

Population pharmacokinetics and dosing optimization of cefathiamidine in children with hematologic infection

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Purpose: Cefathiamidine, a first-generation cephalosporin, has approval from the China Food and Drug Administration for the treatment of infections caused by susceptible bacteria in both adults and children. As pharmacokinetic data are limited in the pediatric population, we aimed to evaluate the population pharmacokinetics of cefathiamidine in children and to define the appropriate dose in order to optimize cefathiamidine treatment.

Methods: Blood samples were collected from children treated with cefathiamidine, and concentrations were quantified by high-performance liquid chromatography and tandem mass spectrometry. Population pharmacokinetic analysis was conducted using NONMEM software.

Results: Fifty-four children (age range: 2.0–11.8 years) were included. Sparse pharmacokinetic samples (n=120) were available for analysis. A two-compartment model with first-order elimination showed the best fit with the data. A covariate analysis identified that bodyweight had a significant impact on cefathiamidine pharmacokinetics. Monte Carlo simulation demonstrated that the currently used dosing regimen of 100 mg/kg/day q12h was associated with a high risk of underdosing in pediatric patients. To reach the target 70% fT>MIC, a dose of 100 mg/kg/day cefathiamidine q6h is required for effective treatment against *Haemophilus influenzae*.

Conclusion: A population pharmacokinetics model of cefathiamidine in children with hematologic disease was established. A dosing regimen of 100 mg/kg/day cefathiamidine q6h should be used in clinical practice against *H. influenzae* infections.

Keywords: cefathiamidine, pharmacokinetics, dosing, children

Introduction

Cefathiamidine, a first-generation cephalosporin, is approved by the China Food and Drug Administration for the treatment of adults and children with infections due to susceptible bacteria.¹ Pharmacoepidemiology studies have demonstrated that cefathiamidine is one of the most commonly used cephalosporins in Chinese pediatric hospitals.^{2,3} According to the database of the China Medical Information Centre, cefathiamidine was the third most frequently prescribed agent in the list of the most commonly used antimicrobials in 2012. It has a wide spectrum of antimicrobial activity against *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, Methicillin-sensitive *Staphylococcus aureus* (MSSA), Methicillin-sensitive *Staphylococcus epidermidis* (MSSE), and *Branhamella (moraxella) catarrhalis*.^{4,5}

Cefathiamidine is not absorbed orally and is, thus, administered through the parenteral route (intravenously or intramuscularly). It is widely distributed in most bodily fluids and tissues; however, it cannot pass through the blood–brain barrier.

The protein-binding capacity of cefathiamidine is 23%, and more than 90% of cefathiamidine is excreted unchanged by the kidney.^{5,6} Although cefathiamidine has been included in the standard care for pediatric antimicrobial therapy, there is a lack of pharmacokinetic data in children, which might result in an improper dosing regimen, contributing thereby to risks of failure of antimicrobial therapy and emergence of antibiotic resistance in this vulnerable population. Thus, the objectives of this study were to evaluate the pharmacokinetics of cefathiamidine in children by using a population approach and to establish a simulation-based dosing regimen of cefathiamidine in this vulnerable population.

Methods

Study design

This trial was a prospective, open-label pharmacokinetic study of cefathiamidine and was conducted at the Children's Hospital, Hebei Province. The inclusion criteria were as follows: children aged between 2 and 12 years with confirmed or suspected bacterial infection and cefathiamidine used as a part of regular treatment of bacterial infection. The exclusion criteria were as follows: expected survival time less than the treatment cycle; patients enrolled in a clinical trial; patients with other factors that the researcher considered unsuitable for inclusion. This study was designed in accordance with legal requirements and the Declaration of Helsinki and was approved by the institutional ethics board (Children's Hospital of Hebei Province, approval no 100). Written informed consent was obtained from parents or guardians of patients.

Dosing regimen and pharmacokinetic sampling

Cefathiamidine 100 mg/kg/day (Xianlisu[®], Guangzhou Baiyunshan Pharmaceuticals, Guangzhou, People's Republic of China) was administered q12h as an intravenous infusion. The total number of study-specific blood samples was restricted to two per participant. Patients were randomly assigned to either of the two predefined, sparse, pharmacokinetic sampling schedules: Group 1: the end of infusion (3–5 minutes) and 4–8 hours after the start of infusion; and Group 2: 1–2 and 8–12 hours after the start of infusion. Precise infusion and sample times were recorded. Samples of 0.2 mL were obtained for pharmacokinetic analyses at each sampling. Blood samples were refrigerated and centrifuged, and the plasma was stored at -80°C . Processed samples were shipped on dry ice to the Department of Clinical Pharmacy at Shandong Provincial Qianfoshan Hospital, where they were stored at -80°C prior to analysis.

Analytical methods for cefathiamidine

Cefathiamidine concentrations were detected on an ultra-performance liquid chromatography tandem mass spectrometry (UPLC MS/MS) system comprising a API 4000 triple quadrupole mass spectrometer equipped with an electrospray ionization (ESI) source (Framingham, MA, USA). A series Waters UPLC system (Waters, USA) – consisting of a binary pump, an automatic sampler, and an online degasser – were used for LC-MS/MS analysis. Separation was achieved by using an ACQUITY UPLC[®] BEH C18 column (1.7 μm , 2.1 \times 50 mm) purchased from Waters (USA). The mobile phase consisted of water and methanol at a flow rate of 0.4 mL/min. Determination of cefathiamidine was based on the internal standard method, using ceftiofur as the internal standard (IS). The multiple reaction monitoring transitions of m/z 473.5⁺ \rightarrow 201.3⁺ and 524.3⁺ \rightarrow 241.4⁺ were used to quantify cefathiamidine and IS, respectively. The heated nebulizer was set at 300 $^{\circ}\text{C}$, and the needle voltage (IS) was set at 4,000.00 V; the nebulizer gas (GS1), auxiliary nitrogen gas (GS2), curtain gas (CUR), and collision gas (CAD) were set at 20 psi, 20 psi, 10 psi, and medium, respectively. Nitrogen was used as the collision gas. The calibration curve ranged from 30 to 10,000 ng/mL. The interday and intraday coefficients of variation of controls were less than 5%. The lower limit of quantification was 30 ng/mL.

Population pharmacokinetic modeling of cefathiamidine

The nonlinear mixed effects modeling program (NONMEM v7.2, Icon Development Solutions, Columbia, MD, USA) was used for pharmacokinetic analysis. The estimation of pharmacokinetic parameters and their variabilities was carried out using a first-order conditional estimation method with an interactive option.

An exponential model was selected to estimate the inter-individual variability of the pharmacokinetic parameter and could be expressed as follows:

$$\Theta_i = \theta_{\text{mean}} * e^{\eta_i}$$

where η_i represents the individual pharmacokinetic parameter value of the i th subject; θ_{mean} and θ_i are the typical values of the parameter in the population and the variability between subjects (assumed to follow a normal distribution), respectively.

Covariate analysis used a forward and backward selection method. Stepwise covariate modeling and likelihood ratio test were used to evaluate the potential impact of each covariate relationship on model parameters. During the

forward selection step, a covariate was included into the model if a significant ($p < 0.05$, χ^2 distribution with one degree of freedom) decrease (reduction > 3.84) in the objective function value (OFV) from the base model was achieved. Then, all the significant covariates were added simultaneously into the full model. At the backward selection step, the contribution of each significant covariate was removed one by one from the full model and was again retained in the final model if a significant increase in the OFV was obtained.

Both graphical and statistical criteria were used for model validation. Goodness-of-fit plots, including observed versus predicted concentrations (DV) versus population prediction (PRED), DV versus individual prediction (IPRED), conditional weighted residuals (CWRES) versus time, and CWRES versus PRED, were initially used for diagnostic purposes.⁷ Moreover, the stability and performance of the final model was evaluated by a nonparametric bootstrap with re-sampling and replacement 1,000 times using PsN (v2.30). Furthermore, the final model was evaluated graphically and statistically by normalized prediction distribution errors (NPDEs).^{8,9} In total, 1,000 data sets were simulated using the final population model parameters. The NPDE results are shown graphically by the NPDE R package (v1.2),¹⁰ including a QQ plot and histogram of the NPDE. The NPDE is assumed to follow normal distribution.

Dosing regimen evaluation and optimization based on a pharmacokinetic model

The pharmacokinetic–pharmacodynamic relationship of cephalosporin is the duration (T) of free antimicrobial drug concentration above the minimum inhibitory concentration

($fT > MIC$). For the maximal bactericidal activity of a cephalosporin, a probability of target attainment of 70% was required for the plasma concentrations during the times of the dosing interval when the T_{MIC} was 70%.^{11–13}

The free fraction of cefathiamidine was reported to be 0.77.⁴ *S. pyogenes*, *H. influenzae*, and MSSA (MICs of 0.5, 2, and 8 mg/L, respectively, for susceptible isolates) can cause severe and fatal infections in children. Furthermore, *S. pneumoniae* is a common pathogen but is very sensitive to cefathiamidine, with an MIC of 0.25 mg/L.¹⁴ Monte Carlo simulations were undertaken using the parametric estimates obtained from the final model. The pediatric dose of cefathiamidine was simulated on a milligram per kilogram basis. One hundred simulations were carried out using the original data set, and the time above the MIC was calculated for each simulated patient. If the current dosing regimen showed underdosing in the majority of patients, the optimal dosing regimen with an increased dose and/or frequency was given to the virtual patient.^{15–17} The probability of target attainment was then calculated for each dosing regimen to optimize antimicrobial therapy.

Results

Study population

Fifty-four patients were included from April 2015 to March 2016. All patients fulfilled the inclusion and exclusion criteria. All of them received 100 mg/kg/day cefathiamidine q12h. The mean (SD; range) age and bodyweight of the 54 patients at the time of study were 5.2 (2.4; 2.0–11.8) years and 18.4 (6.5; 8.0–36.0) kg, respectively. Age and bodyweight were all normally distributed ($p = 0.69$ and $p = 0.34$, respectively, Kolmogorov–Smirnov test). A summary of patient characteristics is presented in Table 1.

Table 1 Baseline characteristics in 54 children

Characteristics	Number	Mean (SD)	Median (range)
Patients	54		
Gender	37 males/17 females		
Samples	120		
Age (years)		5.2 (2.4)	4.9 (2.0–11.8)
Current weight (kg)		18.4 (6.5)	17.8 (8.0–36.0)
Serum creatinine concentration ($\mu\text{mol/L}$)		27 (8)	27 (10–47)
Creatinine clearance (mL/min)		211 (70)	193 (130–462)
Cefathiamidine dose (mg/dose)		910 (310)	950 (500–1,800)
Cefathiamidine dose (mg/kg/dose)		50	50 (28–112)
Hematologic disease			
Leukemia	23		
Immune thrombocytopenia	10		
Infectious mononucleosis syndrome	2		
Anemia	9		
Neuroblastoma	2		
Hemophagocytic syndrome	2		
Others	6		

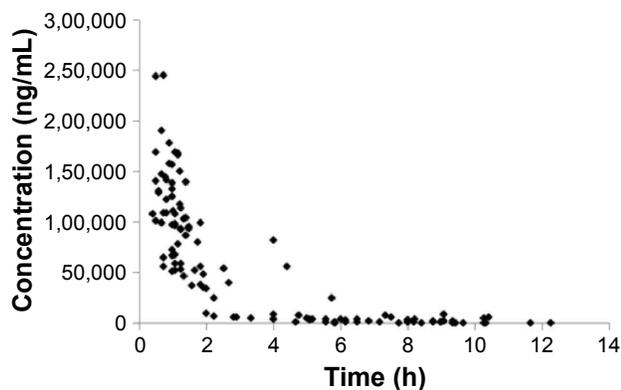


Figure 1 Cefathiamidine concentrations versus time.

Model building

In total, 120 cefathiamidine concentrations were available for population pharmacokinetic modeling. The cefathiamidine concentrations of pharmacokinetic samples ranged from 65 to 245,000 ng/mL. The concentration versus time profile is shown in Figure 1.

A two-compartment model with first-order elimination fitted the data well. The model was parameterized in terms of volume of central volume of distribution (V_1), peripheral volume of distribution (V_2), intercompartmental clearance (Q), and clearance (CL) of cefathiamidine. The interindividual variability was best described by an exponential model and was then estimated for CL and V_2 . This exponential model best described the residual variability.

Covariate analysis

The allometric size approach was used by incorporating, a priori, the body weight into the base model (allometric

coefficients of 0.75 for CL and Q , and 1 for V_1 and V_2), which caused a significant drop of 16.30 points in the OFV. However, age and creatinine clearance concentration, separately, did not produce a significant decrease in OFV. Therefore, only the effect of bodyweight on CL/F and V_2/F was found to be significant.

The median (range) of estimated weight-normalized CL and volume distribution at steady state (sum of V_1 and V_2) were 0.25 (0.05–0.43) L/h/kg and 0.31 (0.26–0.38) L/kg, respectively. The AUC_{0-24} at steady state for the evaluated dose regimen ranged from 120 to 550 mg-h/L. Cefathiamidine CL increased allometrically with weight in children (Figure 2).

Model evaluation

Model diagnostics showed acceptable goodness-of-fit for the final model of cefathiamidine. As shown in Figure 3A and B, predictions are unbiased. In the diagnostic plots of CWRES versus time and PRED, no trends were observed (Figure 3C and D). Moreover, the mean pharmacokinetic parameters obtained from the bootstrap were in agreement with the respective values estimated from the final model, indicating that the final model was stable and the estimated parameters were accurate (Table 2). NPDE results are presented in Figure 3E and F. The mean and variance of NPDE were -0.0723 (Wilcoxon signed-rank test $p=0.424$) and 1.03 (Fisher variance test 0.789), respectively, indicating a good fit of the model to the individual data.

Dosing regimen evaluation and optimization

The target attainment rates as a function of dose for different organisms are shown in Figure 4. With the dosing

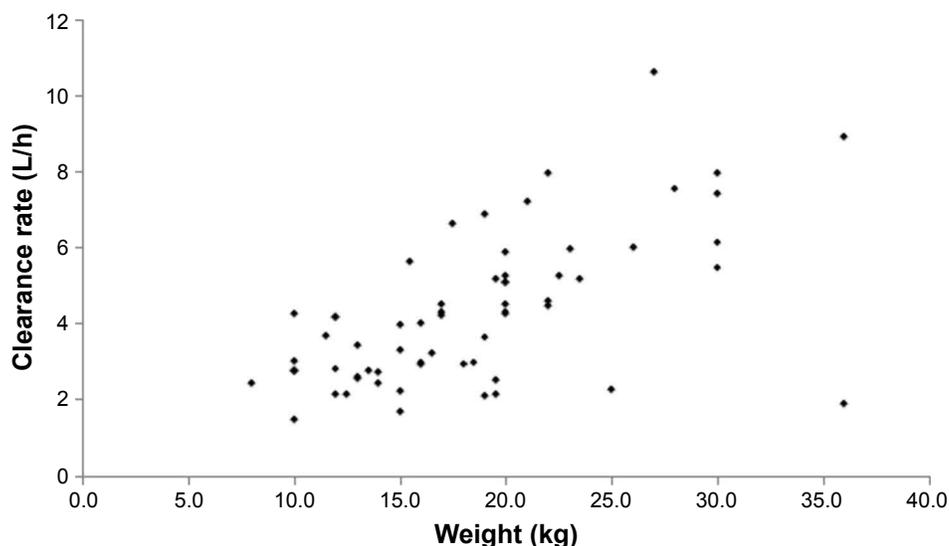


Figure 2 Weight versus cefathiamidine clearance (CL).

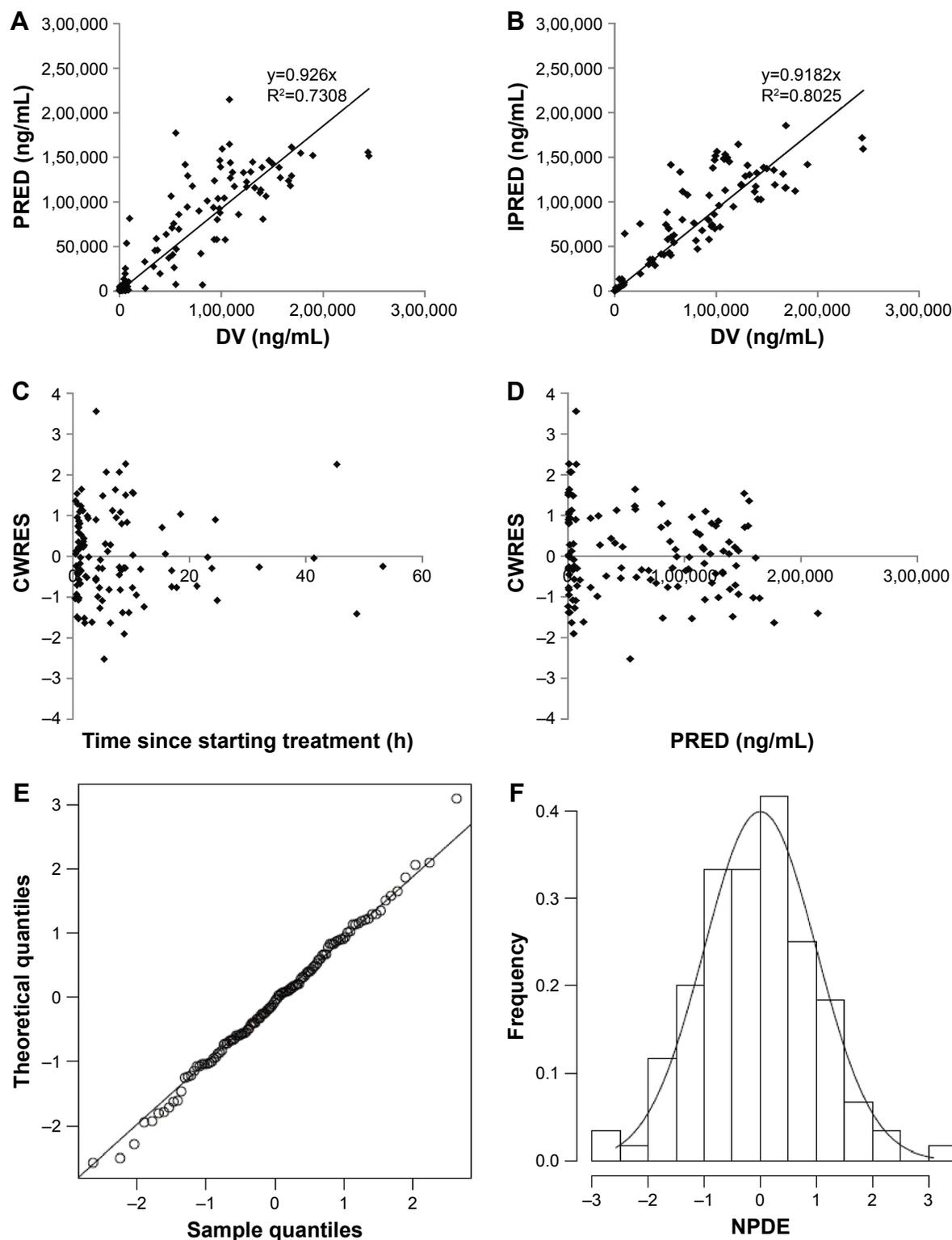


Figure 3 Model evaluation for cefthiamidine. (A) Population predicted (PRED) versus observed concentrations (DV); (B) individual predicted (IPRED) versus DV; (C) conditional weighted residuals (CWRES) versus time; (D) CWRES versus PRED; (E) QQ plot of the distribution of the normalized prediction distribution errors (NPDEs) versus the theoretical $N(0, 1)$ distribution; (F) histogram of the distribution of the NPDE, overlaid with the density of the standard Gaussian distribution.

regimen prescribed in the study (100 mg/kg/day q12h), 67.2% of children achieved the pharmacodynamic target (70% $fT > MIC$) against the sensitive organism – *S. pyogenes* (MIC 0.5 mg/L) – whereas 34.5% achieved the

target against *H. influenzae* (MIC 2 mg/L). With the dosing interval extended to 6 hours, the pharmacodynamic target (70% $fT > MIC$) could be achieved in 86.6% of patients against *S. pyogenes* (MIC 0.5 mg/L) and 59.3% against

Table 2 Population pharmacokinetic parameters of cefathiamidine and bootstrap results

Parameters	Full data set		Bootstrap	
	Final estimate	RSE (%)	Median	5th–95th
CL (L/h)				
$CL = \theta 1 \times (CW/17.75)^{0.75} \times EXP(\eta_1)$				
$\theta 1$	3.93	6.90	3.93	3.47–4.42
V1 (L)				
$V = \theta 2 \times (CW/17.75)$				
$\theta 2$	4.18	7.80	4.11	3.11–4.78
Q (L/h)				
$Q = \theta 3 \times (CW/17.75)^{0.75}$				
$\theta 3$	0.50	30.90	0.51	0.25–1.75
V2 (L)				
$V = \theta 4 \times (CW/17.75) \times EXP(\eta^2)$				
$\theta 4$	1.30	33.50	1.45	0.77–2.68
Interindividual variability (%)				
CL	41.83	30.0	39.62	29.14–51.38
V2	74.23	65.2	74.70	40.82–123.69
Residual variability (%)				
ERR (I)	35.78	16.60	35.07	28.87–40.34

Note: In our population, 17.8 kg, 4.9 years, and 193 mL/min are the median current weight (day of the study), age, and creatinine clearance, respectively.

Abbreviations: V1, central volume of distribution; V2, peripheral volume of distribution; Q, intercompartmental clearance; CL, clearance.

H. influenzae (MIC 2 mg/L). However, the extended dosing regimen (100 mg/kg/day four times daily) results in only 25.0% of children achieving the pharmacodynamic target against MSSA (MIC 8 mg/L) and indicates that a higher dosing regimen is required (Figure 5).

Discussion

This is the first model developed to describe the pharmacokinetics of cefathiamidine in children. Our results show that a two-compartment model with first-order elimination was optimal for pharmacokinetic data modeling.

As cefathiamidine is almost exclusively eliminated by the renal route, both renal function and size should have

important influences on the dosing regimen in children.¹⁸ Covariate analysis identified that body weight significantly influenced cefathiamidine clearance, whereas creatinine clearance did not. This can be explained by the limited range of creatinine clearance (130–462 mL/min). None of the included patients had insufficient renal function. The plot of cefathiamidine versus creatinine clearance did not show any trend. It should be noted that most of the children included in this study had malignant hematologic disease and represent a critical population in whom disease may also impact pharmacokinetics due to hyperfiltration, along with the maturation.¹⁹ The estimated vancomycin^{20,21} and teicoplanin²² CLs in children with malignant hematologic

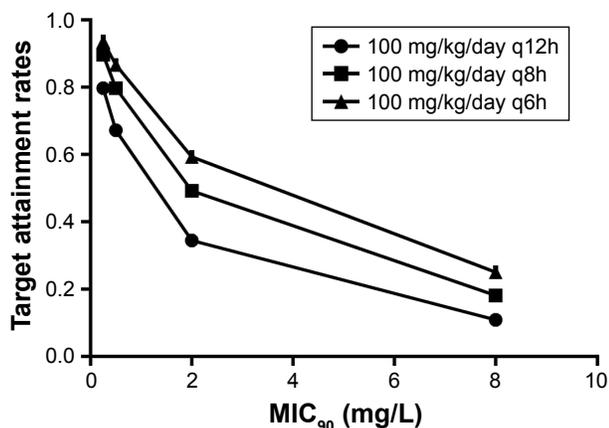


Figure 4 Probability of target (70% $fT > MIC$) attainment for cefathiamidine 100 mg/kg/day q12h, q8h, and q6h against target organisms in children ($2 \leq \text{age} < 12$).

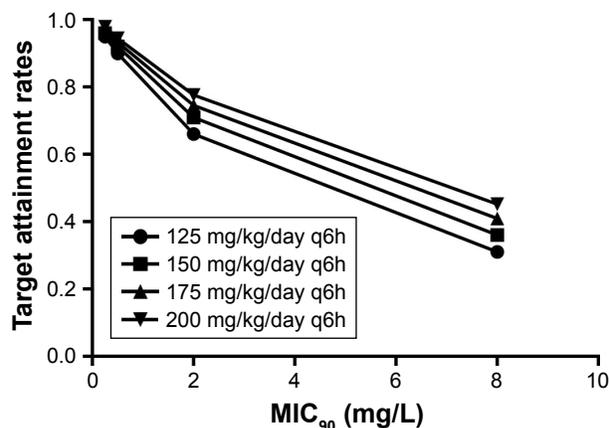


Figure 5 Probability of target (70% $fT > MIC$) attainment for cefathiamidine 125, 150, 175, and 200 mg/kg/day q6h against target organisms in children ($2 \leq \text{age} < 12$).

Table 3 Pharmacokinetics of cefthiamidine obtained from different studies

Parameter	Value for the group (reference or source)		
	Adults reference 5 mean	Adults reference 6 mean	Children with malignant hematologic disease (this study), median (range)
No of patients	9	7	54
Age (year)	22.5±1.1	Adults	4.9 (2.0–11.8)
Weight (kg)	61.7±6.2	47–68	17.8 (8.0–36.0)
CL (liters/h/kg)	0.17±0.02	0.15±0.035	0.25 (0.05–0.43)
V (liters/kg)	0.11±0.02 ^a	0.59±0.40	0.31 (0.26–0.38)

Note: ^aVolume of the central compartment.

disease were higher than in the general nonselected pediatric populations. The estimated cefthiamidine CL and V in this study and the reported values in general adult patients are summarized in Table 3.^{5,6}

The time of free antimicrobial drug concentration above the minimum inhibitory concentration was regarded as a surrogate marker of therapeutic efficacy for cephalosporin. A target of 40%–50% fT>MIC is generally accepted for cephalosporin in adult patients.^{23,24} However, a higher fT>MIC target of 70%–80% is recommended to ensure efficacy and avoid the induction of antibiotic resistance for the critically ill and with the immunocompromised status of pediatric population.^{25–28} As shown in the simulation results, the currently used dosing regimen (100 mg/kg/day q12h) could have approximately 34.5% children achieving the pharmacodynamic target against *H. influenzae* (MIC 2 mg/L). To achieve maximal bactericidal activity, an increased dose and/or dosing frequency were necessary. As the safety of a higher dose has not been tested, the option of an increased frequency was considered. An optimal dosing regimen of 100 mg/kg/day q6h was required against *H. influenzae* (MIC 2 mg/L). For more resistant bacterial strains (eg, MSSA, MIC 8 mg/L), a different antimicrobial drug should be considered in clinical practice.

Our study had some limitations. Most of the children included in this study had malignant hematologic disease. The clearance of cefthiamidine might be augmented due to hyperfiltration. The pharmacokinetics of cefthiamidine in the “general” pediatric population still needs to be evaluated. In addition, the pharmacokinetic model of cefthiamidine was only internally validated. External validation was not undertaken because of the limited number of patients. Ultimately, an optimal dose regimen based on modeling and simulation should be evaluated in clinical practice to confirm its clinical benefits.

Conclusion

A population pharmacokinetic model of cefthiamidine was developed in children. Body weight had a significant impact on cefthiamidine clearance. The currently used dose regimen of 100 mg/kg/day q12h is associated with a high risk of underdosing in pediatric patients. To reach the target 70% fT>MIC, a dosage of 100 mg/kg/day q6h is required against *H. influenzae* (MIC 2 mg/L). Until the safety of a higher dose of cefthiamidine is tested in studies, other antibiotics should be considered for more resistant bacterial strains (eg, MSSA). The model-based dosing regimen of cefthiamidine in children was established on the basis of population pharmacokinetic–pharmacodynamic analysis.

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Disclosure

All authors have completed the Unified Competing Interest form (available on request from the corresponding author). None of the authors have any other relationships or activities that could appear to have influenced the submitted work.

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