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Population Pharmacokinetics and Pharmacodynamics of Extended-Infusion Piperacillin and Tazobactam in Critically Ill Children

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The study objective was to evaluate the population pharmacokinetics and pharmacodynamics of extended-infusion piperacillin-tazobactam in children hospitalized in an intensive care unit. Seventy-two serum samples were collected at steady state from 12 patients who received piperacillin-tazobactam at 100/12.5 mg/kg of body weight every 8 h infused over 4 h. Population pharmacokinetic analyses were performed using NONMEM, and Monte Carlo simulations were performed to estimate the piperacillin pharmacokinetic profiles for dosing regimens of 80 to 100 mg/kg of the piperacillin component given every 6 to 8 h and infused over 0.5, 3, or 4 h. The probability of target attainment (PTA) for a cumulative percentage of the dosing interval that the drug concentration exceeds the MIC under steady-state pharmacokinetic conditions (T_{MIC}) of $\geq 50\%$ was calculated at MICs ranging from 0.25 to 64 mg/liter. The mean \pm standard deviation (SD) age, weight, and estimated glomerular filtration rate were 5 ± 3 years, 17 ± 6.2 kg, and 118 ± 41 ml/min/1.73 m², respectively. A one-compartment model with zero-order input and first-order elimination best fit the pharmacokinetic data for both drugs. Weight was significantly associated with piperacillin clearance, and weight and sex were significantly associated with tazobactam clearance. Pharmacokinetic parameters (mean \pm SD) for piperacillin and tazobactam were as follows: clearance, 0.22 ± 0.07 and 0.19 ± 0.07 liter/h/kg, respectively; volume of distribution, 0.43 ± 0.16 and 0.37 ± 0.14 liter/kg, respectively. All extended-infusion regimens achieved PTAs of $>90\%$ at MICs of ≤ 16 mg/liter. Only the 3-h infusion regimens given every 6 h achieved PTAs of $>90\%$ at an MIC of 32 mg/liter. For susceptible bacterial pathogens, piperacillin-tazobactam doses of $\geq 80/10$ mg/kg given every 8 h and infused over 4 h achieve adequate pharmacodynamic exposures in critically ill children.

Piperacillin-tazobactam (TZP) is a broad-spectrum β -lactam- β -lactamase inhibitor antibiotic that is commonly used in children with suspected or documented infection. For penicillin antibiotics like piperacillin, microbiological and clinical outcomes are associated with the cumulative percentage of the dosing interval that the drug concentration exceeds the MIC for the organism(s) under steady-state pharmacokinetic conditions (T_{MIC}); optimal activity is seen when the T_{MIC} is $\geq 50\%$ (1, 2). Prolongation of the infusion time is one strategy that has been utilized to increase the T_{MIC} and optimize the pharmacodynamics of TZP, particularly for isolates with elevated MICs (1). Administration of TZP every 8 h with an infusion time of 4 h has been well described in adult patients (3–12). It has been demonstrated that 3.375 g given every 8 h and infused over 4 h achieves pharmacodynamic targets as effectively as 3.375 g given every 6 h, while it utilizes less total drug per day, resulting in a cost reduction (9, 10). Additionally, data support the improvement of clinical outcomes with extended-infusion dosing regimens compared to those achieved with traditional dosing regimens (4, 5).

Extended-infusion TZP dosing (with a piperacillin component of 100 mg/kg of body weight given every 8 h and infused over 4 h) was demonstrated to be feasible in over 90% of children, but currently available pediatric data on the pharmacodynamics of extended-infusion TZP are limited to those from Monte Carlo simulations incorporating pharmacokinetic data derived from the single or first dose of TZP infused over 0.5 h (13–16). Children exhibit pharmacokinetic changes throughout development, and the pharmacokinetics of drugs in children show significant differences from those in adults. Dose extrapolation from adults to

children has been shown to be associated with adverse outcomes (17–19). While pharmacodynamic principles for many drugs can change significantly from childhood to adulthood, antibiotics are unique in that the target exposures for efficacy are based on the interaction between the antibiotic and the infecting organism. Pharmacodynamic predictors of efficacy (e.g., T_{MIC}) for antibiotics do not change from the adult to the child. While evaluations of TZP pharmacokinetics in children are available, there are currently no published pharmacokinetic and pharmacodynamic data from children receiving extended-infusion TZP to guide optimal dosing on the basis of attainment of the target T_{MIC} (14, 15, 20–28). In addition, data regarding the population pharmacokinetics of tazobactam in children are limited (27, 28).

The objective of this study was to determine the steady-state population pharmacokinetics of piperacillin and tazobactam

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when administered by extended infusion in children hospitalized in a pediatric intensive care unit (ICU). Additionally, we evaluated the pharmacodynamics of TZP using various dosing regimens and infusion times over a range of MICs to determine the optimal dosing regimens in this patient population.

MATERIALS AND METHODS

Patient population. Patients 9 months to 11 years of age who were admitted to a pediatric intensive care unit were eligible for the study if they were already receiving extended-infusion TZP as part of routine care for a suspected or proven bacterial infection. Patients had to have received at least one prior dose to qualify for the study, and adequate vascular access was required to obtain serum samples without additional venipuncture. Patients with an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m², as determined by the modified Schwartz equation (29), were excluded, as were patients receiving any form of dialysis or renal replacement therapy. The study was approved by the Institutional Review Board at Indiana University, and written informed consent was obtained from the parent or legal guardian of each child prior to sample collection. Written informed assent was obtained from children who were awake, cognitively appropriate, and capable of understanding the assent process.

Study design and blood sampling. Dosing regimens were prescribed by the treating physician as part of routine care. TZP was dosed at 100 mg/kg of the piperacillin component (112.5 mg/kg of total TZP) every 8 h infused over 4 h up to a usual adult dose of 3,000 mg of the piperacillin component and 375 mg of the tazobactam component per dose, according to a dosing protocol approved by the Pharmacy and Therapeutics Committee at the institution. TZP was provided in a labeled syringe by the hospital pharmacy for each patient from a stock dilution of 112.5 mg of TZP per ml. Blood samples were collected at steady state from an already-present indwelling intravenous or intra-arterial catheter which was not utilized for TZP administration. Samples were obtained from each patient immediately prior to the study dose and at 2, 4 (end of infusion), 5, 6, and 8 h after the start of the infusion of the study dose. At each time point, 0.5 ml/kg (maximum, 5 ml) of whole blood was collected in non-anticoagulant-containing (red-top) tubes. After the blood was allowed to coagulate, samples were centrifuged, and serum samples were stored frozen at -70°C . Serum samples were shipped on dry ice by overnight carrier to the University of Cincinnati Academic Health Center (Cincinnati, OH) for determination of piperacillin and tazobactam concentrations.

Piperacillin and tazobactam assay. Piperacillin and tazobactam concentrations were measured using a validated high-performance liquid chromatography (HPLC) assay, as described previously (12, 30). The standard curve for piperacillin was linear over the concentration range of 2 to 400 mg/liter ($r \geq 0.993$). The within-day ($n = 6$) and between-day ($n = 8$) coefficients of variation for control specimens spiked with piperacillin were less than 8%. The standard curve for tazobactam was linear over the concentration range of 2 to 100 mg/liter ($r \geq 0.991$). The within-day and between-day coefficients of variation for control specimens spiked with tazobactam ranged from 3.9% to 10.8% over the concentration range tested. The limit of quantification for both drugs was considered to be the lowest standard concentration.

Population pharmacokinetic modeling. Serum concentration-time data for piperacillin and tazobactam from all individual patients were analyzed simultaneously by a population compartmental pharmacokinetic modeling approach using NONMEM (version VII; Globomax LLC, Ellicott City, MD, USA), as previously described (11). Pharmacokinetic models were built separately for piperacillin and tazobactam. For both drugs, the first-order conditional estimation method with interaction was used. On the basis of previous publications describing piperacillin pharmacokinetics in children, one- and two-compartment models with zero-order input and first-order (i.e., linear) elimination were evaluated as potential structural pharmacokinetic models for both piperacillin and tazobactam. The interindividual variability (η) of the population pharmacokinetic parameters was assumed to follow a log-normal dis-

tribution with a mean of zero and a variance of ω^2 (31). Possible correlations among the interindividual variabilities for pharmacokinetic parameters in the model were examined using the OMEGA BLOCK functionality in NONMEM.

For residual errors (ϵ) unexplained by the model, additive (ϵ_{add}), proportional (ϵ_{prop}), and combinational models were evaluated, and residual error was assumed to be normally distributed with a mean of zero and a variance of σ^2 (31). The best structural pharmacokinetic models with stochastic error terms for piperacillin and tazobactam were selected on the basis of the visual inspection of observed concentration-time plots, goodness-of-fit plots, individual plots of observed and individual predicted concentration-time profiles, relative standard errors, the change in the minimum objective function value (OFV), and the Akaike information criterion (32). Standard errors were deemed acceptable if they were $<50\%$ for fixed effects and $<75\%$ for random effects.

The final pharmacokinetic model was built by evaluating the effects of covariates on the pharmacokinetic parameters of piperacillin and tazobactam using stepwise forward inclusion (decrease in the OFV by >3.84 ; $P < 0.05$; χ^2 distribution; 1 degree of freedom [df]) followed by the backward elimination process (increase in the OFV by >5.024 ; $P < 0.025$; χ^2 distribution; 1 df) as previously described, with modified covariates (27). The covariates tested included age (in years); sex; height (in centimeters); body size descriptors, including body weight (WT; in kilograms) and body mass index (BMI), calculated as WT (in kilograms) divided by height (in meters) squared; and eGFR, as calculated by the modified Schwartz equation (29). Continuous covariates (e.g., age; height; body size descriptor, including WT and BMI; and eGFR) were centered at their median values. The full model was constructed when all significant covariates were added to the model in the stepwise forward inclusion process. Throughout the covariate model-building process, in addition to the model OFV, shrinkage and standard errors were used to evaluate the interindividual variability term of the PK parameters. Acceptable standard error criteria for random and fixed effects were previously described. Covariate models with shrinkage values of $<30\%$ were considered appropriate. The physiologic plausibility of the relationship between each covariate and pharmacokinetic parameter in the model was evaluated as well.

The final model was evaluated by the use of goodness-of-fit plots and individual plots of the observed and individual predicted concentration-time profiles. The predictive accuracy of the final pharmacokinetic model was examined by visual predictive checks (VPCs) (33). Visual predictive checks were performed by simulating the serum concentration-time profiles for piperacillin and tazobactam using NONMEM (version VII; Globomax LLC, Ellicott City, MD, USA). One thousand simulations were conducted to create serum concentration-time profiles of piperacillin and tazobactam for 12,000 virtual patients, using the data for all of the study patients included in this study to build the population pharmacokinetic model ($n = 12$). Curves for the 5th, 50th, and 95th percentiles of simulated drug concentrations were graphed with the observed concentrations. Descriptive statistics were used to summarize patient demographics and pharmacokinetic parameters.

Monte Carlo simulations. Pharmacodynamic exposures were modeled for the following TZP dosing regimens: 80/10 mg/kg every 8 h, 80/10 mg/kg every 6 h, 100/12.5 mg/kg every 8 h, and 100/12.5 mg/kg every 6 h. Each dosing regimen was simulated as a 0.5-h infusion, a 3-h infusion for regimens of administration every 6 h, and a 4-h infusion for regimens of administration every 8 h. Monte Carlo simulations for piperacillin were performed on the basis of our study patient characteristics using NONMEM to create steady-state serum piperacillin concentration-time curves for 5,040 virtual patients using the final population pharmacokinetic model per dosing regimen. All serum concentration-time curves were simulated in 0.1-h intervals, and the unbound serum concentrations were calculated as the simulated serum drug concentrations multiplied by the unbound fraction, which was assumed to be 0.7 for piperacillin (34). On the basis of the simulated unbound serum concentration-time profiles, the probability of

TABLE 1 Individual baseline characteristics of study patients^c

Patient no.	Age	Sex	Wt (kg)	TZP dose ^a (mg)	eGFR ^b	Underlying disease process(es)	Infectious indication	Type of therapy	Site, isolated organism(s)	TZP MIC (mg/liter)
1	8 yr	M	20	2,250	106	CP, small bowel resection s/p volvulus	Sepsis due to CLABSI	Directed	Blood, <i>Candida parapsilosis</i>	
2	5 yr	F	18.8	2,100	98	CCHD, tracheostomy	VAP	Directed	Blood, <i>Klebsiella pneumoniae</i> Blood, CoNS Blood, <i>Enterococcus faecalis</i> Fluid from mini-BAL, <i>P. aeruginosa</i> Fluid from mini-BAL, <i>Serratia marcescens</i>	8 NR NR 1 NR
3	12 mo	F	11.9	1,465	93	Previously healthy, ARDS	Pneumonia	Empirical	None	
4	5 yr	M	19.7	2,200	107	s/p MVA with TBI	Pneumonia	Empirical	Fluid from mini-BAL, <i>Staphylococcus aureus</i> (MSSA)	NR
5	2 yr	F	9.5	1,070	86	CCHD	Suspected sepsis	Empirical	None	
6	13 mo	M	10	1,125	102	Laryngomalacia	Pneumonia	Empirical	Adenovirus	
7	5 yr	M	14.5	1,630	98	Epilepsy, microcephaly	Pneumonia	Empirical	Influenza A virus	
8	8 yr	F	16.8	1,860	189	CCHD, CLLD	Open sternum	Empirical	None	
9	6 yr	F	23	2,600	105	Heart transplant, B cell lymphoma	Pneumonia	Empirical	None	
10	9 yr	F	30.1	3,375	90	Optic glioma	Neutropenic fever, typhilitis	Empirical	Blood, <i>Bacteroides ovatus</i>	NR
11	13 mo	M	9.6	1,078	129	Previously healthy, HHV encephalitis	VAP	Directed	Fluid from mini-BAL, <i>Enterobacter cloacae</i>	NR (P ≤ 4)
12	6 yr	M	20	2,081.25	122	Cornelia de Lange syndrome, epilepsy	Pneumonia	Empirical	Fluid from mini-BAL, <i>Haemophilus influenzae</i> Fluid from mini-BAL, <i>S. aureus</i> (MRSA)	β-Lactamase negative NR

^a All doses were administered every 8 h.^b eGFR values are reported in ml/min/1.73 m² and were rounded to the nearest whole number.^c Abbreviations: ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; CCHD, complex congenital heart disease; CLABSI, central line-associated bloodstream infection; CLLD, chronic liver disease; CoNS, coagulase-negative *Staphylococcus*; CP, cerebral palsy; eGFR, estimated glomerular filtration rate (determined bedside by the modified Schwartz equation [29]); F, female; HHV, human herpesvirus; M, male; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MVA, motor vehicle accident; NR, not reported; P, piperacillin; s/p, status post; TBI, traumatic brain injury; VAP, ventilator-associated pneumonia.

TABLE 2 Final population pharmacokinetic model parameters of piperacillin and tazobactam^a

Parameter	Final piperacillin model		Final tazobactam model	
	Estimate (% SE)	% shrinkage	Estimate (% SE)	% shrinkage
θ_1 (liters/h)	3.51 (6.5)	NA	3.43 (5.9)	NA
θ_2 (liters)	6.58 (10.6)	NA	5.54 (8.9)	NA
θ_3	0.0814 (45.1)	NA	-0.285 (20.9)	NA
θ_4 (liters/h)	NA	NA	0.0676 (38.6)	NA
Interindividual variability (ω)				
ω_{CL}	17.3% (59.0)	10.3%	13.1% (52.1)	11.2%
ω_V	25.2% (59.1)	18.0%	NA	NA
Residual error (σ)				
$\sigma_{proportional}$	25.3% (28.7)	10.3%	27.2% (35.2)	5.8%
$\sigma_{additive}$	NA	NA	0.76 mg/liter (47.8)	5.8%

^a The final piperacillin model was $TVCL = \theta_1 + [\theta_3 \cdot (WT - 18)]$ and $TVV = \theta_2$. The final tazobactam model was $TVCL = [\theta_1 \cdot (1 + \theta_3 \cdot \text{sex})] + [\theta_4 \cdot (WT - 18)]$ and $TVV = \theta_2$, where sex is coded 1 if female and 0 otherwise, TVCL is the typical population value of clearance (in liters per hour), WT is body weight (in kilograms), and TVV is the typical population value of the volume of distribution (in liters). NA, not applicable.

target attainment (PTA) for piperacillin was calculated for each dosing regimen using the pharmacodynamic targets of T_{MICs} of $\geq 50\%$ and 100% at specific MICs ranging from 0.25 to 64 mg/liter (15, 35).

RESULTS

Patients. Twelve patients who were receiving care in the pediatric intensive care unit at our institution participated in the study. Table 1 shows select demographics, TZP doses, infectious indications, and any organisms isolated for each patient. The median age, height, weight, and eGFR were 5 years (interquartile range [IQR], 1.75, 6.5 years), 103 cm (IQR, 81.75, 109.25 cm), 17.8 kg (IQR, 11.4, 20 kg), and 103 ml/min/1.73 m² (IQR, 96, 111 ml/min/1.73 m²), respectively. The patients received a mean \pm standard deviation (SD) TZP dose of 112.4 mg/kg \pm 4.1 mg/kg and 1,903 mg \pm 686 mg. Patients had received a median of 5 doses (range, 2 to 11 doses) before the study dose. TZP appeared to be well tolerated during the study.

Population pharmacokinetic analysis. Seventy-two piperacillin and tazobactam concentrations (6 samples from each of 12 patients) were included. The observed serum concentration-time profiles of piperacillin and tazobactam were best described by a one-compartment model with zero-order input and first-order (linear) elimination. The model-derived pharmacokinetic parameters for piperacillin and tazobactam were clearance (CL) and volume of distribution (V). For piperacillin, interindividual variability was estimated for both CL and V. The model did not support the correlation between CL and V (change in OFV [Δ OFV] = -0.783, correlation coefficient between CL and V [ρ_{CL-V}] = 38.8%). Residual error was best modeled by the proportional form. For tazobactam, interindividual variability was estimated only for CL. Addition of the interindividual variability term on V did not significantly decrease the model OFV (Δ OFV = -1.601). Also, the standard error and the shrinkage value associated with the interindividual variability term on V were large (>100% and >30%, respectively) (36, 37). Therefore, the interindividual variability term on V was not estimated. Residual error was best modeled by the combinational form.

Covariates that significantly decreased the model OFV and interindividual variability in the stepwise forward process were WT added to piperacillin CL (Δ OFV = -4.517) and sex (where 1 was used for female and 0 was used for male), followed by WT added to

tazobactam CL (Δ OFV = -4.402 for sex; Δ OFV = -7.528 for WT). None of these covariates were removed from the models in the backward elimination step. Therefore, the final model for piperacillin (OFV = 448.641) was CL (in liters per hour) = $3.51 + [0.0814 \cdot (WT - 18)]$, and V was equal to 6.58 liters. The final model for tazobactam (OFV = 195.425) was CL (in liters per hour) = $\{3.43 \cdot [1 - (0.285 \cdot \text{sex})]\} + [0.0676 \cdot (WT - 18)]$, and V was equal to 5.54 liters.

Table 2 summarizes the model-estimated population pharmacokinetic parameters and their associated interindividual variability for piperacillin and tazobactam. Figures 1 and 2 show basic goodness-of-fit plots for the final population pharmacokinetic models for piperacillin and tazobactam, respectively. For piperacillin, the final model appeared to slightly underpredict the observed concentrations at high observed concentrations (>130 mg/liter). For tazobactam, few data points were notably deviated from the line of identity near the observed tazobactam concentrations of 5, 10, and 20 mg/liter. Overall, the goodness-of-fit plots demonstrated no apparent systematic bias for the final pharmacokinetic models for both piperacillin and tazobactam. Visual predictive checks with the 90% prediction intervals using the final population pharmacokinetic model graphed with the observed drug concentrations are shown in Fig. 3a and b for piperacillin and tazobactam, respectively. On the basis of the VPC plots (Fig. 3a and b), the final models adequately predicted the observed drug concentrations, with most of the observed data being within the 90% prediction interval. Table 3 summarizes the values for the piperacillin and tazobactam pharmacokinetic parameters estimated by the final models.

Monte Carlo simulation. Figure 4 shows the PTA for piperacillin at the pharmacodynamic targets of T_{MICs} of $\geq 50\%$ and $\geq 100\%$ for the TZP dosing regimens evaluated. At the pharmacodynamic target of a T_{MIC} of $\geq 50\%$ (Fig. 4a), all simulated dosing regimens achieved a PTA of >90% at MICs of ≤ 8 mg/liter. Only 0.5-h infusion regimens of 80 mg/kg and 100 mg/kg every 8 h did not achieve a PTA of >90% at an MIC of 16 mg/liter. At an MIC of 32 mg/liter, 80 to 100 mg/kg given every 6 h and infused over 3 h achieved a PTA of >90%.

At the pharmacodynamic target of a T_{MIC} of 100% (Fig. 4b), none of the regimens achieved a PTA of >90% at an MIC of ≥ 16

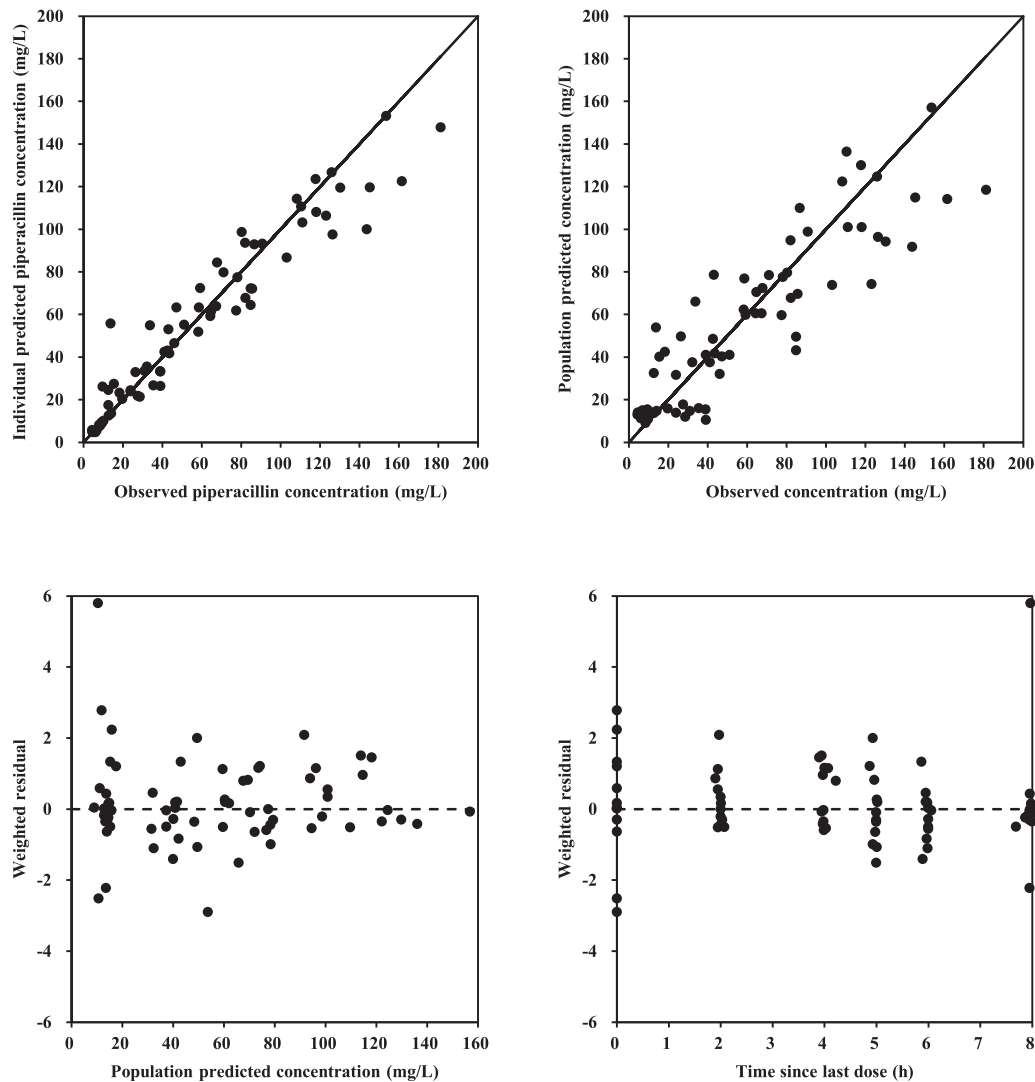


FIG 1 Goodness-of-fit plot of the final piperacillin pharmacokinetic model.

mg/liter, and only 100 mg/kg given every 6 h and infused over 3 h achieved a PTA of >90% at an MIC of 8 mg/liter.

DISCUSSION

To our knowledge, this is the first study to evaluate the pharmacokinetics and pharmacodynamics of extended-infusion TZP in children hospitalized in an intensive care unit. The population pharmacokinetic model that best described the observed serum concentration-time data for piperacillin and tazobactam was a one-compartment model with first-order (linear) elimination. The same population pharmacokinetic model was recently described for adults receiving TZP by extended infusion (11), and a one-compartment model has best described extended-infusion pharmacokinetic data for β -lactams in adults (10, 12, 38, 39). Previous studies have utilized one- and two-compartment models to describe piperacillin and/or tazobactam serum concentration-time data in pediatric patients receiving TZP by the traditional 0.5-h infusion (14, 15, 24, 27, 28, 40). However, the rate constants for the transfer of piperacillin between the central and peripheral compartments are rapid in young children and distribution may

be complete (or nearly complete) by the end of the 4-h infusion, which results in a better fit with a one-compartment model (14). Piperacillin CL was significantly associated with weight, and tazobactam CL was significantly associated with weight and sex (Table 2). Female patients exhibited significantly slower tazobactam CL than male patients, a finding that has not been previously reported. The glomerular filtration rate (GFR), estimated using the modified Schwartz equation (29), was not associated with piperacillin or tazobactam CL, similar to the findings of previous studies (14, 15). Potential explanations for this finding include the relatively small sample size ($n = 12$), the exclusion of patients with an eGFR of <60 ml/min/1.73 m², or an inaccurate estimate of the patient's actual GFR.

Due to the extended infusion time, maximum serum concentrations (C_{max} s) for piperacillin and tazobactam were substantially lower in the present study than in previous studies where comparable doses were infused over 0.5 h (20, 22). The lower C_{max} is not likely to adversely impact clinical outcomes in children, since β -lactams exhibit time-dependent bactericidal activity and T_{MIC} predicts outcome. It is currently unknown whether a lower

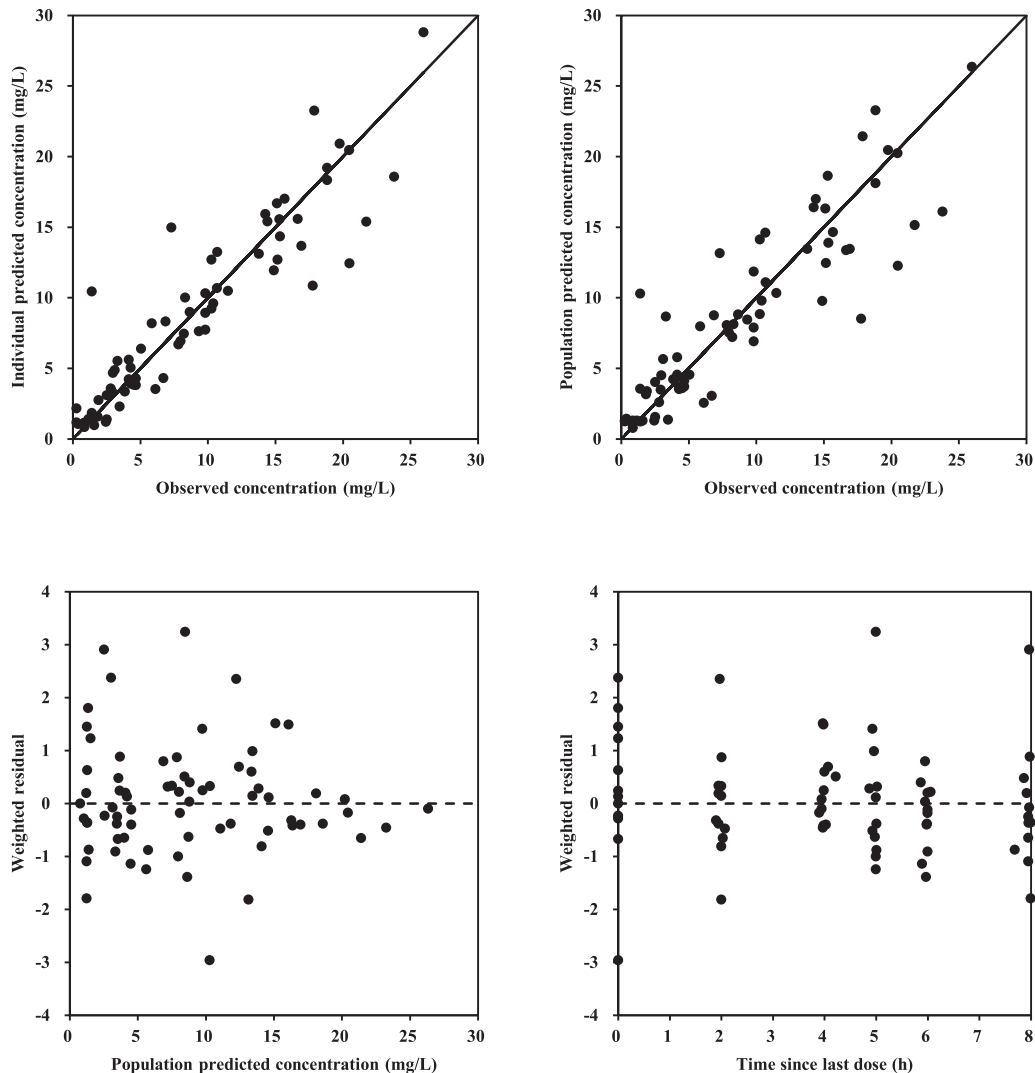


FIG 2 Goodness-of-fit plot of the final tazobactam pharmacokinetic model.

C_{\max} might result in fewer adverse events. On the other hand, the minimum serum concentrations (C_{\min} s) at 8 h in the present study were similar to the concentrations at 4 h in the previous study (20). In the present study, piperacillin CL was slower and V was larger than those in the study by Reed and colleagues (20). They enrolled pediatric patients with suspected or proven bacterial infections outside the central nervous system, but they did not report the actual infection-related diagnoses for the patients. Differences in CL and V may be due to physiologic changes related to the infection, some degree of undetected renal dysfunction, or severity of illness, since all of our patients were hospitalized in an intensive care unit. Differences may also be related to the small sample size and age groupings selected for this study. Piperacillin CL was faster and V was larger in a study by Cies and colleagues, but differences in pharmacokinetic parameters between these studies may be due to the physiologic changes associated with sepsis and burn injury (14). Eleven of their 13 patients were diagnosed with sepsis, and 3 patients were admitted with burn injury.

As patients in the ICU may be infected with less susceptible bacteria and because the margin for error may be low, more ag-

gressive dosing for empirical therapy may be warranted to provide adequate pharmacodynamic exposures before susceptibility data are known. In an evaluation of 30-day mortality in children who received TZP for the treatment of *Pseudomonas aeruginosa* bacteremia, 72% of isolates had TZP MICs of ≤ 16 mg/liter and 28% had MICs of 32 or 64 mg/liter (41). Mortality was significantly higher in children infected with the less susceptible strains (41). At an MIC of 32 mg/liter, only 3-h infusions of 80 to 100 mg/kg every 6 h in our study achieved a PTA of $>90\%$, while none of the regimens achieved optimal exposures at an MIC of 64 mg/liter. Depending on the MIC distribution at an individual institution, less aggressive empirical dosing regimens may be possible if isolates with elevated MICs are infrequent. It may be appropriate to utilize standard FDA-approved dosing regimens or decrease the empirical extended-infusion dose after the MIC of the infecting pathogen is known, depending on the site and severity of the infection. Our data suggest equivalent exposures between traditional and extended-infusion regimens for pathogens with MICs of ≤ 8 mg/liter. Extended-infusion regimens, including the 80-mg/kg regimen given every 8 h, demonstrated an acceptable PTA

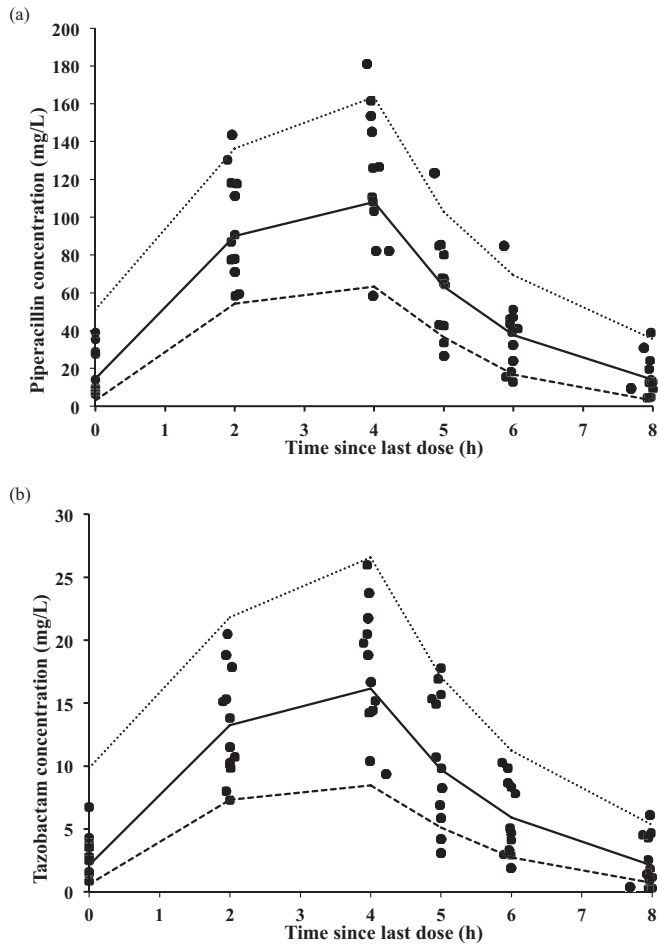


FIG 3 Visual predictive checks for piperacillin (a) and tazobactam (b) at 100/12.5 mg/kg every 8 h infused over 4 h.

($T_{MIC} > 50\%$) against isolates with slightly elevated MICs of 16 mg/liter. However, this potential for dose deescalation should be weighed against the pharmacokinetic variability between patients and the potential labor associated with alteration of the doses.

In addition to improved clinical outcomes, evaluations of extended-infusion TZP in adults have demonstrated a financial benefit. Extended infusions allow administration of the same dose every 8 h instead of every 6 h, thus eliminating the nursing, pharmacy, and medication costs of 1 dose of TZP per patient on every day of therapy. Our patients received 4-h infusions of 100/12.5 mg/kg every 8 h during this study, which is the current dosing protocol at the Riley Hospital for Children. For stable patients who demonstrate infection with a pathogen with an MIC of ≤ 16 mg/liter, employing a dose of 80/10 mg/kg given every 8 h and infused over 4 h would potentially result in a cost benefit by decreasing the medication cost via lowering of the total daily dose.

For similar dosing regimens, the present study tended to predict PTAs higher than those predicted by previous studies (13, 14). These differences in PTAs are likely explained by the differences in pharmacokinetic parameters described previously. Courter and colleagues (13) performed Monte Carlo simulations incorporating the pharmacokinetic data reported by Reed and colleagues (20). Their simulations predicted lower PTAs across a range of

TABLE 3 Piperacillin and tazobactam pharmacokinetic parameters estimated by the final population pharmacokinetic model^c

Drug	C_{max} (mg/liter) ^a	C_{min} (mg/liter) ^a	CL (liters/h)	CL (liters/h/kg)	V (liters)	V (liter/kg)	k (h^{-1})	$t_{1/2}$ (h)	$AUC_{0-\tau}$ ($mg \cdot h/liter$) ^a
Piperacillin	119.9 \pm 36.3 (58.6–181.2)	15.5 \pm 11.0 (4.4–39.1)	3.5 \pm 0.7 (2.3–5.0)	0.22 \pm 0.07 (0.14–0.37)	6.6 \pm 1.4 (4.8–9.7)	0.43 \pm 0.16 (0.24–0.76)	0.54 \pm 0.15 (0.32–0.79)	1.4 \pm 0.4 (0.9–2.2)	487 \pm 127 (270–700)
Tazobactam	17.6 \pm 5.1 (9.3–26.0)	2.4 \pm 2.0 (0.3–6.1)	2.9 \pm 0.6 (1.1–4.6)	0.19 \pm 0.07 (0.10–0.33)	5.5 ^b	0.37 \pm 0.14 (0.18–0.58)	0.52 \pm 0.11 (0.29–0.67)	1.4 \pm 0.4 (1.0–2.4)	74 \pm 24 (38–128)

^a At the actual studied doses given to the patients in the study.

^b Fixed. No interindividual variability was estimated.

^c Data represent the mean \pm SD (range) for 12 patients for each drug. Abbreviations: C_{max} , maximum observed serum concentration; C_{min} , minimum observed serum concentration; CL, clearance; V, volume of distribution; k, elimination rate constant; $t_{1/2}$, terminal elimination half-life; $AUC_{0-\tau}$, area under the serum concentration-time curve for one dosing interval (i.e., 8 h in this study) at steady state.

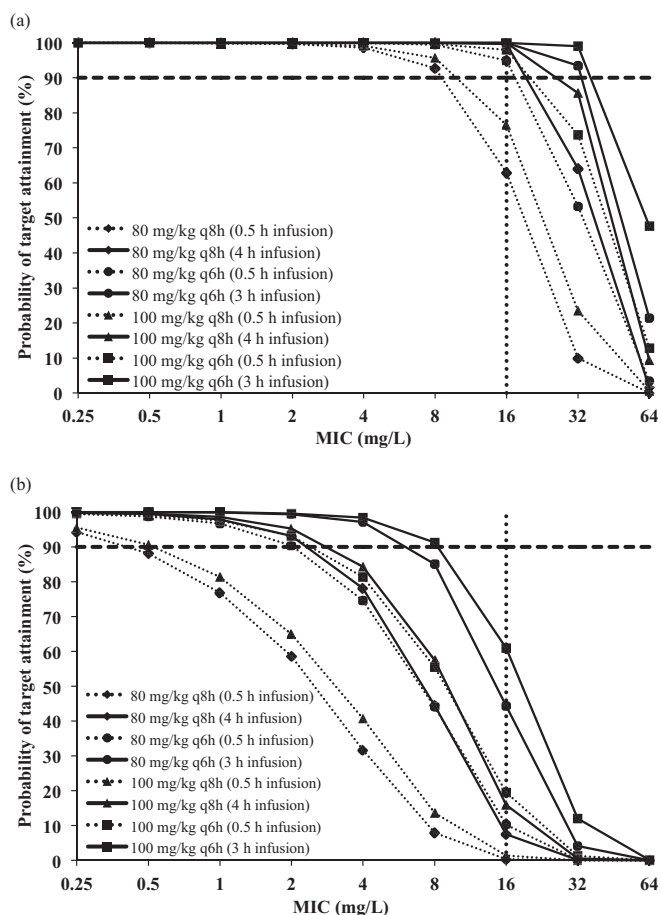


FIG 4 PTA for piperacillin at a T_{MIC} of $\geq 50\%$ (a) and a T_{MIC} of 100% (b) for 4 intermittent-infusion and 4 prolonged-infusion regimens of piperacillin-tazobactam at specific MICs in critically ill children. The dashed, horizontal line represents a PTA of 90%. T_{MIC} , the cumulative percentage of the dosing interval that the drug concentration exceeds the MIC for the organism(s) under steady-state pharmacokinetic conditions; q8h, every 8 h; q6h, every 6 h.

doses, most notably, a lack of optimal exposures with 0.5-h infusion regimens (13). Similarly, Cies and colleagues found PTAs for the lowest 0.5-h infusion dose in critically ill children that were slightly lower than those that we found in our study (14). A 4-h infusion of 100 mg/kg every 8 h was not simulated in their study, but it is likely that it would have achieved optimal pharmacodynamics at 16 mg/liter, similar to our findings (14). Cies and colleagues reported PTAs similar to those found in our study for various regimens in patients with febrile neutropenia (15). The values of the pharmacokinetic parameters were similar between the 2 studies, a finding which likely explains the comparable PTAs. When this information is applied to clinical practice, it is important to note that only serum concentrations were measured in these studies, and the pharmacokinetics of TZP in tissues and at the site of the infection are unknown. While this information may be used to predict doses that achieve PTAs of $\geq 90\%$ for bloodstream infections, it is possible that target attainment is underpredicted for urinary tract infections and overpredicted for more deep-seated infections. Optimal dosing for pneumonia, abscesses, and intra-abdominal infections may be higher than that for isolated bloodstream infections caused by organisms with the same

MIC. Additionally, though our pharmacokinetic data should not be extrapolated to nonrepresentative populations, certain infections or patient populations may require a T_{MIC} of $>50\%$ for optimal bactericidal activity (15). As a result, it may be prudent to target a higher T_{MIC} , strengthening the argument for empirical or directed 4-h infusion regimens in certain patient populations even when traditionally infused doses are likely to achieve a target of a T_{MIC} of 50%.

Dosing simulations were performed on the basis of the pharmacokinetics and the target pharmacodynamic parameter for the piperacillin component only, but tazobactam pharmacokinetics and pharmacodynamics should not be ignored. Adequate amounts of the β -lactamase inhibitor are required to preserve the activity of the β -lactam agent against organisms producing inhibitor-susceptible β -lactamases (42–44). The optimal pharmacodynamic target for tazobactam against multiple β -lactamases has not been well characterized, especially in pediatric patients, so the dosing recommendations in our study are based on the findings for the piperacillin component only. Additional studies are needed to determine the target tazobactam pharmacodynamic parameter for maximum inhibition for multiple common β -lactamases.

There are some limitations that should be considered when evaluating the results of this study. The number of patients evaluated is relatively small ($n = 12$), and six samples were collected from each patient. Seventy-two samples may not be sufficient to provide robust estimates of pharmacokinetic parameters in a population of pediatric patients hospitalized in an ICU. However, previous studies incorporated only 31 and 48 piperacillin concentrations into development of the population pharmacokinetic models (14, 15). Therefore, the number of piperacillin and tazobactam concentrations was greater in this study. The presence of concomitant medications such as vasopressors, which could impact the disposition of TZP, was not evaluated. The study results may not be applicable to younger infants or older children, since the children completing this study were 1 to 9 years of age. Underlying conditions were limited in our population and may not adequately predict the range of possible piperacillin exposures for patients with other underlying conditions. Monte Carlo simulations for the 0.5-h and extended-infusion dosing regimens were performed using the piperacillin pharmacokinetic parameters estimated using a one-compartment model. Piperacillin exhibits bi- or triexponential pharmacokinetics when infused over 0.5 h or less. The use of a one-compartment model to simulate dosing regimens infused over 0.5 h may not accurately estimate the serum concentration-time profiles for piperacillin, which may affect the PTA data. Therefore, clinicians should exercise caution when interpreting the PTA data for 0.5-h infusion regimens.

In conclusion, the pharmacokinetics of piperacillin and tazobactam administered as an extended infusion to children in an ICU differed slightly from those in previous studies infusing TZP over 0.5 h. These differences may be due to the patient population studied and their underlying conditions. For bacterial pathogens with MICs of ≤ 8 mg/liter, extended-infusion dosing regimens do not substantially improve PTA, and standard dosing regimens are likely sufficient. However, 100/12.5 mg/kg of TZP administered as an extended infusion every 6 to 8 h may be considered for empirical or directed therapy in critically ill pediatric patients with infections caused by less susceptible pathogens or if the desirable T_{MIC} is greater than 50%. The optimal empirical regimens will be impacted by the typical pathogens and MIC distributions encoun-

tered at a given institution. Prospective studies comparing outcomes in children receiving traditional and extended-infusion dosing regimens are needed.

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