)$] [20], serum creatinine (Scr), creatinine clearance rate [CLcr: Schwartz CLcr (mL/min/1.73 m^2)=k × HT (cm)/Scr (mg/dL), where k=0.45 for term infants throughout the first year of life] [21], and concomitant drug therapy.

Patients who met inclusion/exclusion criteria were assigned to receive piperacillin/tazobactam. The drug was reconstituted with 0.9 % sodium chloride for injection and was further diluted to a total volume of 2 ml. The study drug was infused intravenously over 5 min by a nurse by using a calibrated syringe. Immediately following infusion of the study drug, the intravenous infusion tubing was flushed with 2 ml of 0.9 % sodium chloride to ensure administration of the total dose. Patients were divided into four groups according to the dosing scheme, and sampling times are shown in Table 1. Blood (0.5 ml) was collected in disposable syringes and was transferred immediately into heparinized tubes. After gentle infusion, blood samples were centrifuged, separated, and frozen at −70°C until the time of analysis.

HPLC/MS/MS analysis

Piperacillin and tazobactam concentrations were simultaneously determined by a liquid chromatography/tandem mass spectrometry (LC/MS/MS) system consisting of an API 3000 mass spectrometer (Applied Biosystems, Foster City, CA) equipped with a turbo ion spray source in the electro-spray positive ion mode (ESI^+) and a chromatographic Shimadzu 20A system (Shimadzu, Kyoto, Japan) consisting of two LC-20 AD pumps, a vacuum degasser, a SIL-HTC autosampler, and a controller module. The concentration ranges of standard curves were approximately 0.1–10 mg/L for piperacillin and 0.03–3 mg/L for tazobactam. There were duplicates of four quality controls, including for the LLOQ (lower limit of quantification) for each standard curve to ensure assay accuracy and precision. The intra- and inter-day accuracy of piperacillin was approximately 95.8–103.7 % and 94.9–104.4 %, respectively. The intra- and inter-day accuracy of tazobactam was approximately 93.7–97.5 % and 88.9–99.8 %, respectively. The coefficient variations of the intra- and inter-assays for total piperacilln were less than 10 and 7.3 %, respectively; for tazobactam, these were less than 5.3 and 5 %, respectively. The concentrations of the unknown samples above the qualification limits were prediluted with tested drug-free human serum [22].

Table 1 Dosing scheme and sampling times of piperacillin/tazobactam

Interval	Group	Day	Sampling times[a]		
q12h	A	1 (first dose)	T0.5 h	T3 h	T8 h
		5	T0.5 h	T3 h	T8 h
	B	1 (first dose)	T1 h	T6 h	T12 h
		5	T1 h	T6 h	T12 h
q8h	C	1 (first dose)	T0.5 h	T3 h	T6 h
		5	T0.5 h	T3 h	T6 h
	D	1 (first dose)	T1 h	T4 h	T8 h
		5	T1 h	T4 h	T8 h

q, Each day

[a] The T0.5 h sample was taken within 3 min after the end of the infusion. The T12h sample was taken just before the next dose. To ensure that the samples provided accurate data, additional samples were required within a 20-min interval of the allocated sampling time (10 min before or after sampling)

PK analysis

Data analysis was performed with the NONMEM program (ver. VII; Icon Development Solutions, Ellicott City, MD) in conjunction with Wings for NONMEM. The first order conditional estimation (FOCE) method with the interaction option was used to estimate PK parameters and their variability. One- and two-compartment models were employed as the PK base model, respectively. The one-compartment PK parameters were clearance (CL) and apparent volume of distribution (V). The two-compartment PK parameters were central clearance (CL), apparent central volume of distribution (V_1), inter-compartmental clearance (Q), and apparent peripheral volume of distribution (V_2). The initial parameters were obtained by the $ESTIMATION of NONMEM according to the literature.

The demographic factors obtained for PK parameters were used to perform an initial selection of covariates. The selection was carried out by plotting the parameter estimates against demographic factors and then retaining those with statistical significance (P <0.05) as initial covariates. In the case of continuous covariates (GA, PNA, PMA, BBW, BW, HT, BSA, Scr, CLcr), the statistical significance of the PK parameters was evaluated by means of the correlation coefficient, whereas in the case of categorical covariates (SEX, concomitant drug therapy), Student's t-test was applied. Continuous covariates were separately implemented in the model, using an allometric equation:

$$P_i = P_P \cdot (Cov/Cov_{Median})^k$$

where P_i represents the individual parameter estimate of the ith subject, P_p represents the population parameter estimate, Cov is the covariate, and k is the exponent. If weight was included in the PK base model, parameter values were standardized for a body weight of 70 kg using an allometric model:

$$P_i = P_{std} \cdot (Wi/70)^{PWR}$$

where P_i represents the individual parameter estimate of the ith subject, P_{std} represents the individual parameter estimate with a

body weight of 70 kg, and W_i represents the body weight of the *i*th subject. Allometric scaling has a strong theoretical and empirical basis with a PWR exponent of 0.75 for clearance parameters (CL and Q) and 1 for volume parameters (V_1 and V_2). Categorical covariates were included using a category variable equation. The selection of covariates was determined using a forward selection process and a backward elimination process. During forward selection, any covariate that reduced the objective function value by >3.84 (P <0.05, χ^2 distribution with 1 *df*) was considered to be significant and added to the model. A full model was constructed with all statistically significant covariates included. The importance of each covariate was then re-evaluated by backward elimination. Each covariate was independently removed from the model one at a time to identify its relevance. An increase in the objective-function value (OFV) of >10.83 (P <0.001, χ^2 distribution) was required for confirmation. When two or more covariates were found to significantly improve the model, the covariate causing the largest reduction in the OFV was left in the model. The resulting model was called the final model and included all significant covariates that cannot be eliminated from the full model.

The residual variability was evaluated with additive, proportional, and combined residual error models, respectively.

Model evaluation

The goodness of fit was evaluated by using several diagnostic scatter plots as follows: (1) observed versus population predicted concentrations (DV vs. PRED); (2) observed versus individual predicted concentrations (DV vs. IPRED); (3) conditional weighted residuals versus time (CWRES vs. TIME); (4) conditional weighted residuals versus population predicted concentrations (CWRES vs. PRED).

The stability of the final model was assessed by means of an internal validation method involving a non-parametric bootstrap. Re-sampling of the dataset was repeated 1,000 times using NONMEM in the final model. The values of estimated parameters, such as the median and standard error (SE) from the bootstrap procedure were compared with those estimated from the original dataset. It could be proved that the model was stable if the values of parameters were not significantly different. The 95 % confidence intervals (CIs) were obtained as the point estimate±1.96 × SE of the estimate.

A visual predictive check (VPC) was performed to evaluate the predictive performance of the model. One thousand datasets were simulated based on the final model. The observed concentration versus time data was graphically overlaid with the median values along with the 5th and 95th percentiles from the simulated data profiles. The model was deemed precise if the observed concentration data were appropriately approximately distributed within the 5th to 95th prediction interval.

To perform an external evaluation for the final piperacillin/tazobactam two-compartment model, we enrolled an additional 20 neonates and infants in the study. Each patient was simulated 1,000 times according to the final piperacillin model to determine the optimal dosing regimen by NONMEM. The population-predicted piperacillin/tazobactam concentrations were compared to the observed piperacillin/tazobactam concentrations, and the predictive performance of the final models was evaluated by means of precision and bias. The median prediction error (MDPE), median absolute prediction error (MDAPE), and BIAS were used as measures of precision and bias. These are calculated by using the following equations:

$$MDPE = median\{(Obs_i - \Pr ed_i)/\Pr ed_i, i = 1, \cdots, n\}$$

$$MDAPE = median\{|Obs_i - \Pr ed_i)/\Pr ed_i|, i = 1, \cdots, n\}$$

$$BIAS = \frac{1}{N}\sum_{i=1}^{N}(Obs_i - \Pr ed_i)/\Pr ed_i$$

where Obs_i represents the observed concentration of the ith subject, and $Pred_i$ represents the population-predicted concentration of the ith subject. MDPE and MDAPE are expressed in the results as a percentage by multiplying by 100.

Assessment of PD target

The final model was used to simulate concentrations to evaluate whether the optimal piperacillin (the determinate component of this combination) f%T >MIC% had been obtained when the original dosing regimen was applied. One hundred serum piperacillin concentration datasets were generated after half of the dosing interval on day 1 and one-half on the day when steady state concentrations were reached for virtual neonates and young infants with characteristics similar to those observed for the study patients. A piperacillin MIC_{50} value of ESBL *E. coli* in the Asia-Pacific region of 4 mg/L [10] was chosen as a representative value. The level of unbound piperacillin was set at 70 % [6].

To explore the appropriate dosing regimen, we performed additional simulations using NONMEM based on 1,000 patients to evaluate 10, 20, 40, 60, 80, and 100 mg/kg doses administered every 6, 8, or 12 h in neonates and young infants with a BW of approximately 0.5–5 kg and a PNA of approximately 1–60 days. As the safety of piperacillin in the treatment of infections of neonates and young infants of less than 2 months of age was unknown, 100 mg/kg piperacillin was restricted

Table 2 Characteristics of patients

Characteristic[a]	Mean (±SD)	Median	Range[b]
GA (week)	35.51 (3.81)	36.04	26.03~41.07
PNA (day)	14.39 (13.95)	6	1~56
PMA (week)	37.46 (4.95)	39	26.06~45.03
BBW (kg)	2.58 (0.88)	2.62	1~4.2
BW (kg)	2.76 (1)	2.78	0.93~4.72
HT (cm)	47.36 (4.74)	48	36~56
BSA (m^2)	0.19 (0.05)	0.19	0.10~0.26
CLcr (L/h)	0.692 (0.389)	0.641	0.106~1.835
Scr (μM/L)	41.7 (25.3)	35	12~178

SD, Standard deviation

[a] GA, Gestational age; PNA, postnatal age; PMA, postmentrual age; BBW, birth body weight; BW, body weight; HT, height; BSA, body surface area; CLcr, creatinine clearance rate; Scr, serum creatinine

[b] Ranges are approximate values

as the maximum dosage in our trial. For purposes of the simulations, the dosing regimens of a PD target of 50 % f%T >MIC was established in >95 % of neonates and young infants younger than 2 months.

Results

Data analysis

The characteristics of the 71 patients enrolled in the study are presented in Table 2. The final PK database consisted of 207 piperacillin concentrations and 204 tazobactam concentrations. Individual piperacillin and tazobactam concentration plots (concentration versus time) are shown in Fig. 1.

Population PK modeling

Preliminary analysis for the base model showed that the OFV of one- and two-compartment models were 1316.620 and 1282.748 for piperacillin, and 452.264 and 412.968 for tazobactam, respectively. Thus, a two-compartment model resulted in a better fit to describe piperacillin and tazobactam

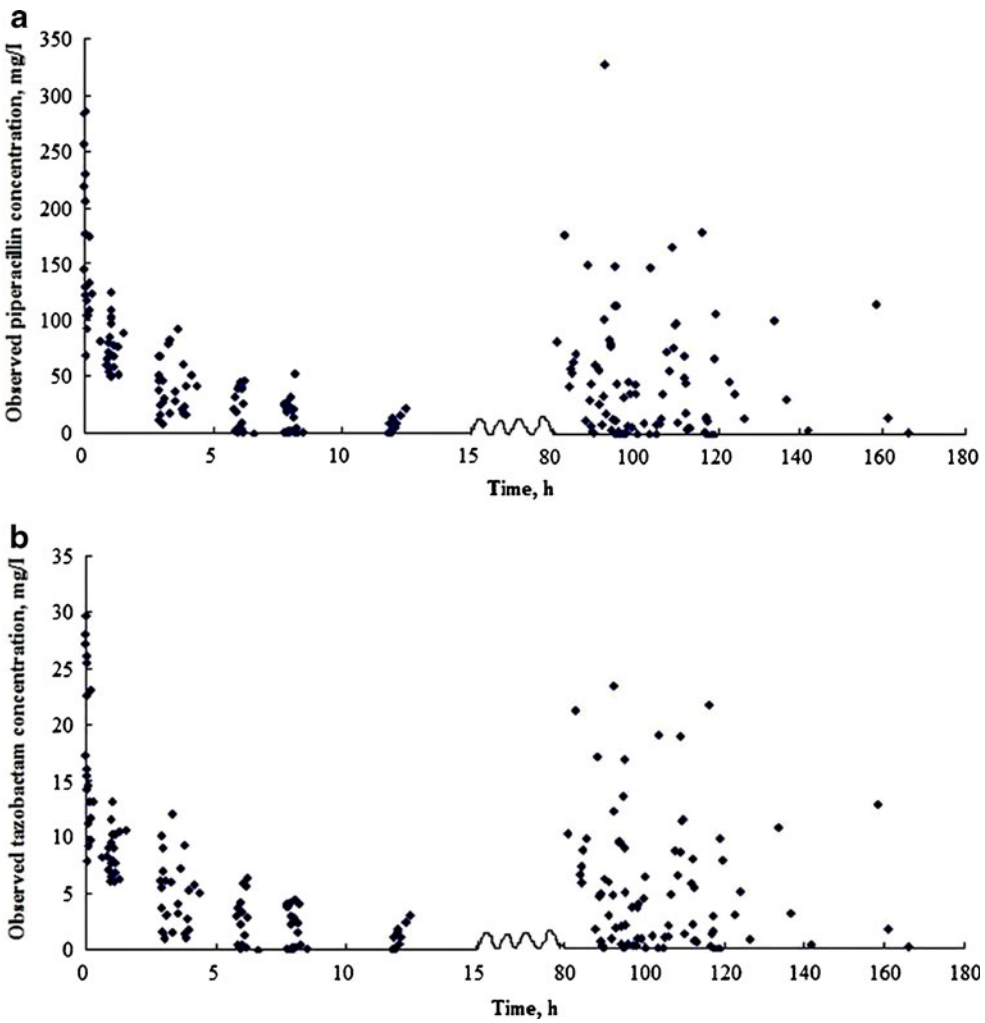

Fig. 1 Individual piperacillin and tazobactam concentration plots

concentrations. Residual variability was best described by a proportional model.

During the procedure for determining the covariates for the model, each covariate that may affect the inter-individual variation was analyzed. As many weight-related covariates were highly correlated in this population, weight was a priori determined to be descriptor included into the model before confirming other weight-related covariates. The inclusion of BW, PNA to CL of piperacillin/tazobactam, and BW to V_1 of piperacillin/tazobactam produced the most significant decrease in the OFV and inter-individual variances of the PK parameters. For piperacillin, the OFV was 1116.897, and the between-subject variance (BSV_S) for CL and V_1, and η_{CL} and η_{V1} decreased from 0.83 to 0.34 and from 0.41 to 0.21, respectively, with the inclusion of BW in the base model. For tazobactam, the OFV was 234.835, and η_{CL} and η_{V1} decreased from 0.85 to 0.35 and from 0.34 to 0.20, respectively. Given the strong physiological basis, allometric scaling was explored as potential covariates for the model. However, no improvement was observed in model fit when exponents for weight were fixed at 0.75 and 1 for clearance parameters (CL and Q, respectively) and at 1 for volume parameters (V_1 and V_2, respectively). The OFV were 1201.593 and 312.297 for piperacillin and tazobactam, respectively. For piperacillin, η_{CL} and η_{V1} decreased from 0.83 to 0.63 and from 0.41 to 0.33, respectively; for tazobactam, η_{CL} and η_{V1} decreased from 0.85 to 0.67, and from 0.34 to 0.21, respectively. Therefore, we insisted on the previous covariates in the model. Further investigation of PNA on CL showed a similar decrease of CL as a function of PNA; the η_{CL} of piperacillin and tazobactam decreased from 0.34 to 0.16, and from 0.35 to 0.16, respectively.

The final population PK models for the disposition of both piperacillin and tazobactam were therefore the base model that included BW and PNA as covariates. The OFV of the final models were 1048.767 and 144.293 for piperacillin and tazobactam, respectively. The final population PK parameter estimates for piperacillin and tazobactam are given in Tables 3 and 4.

Model evaluation

Diagnostic plots for the final models of piperacillin and tazobactam showed a good model fit (Fig. 2). The results of 1,000 bootstrap replicates for piperacillin/tazobactam are summarized in Tables 3 and 4. The number of runs successfully converged was 993 for piperacillin and 994 for tazobactam. The median parameter estimates from the bootstrap procedure were very close to the values of the final population model. In addition, the parameters from the bootstrap procedure followed a normal distribution and contained all of the parameter estimates from the final population model. The results indicate that the estimates for the population PK parameters in the final model were precise and that the model was stable. The VPC of piperacillin/tazobactam is given in Fig. 3. During the procedure, 1,000 datasets on day 1 were simulated to assess the predictive performance of the

Table 3 Parameter estimates of the piperacillin final model and bootstrap validation

Parameter	Final model		Bootstrap n=1,000	
	Population estimate	RSE (%)	Median	95 % CI
Central clearance (L/h): $CL = \theta_1(BW/2.76)^{\theta5}(PNA/6)^{\theta6}$				
θ_1	0.369	3.7	0.368	0.341~0.396
θ_5	1.44	6.4	1.44	1.25~1.63
θ_6	0.271	8.7	0.272	0.22~0.32
Central volume of distribution (L): $V_1 = \theta_2(BW/2.76)$				
θ_2	0.742	9.3	0.731	0.584~0.858
Inter-compartment clearance: $Q = \theta_3$				
θ_3	1.11	48.0	1.12	0.535~3.31
Peripheral volume of distribution distribution distribution: $V_2 = \theta_4$				
θ_4	0.269	22.7	0.275	0.181~0.411
Inter-individual variability (%)				
CL	17.9	19.8	17.5	13.7~21.5
V_1	20.8	38.6	20.4	4.99~28.1
Residual error model (%)				
Proportional	26.9	22.1	9.1	6~15.9

RSE, Relative standard error; CI, confidence interval

Table 4 Parameter estimates of tazobactam final model and bootstrap validation

Parameter	Final model		Bootstrap n=1,000	
	Population estimate	RSE (%)	Median	95 % CI
Central clearance (L/h): $CL = \theta_1(BW/2.76)^{\theta5}(PNA/6)^{\theta6}$				
θ_1	0.414	3.5	0.413	0.382~0.44
θ_5	1.47	6.1	1.47	1.28~1.66
θ_6	0.316	7.9	0.317	0.264~0.37
Central volume of distribution (L): $V_1 = \theta_2\ (BW/2.76)^{\theta7}$				
θ_2	0.803	10.0	0.797	0.621~0.973
θ_7	1.22	10.3	1.23	0.0138~1.56
Inter-compartment clearance: $Q = \theta_3$				
θ_3	2.2	28.0	2.22	1.06~3.91
Peripheral volume of distribution: $V_2 = \theta_4$				
θ_4	0.391	17.6	0.397	0.26~0.535
Inter-individual variability (%)				
CL	16.1	22.5	15.7	10.5~19.3
V_1	20.3	42.6	20.3	7.55~34.7
Residual error model (%)				
Proportional	26.2	23.9	10	6.96~15.7

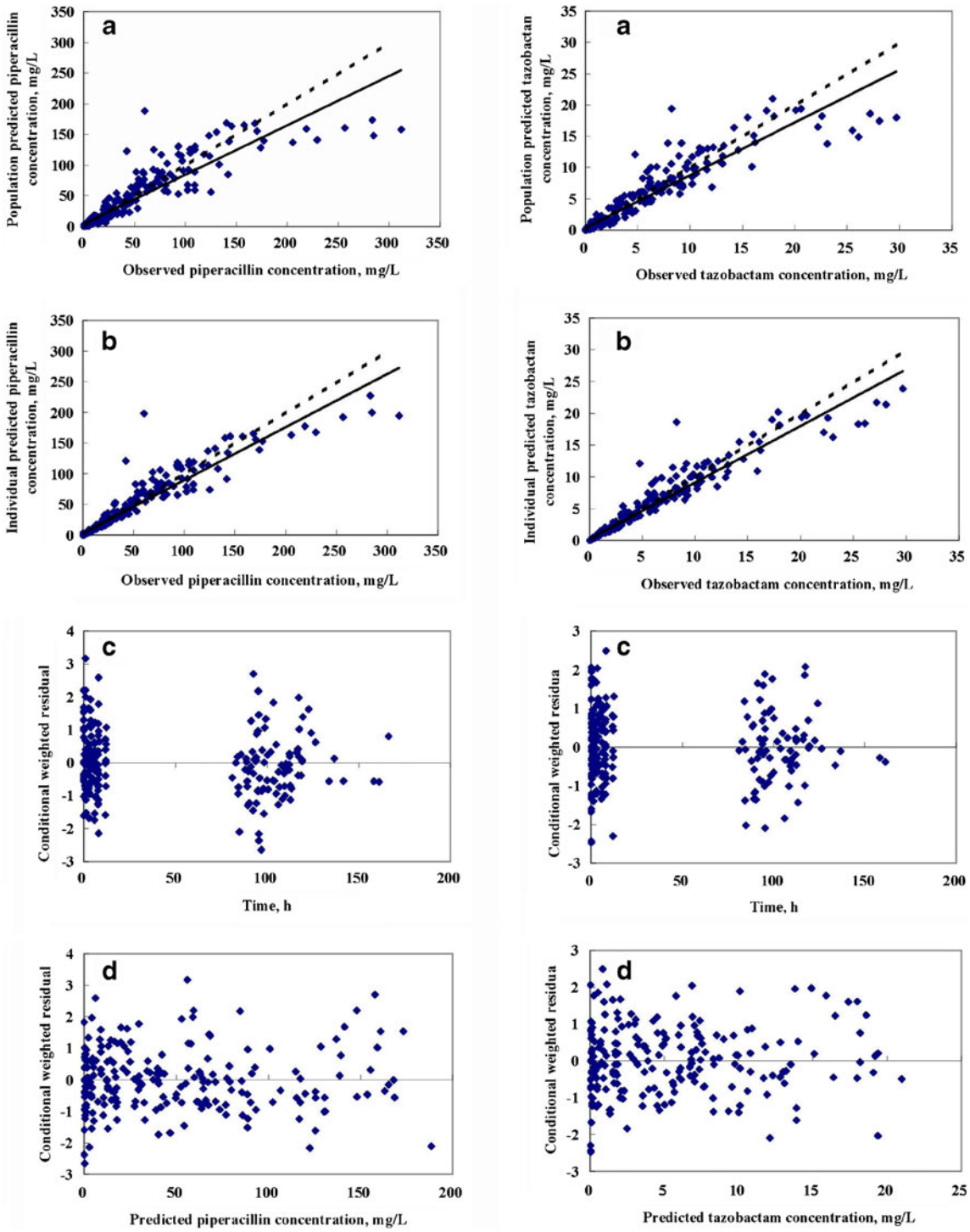

Fig. 2 Diagnostic scatter plots for piperacillin (*left*)/tazobactam (*right*) final model. **a** Population-predicted versus the observed concentration. **b** Individual-predicted versus the observed concentration. **c** Conditional weighted residual versus time. **d** Conditional weighted residual versus the predicted concentration

model. This visual internal validation of the model showed that approximately 90 % of data fit well within the 5th to95th percentiles of simulation (Exact Binomial Test,1.68 % out of limits observed, 95 % CI 0.204–5.94) and were symmetrically distributed (Pearson's chi-square test, χ^2=9.67, *df* =3, *P*value=0.02) for piperacillin. For tazobactam, 90 % of data fit well within approximately the 5th to95th percentiles of simulation (Exact Binomial Test, 2.5 % out of limits observed, 95 % CI 0.527–7.25) and were symmetrically distributed (Pearson's chi-square test, χ^2=11.84, *df*=3, *P* value=0.008).

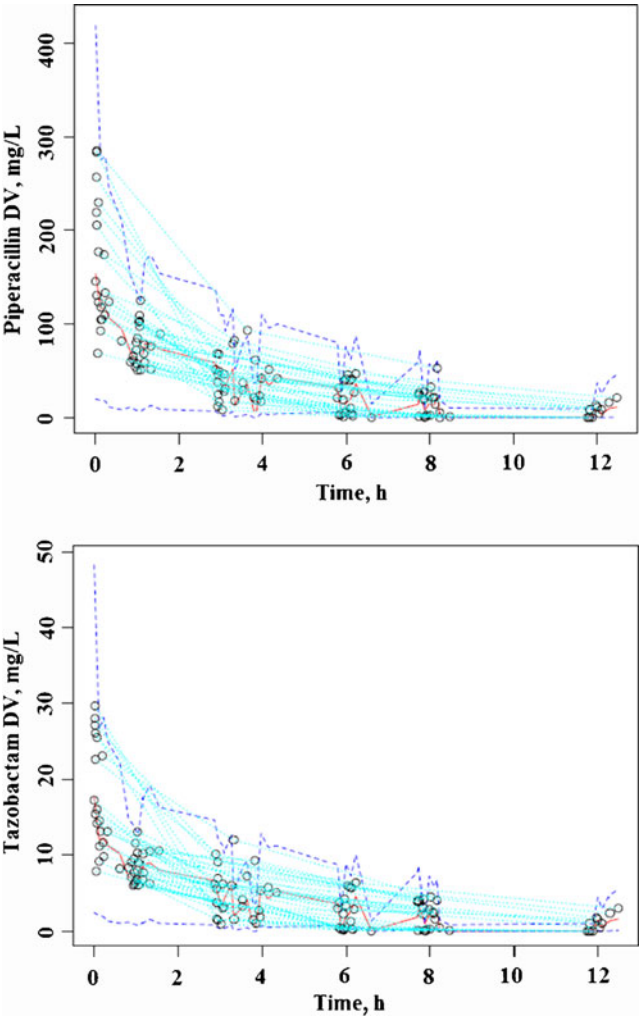

Fig. 3 Piperacillin (*above*)/tazobactam (*below*) visual predictive check (VPC). *Upper and lower dashed lines* 5th and 95th percentiles of simulations, respectively, *median solid lines* 50th percentile of simulations. *DV* Observed concentration

The optimal dosing regimen was determined by simulations according to the final piperacillin model and infections caused by pathogens for each of the additional 20 neonates and infants less than 2 months of age. In the simulation, the most significant covariates of individual BW and PNA were used to calculate the dosing recommendation. The external evaluation suggested that the final models accurately characterized the PK profiles of piperacillin and tazobactam in the population. Plots of population-predicted piperacillin/tazobactam concentrations versus observed concentrations are shown in Fig. 4. The validation of the final model is given in Table 5. As can be seen, MDPE, MDAPE, and BIAS were low for both piperacillin and tazobactam, indicating a satisfactory prediction error and good precision.

Assessment of PD target

The dosing strategy evaluated in this study achieved the PD target (free piperacillin concentrations of >4 mg/L for more than 50 % of the dosing interval) in about 67 % of infants. Furthermore, a more frequent dosing regimen may be more successful in patients administered the same dose, i.e., about 76 % of these infants achieved the target concentration if they received piperacillin/tazobactam every 8 h, while only 63 % of them achieved the target concentration when the dosing interval was increased to 12 h. Piperacillin dosage simulations against ESBL *E. coli* in the Asia-Pacific region were performed for this population (BW range approx. 0.5–5 kg; PNA range approx. 1–40 days). The results of simulations for developing the appropriate dosing regimen are illustrated in Table 6.

Discussion

In a previous PK study conducted in patients aged 2 months to 12 years receiving a single dose of 50/6.25 mg/kg or 100/12.5 mg/kg of piperacillin/tazobactam, the estimated non-compartmental PK parameters (mean ± SD) in young infants approximately 2–5 months were a mean clearance of 0.198± 0.048 L/h/kg for piperacillin and 0.198±0.042 L/h/kg for

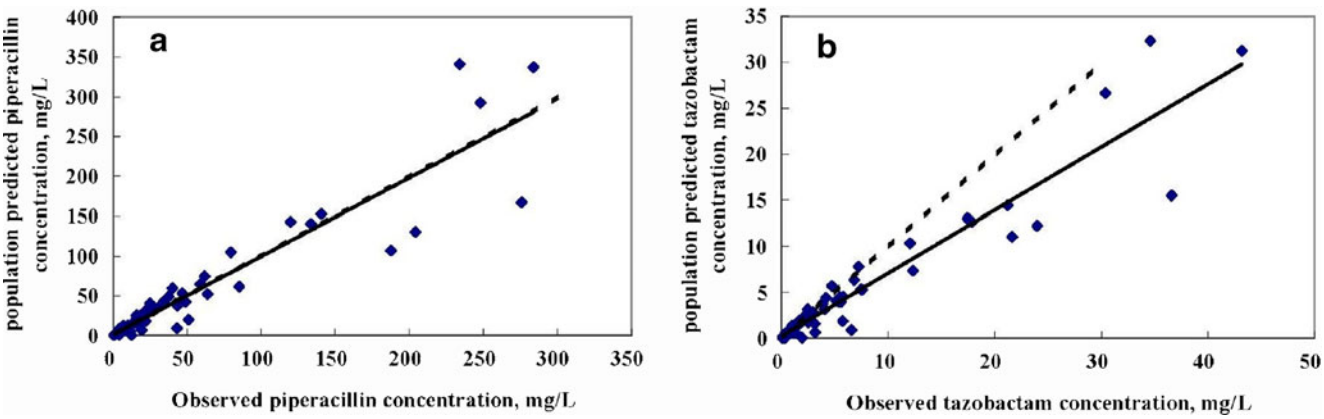

Fig. 4 Population-predicted piperacillin (*left*)/tazobactam (*right*) concentration versus observed piperacillin/tazobactam concentration

Table 5 Validation analysis of the final model

Validation parameters	Piperacillin	Tazobactam
Median predition error (MDPE)%	−12 %	22 %
Median absolute predition error (MDAPE)%	23 %	26 %
BIAS	0.87	1.51

tazobactam [23]. Tornøe et al. developed equations to calculate dosing recommendations for paediatric patients as young as 2 months of age [7]. In our study, piperacillin and tazobactam were well described by two-compartment models. For neonates and young infants (PNA <2 months), the median clearance was 0.133 L/h/kg for piperacillin and 0.149 L/h/kg for tazobactam. The central clearance values for piperacillin and tazobactam decreased to approximately two thirds and three quarters of the respectively values in patients less than 2 months of age compared to young infants approximately 2–5 months of age. Although the precise mechanism underlying the decrease in piperacillin and tazobactam clearance has not been clarified, it might be explained by the immature development of renal function in the younger study group.

Tornøe et al. investigated the influence of demographic covariates of body weight and age on CL in patients aged 2 months to 12 years by non-linear regression [7]. In our study, additional demographic covariates that may influence the PK behavior of the drug were investigated by NONMEM. To our knowledge, no previous studies have assessed the influence of patient covariates on the PK profiles of piperacillin/tazobactam in neonates and infants younger than than 2 months, and no covariate models have been proposed for these patient groups and drugs. During the selection of covariates, most of the demographic covariates showed a statistically significant effect on the CL of piperacillin/tazobactam when they were individually tested, and the greatest decrease in the OFV was obtained with PMA. This result was in accordance with the initial stratification based on the GA; however, with the incorporation of other covariates, piperacillin/tazobactam clearance was best described by a combination of BW and PNA. This may be partly explained by the fact that size parameters, such as BW, were frequently highly correlated with other development- or maturation-related parameters, such as PMA in pediatric PK data sets. Furthermore, allometric size adjustments using the fixed allometric coefficient of 0.75 for clearance terms have repeatedly been used in pediatric PK analyses and have especially been reported in more recent publications [24, 25]. However, careful consideration had to be given to the fact that allometric scaling may not hold for all of the studied populations, and concerns have been raised recently about the values used for allometric coefficients [26]. Hu et al. suggested an exponent of 0.75 for the clearance of drugs that were eliminated mainly by metabolism or by metabolism and excretion combined [27]. In our study, after the identification of the appropriate base model, BW with an allometric exponent of 0.75 for CL or Q and an exponent of 1 for V_1 or V_2 were used as

Table 6 Percentage of 1,000 simulated neonates and young infants less than 2 months of age who achieved antibiotic exposure against ESBL *Escherichia coli* (Asia-Pacific region)

BW (kg)[a]	Dosage of piperacillin (mg/kg)	50 %T >MIC				
		PNA (days)				
		1~5 (3)[a]	5~10 (7)	10~20 (15)	20~30 (25)	30~40 (35)
0.5~2 (1)	10	q8h 95 %[b]	–	–	–	–
	20	q12h 99 %	q8h 99 %	q8h 99 %	q8h 98 %	q8h 97 %
2~3 (2.5)	40	q8h 97 %	–	–	–	–
	60	q8h 100 %	q8h 98 %	–	–	q6h 94 %
	80	q12h 96 %	–	q8h 96 %	–	q6h 98 %
	100	q12h 99 %	–	q8h 98 %	q8h 94 % q6h 99 %	q6h 94 %
3~4 (3.5)	60	q8h 94 %	–	–	–	–
	80	q8h 98 %	–	–	–	–
	100	–	q8h 94 %	q6h 98 %	q6h 92 %	–
4~5 (4.5)	100	q6h 99 %	q6h 97 %	–	–	–

ESBL, Extended-spectrum beta-lactamase

f%T >MIC%, Antibacterial activity is related to the time that the free drug concentration exceeds the minimal inhibitory concentration (MIC) of the infecting pathogen where f is the the free drug fraction and T is time) during a dosing interval

[a] The number in the parenthesis is a representative for the range involved in the simulation

[b] q = daily; 6/8/12 h = dosing interval; % = proportion of patients achieving the target antibiotic exposure

covariate models, but no greater decrease in the objective function was observed. The disposition characteristics defined for tazobactam were very similar to those for the behavior of piperacillin, indicating a compatible match for the combination.

In terms of concomitant therapy, it has been reported that the administration of probenecid prolongs the half-life of piperacillin by 21 % and that of tazobactam by 71 % [6]. In our study, the majority of patients were treated with a single antibiotic (the study drug piperacillin/tazobactam). Furthermore, during the selection of covariates, no other drug was retained as a significant covariate in the final model.

Integrating the concept of time above the MIC with the piperacillin/tazobactam population PK model generated in our study provided a rational basis for the development of preliminary dosing guidelines to neonates and infants less than 2 months of age. The results indicate that a dose of 44.44/5.56 mg/kg every 8 or 12 h may be not enough for controlling infection in neonates and infants less than 2 months of age in the NICU. They also revealed that higher doses or more frequent regimens may be required for this population and are likely to achieve the target concentration.

Simulations using NONMEM for several subgroups were performed in order to obtain the doses required to achieve the presumed most favorable outcome related to f%T >MIC% greater than 50 %. In a typical infant (BW 1 kg and PNA 3 days), the administration of 10 mg/kg every 8 h as the initial piperacillin dose afforded a 95 % probability of achieving an antibiotic exposure against ESBL *E. coli* in the Asia-Pacific region. In order to attain the same result, the piperacillin dose needed to be increased to 100 mg/kg given every 6 h in an infant with a BW of 4.5 kg BW and a PNA of 7 days. This simulated evaluation highlighted how dosage individualization can affect clinical outcomes in this critical population and might explain some clinical failures.

In conclusion, two-compartment PK models were developed for piperacillin/tazobactam in children less than 2 months of age. BW and PNA were identified as significant covariates influencing the PK of piperacillin/tazobactam. The final models were evaluated using bootstrap and a visual predictive check. The final models were also evaluated on an additional 20 neonates and infants enrolled at stage 2 and showed accurate predictive performances. Our results may be used to recommend the initial dosage of piperacillin/tazobactam in hospitals in patient populations with similar characteristics.

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