Population pharmacokinetic modeling and pharmacodynamic assessment of cefozopran in pediatric patients

Kazuro Ikawa*, Toshihiro Kozumi, Kayo Ikeda and Norifumi Morikawa

Department of Clinical Pharmacotherapy, Graduate School of Biomedical Sciences, Hiroshima University

Ryoji Kobayashi

Department of Pediatrics, Sapporo Hokuyu Hospital

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The aims of this study were to develop a population pharmacokinetic model for cefozopran in pediatric patients, and to use this model to evaluate the pharmacodynamics of cefozopran regimens against common bacterial populations. Plasma drug concentration data (110 samples from 31 pediatric patients) were modeled using the NONMEM program. The mean estimate and interindividual variance of the model were used in a Monte Carlo simulation to estimate the probabilities of attaining the bactericidal target for cefozopran (the time which the drug concentration remains above the minimum inhibitory concentration for the bacterium is 70% of the dosing interval). A two-compartment model fitted the data and body weight (BW, kg) was the most significant covariate. The final model was: Cl (l/h)$=0.674\times BW^{0.538}$, V_c (l)$=0.00233\times BW^{2.25}+1.85$, Q (l/h)$=1.46$, and V_p (l)$=0.0964\times BW$, where Cl is the clearance, V_c, and V_p are the volumes of distribution of the central and peripheral compartments, and Q is the intercompartmental clearance. The approved regimens of 20- or 40-mg/kg four times a day (0.5-h infusions), which were more effective than the corresponding three times a day-regimens, provided sufficient bactericidal effects on common bacterial populations (*Escherichia coli*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*) in most typical patients. These results better define the pharmacokinetics of cefozopran and help in the choice of appropriate regimens for pediatric patients.

Introduction

Cefozopran is a parenteral cephalosporin with a broad spectrum of activity against Gram-positive and Gram-negative bacteria. It has been clinically available in Japan since the late 1990s for the

treatment of various infections such as pneumonia, sepsis, urinary-tract- and intra-abdominal-infections, not only in adult patients but also in pediatric patients[1].

Understanding the pharmacokinetics of an antibacterial agent in specific populations, such as pediatric and geriatric patients, is important for adjusting or optimizing dosing regimens. Although the pharmacokinetic profiles of cefozopran have been well defined in adult patients[2], those in pediatric patients have not been fully characterized. Treatment of pediatric patients would benefit by a better definition of cefozopran pharmacokinetics in this population. In particular, a population pharmacokinetic approach has the advantage that it can predict the pharmacokinetic parameters of a particular subject from covariates, such as body size and physiological functions, without the need to take blood samples.

The pharmacology of antibacterial chemotherapy is determined by the interrelationship between its pharmacokinetics and pharmacodynamics. Cephalosporins exhibit time-dependent *in vitro* and *in vivo* activity, and their antibacterial effects correlate with the time that the drug concentration remains above the minimum inhibitory concentration (MIC) for the bacterium (T>MIC)[3]. In order to assess the pharmacodynamics of cephalosporin therapy, the probability that a T>MIC target is attained (the probability of target attainment)[4] should be estimated. These estimations should involve Monte Carlo simulations[5,6] which enable variability to be incorporated into individual pharmacokinetics and antibacterial activities against a population of clinical isolates.

The present study therefore aimed to develop a population pharmacokinetic model for cefozopran in pediatric patients in order to estimate the associated pharmacokinetic parameters, their variability and the influence of potential covariates. By incorporation of this model into a Monte Carlo simulation, this study also aimed to assess the pharmacodynamics of cefozopran regimes against common bacterial populations in order to help in the choice of dosage for pediatric patients.

Materials and Methods

Pharmacokinetic data

Pharmacokinetic data were collected from 31 Japanese pediatric patients, who underwent therapeutic drug monitoring at Sapporo Hokuyu Hospital or were included in clinical studies[7,8]. Plasma samples were obtained after a 0.05- to 0.5-h infusion of 10～40 mg/kg cefozopran. Drug concentrations in plasma were measured using two compatible methods, high-performance liquid chromatography and bioassay, as reported previously[9,10]. Patient characteristics that were determined included sex, age, body weight, serum creatinine, and blood urea nitrogen.

Population pharmacokinetic analysis

Population pharmacokinetic analysis was performed using the NONMEM program version VI (ICON Development Solutions, Ellicott, MD, USA). Both one-compartment and two-compartment

models were tested to define the most appropriate basic pharmacokinetic model. The interindividual variability was modeled exponentially using the following equation:

$$\theta_i = \theta \times \exp(\eta_i)$$

where θ_i is the fixed-effects parameter for the i-th subject, θ is the mean value of the fixed-effects parameter in the population, and η is a random interindividual variable which is normally distributed with a mean of 0 and variance ω^2. The residual (intraindividual) variability was modeled using a proportional error model according to the following equation:

$$C_{obs,\,ij} = C_{pred,\,ij} \times (1 + \varepsilon_{ij})$$

where $C_{obs,\,ij}$ and $C_{pred,\,ij}$ denote the j-th observed and predicted concentrations for the i-th subject, and ε is a random intraindividual error which is normally distributed with a mean of 0 and variance σ^2.

The individual pharmacokinetic parameters obtained from the basic model were plotted against patient characteristics. Covariates that showed a correlation with the pharmacokinetic parameters were then introduced into the model. The significance of the influence of the covariates was evaluated by changes of the -2 log likelihood (the minimum value of the objective function, OBJ). An OBJ decrease of >3.84 from the basic model ($P<0.05$; χ^2 test) was considered statistically significant during the covariate screening process. The full model was built by incorporating the significant covariates, and the final model was developed by a backward deletion method. The coefficients in the full model were excluded from the model one at a time, and an OBJ increase of >6.63 from the full model ($P<0.01$; χ^2 test) was considered statistically significant.

Microbiological data

Four common types of pathogenic bacteria were selected for study, and the MIC distribution data of their clinical isolates (from pediatric, adult, and geriatric patients) were based on a recent nationwide susceptibility surveillance[11]: *Pseudomonas aeruginosa* (n=306; MIC_{50}=2 μg/ml; MIC_{90}=16 μg/ml), *Haemophilus influenzae* (β-lactamase negative ampicillin-susceptible, β-lactamase negative ampicillin-resistant, and β-lactamase positive ampicillin-resistant strains) (n=253; MIC_{50}=1 μg/ml; MIC_{90}=16 μg/ml), *Streptococcus pneumoniae* (penicillin-susceptible, penicillin-intermediate, and penicillin-resistant strains) (n=184; MIC_{50}=0.5 μg/ml; MIC_{90}=2 μg/ml), and *Escherichia coli* (n=130; MIC_{50}=0.06 μg/ml; MIC_{90}=0.12 μg/ml).

Pharmacodynamic evaluation using a Monte Carlo simulation

A Monte Carlo simulation was conducted to evaluate the pharmacodynamics of cefozopran regimens approved in Japan (40～160 mg/kg daily, divided into three or four doses). For each tested regimen, the following process was repeated 10000 times using Crystal Ball 2000 software (Oracle, Redwood Shores, CA, USA). A set of fixed-effects parameters was randomly generated according to each mean estimate (θ) and interindividual variance (ω) of the final population pharmacokinetic

model. The curve of the plasma concentration of cefozopran versus time was simulated using the fixed-effects parameters. The total drug concentration was employed for this purpose because it is clinically equivalent to the free concentration due to negligible protein binding (6.2%)[12]. The time point at which the drug concentration coincided with a specific MIC value was determined, and the time for which the drug concentration remained above the MIC was finally calculated as a percentage of the dosing interval.

The probability of target attainment (%) was determined as the fraction that achieved at least 70% T>MIC (the bactericidal target)[2,13] of 10000 estimates. The probability at a specific MIC was then multiplied by the fraction of the population of the bacterium in each MIC category, and the sum of the individual products was defined as the expected population probability of target attainment (%)[4].

Results

In order to develop a population pharmacokinetic model for cefozopran in pediatric patients, we first carried out a population pharmacokinetic analysis of cefozopran plasma concentration data (110 samples from 31 pediatric patients). The characteristics of the patients (18 males and 13 females) were as follows: age, 5.6±2.7 years (mean±standard deviation; range, 2.0～13.0 years); body weight, 18.0±5.2 kg (11.0～43.5 kg); serum creatinine, 0.31±0.20 mg/dl (0.10～0.90 mg/dl); and blood urea nitrogen, 6.8±4.5 mg/dl (2.5～22.0 mg/dl).

Because Akaike information criterion values indicated that the two-compartment model described the data better than the one-compartment model, the two-compartment model was selected as the basic model. Therefore, the pharmacokinetic parameters used were: clearance (Cl, l/h), volume of distribution of the central compartment (V_c, l), intercompartmental clearance (Q, l/h), and volume of distribution of the peripheral compartment (V_p, l).

During the forward inclusion process of building the covariate model, incorporation of body weight (BW) into Cl, V_c or V_p caused the largest OBJ change, although age also had a significant effect on each of these parameters. Because age showed a high correlation with BW, it was not additionally incorporated into these three pharmacokinetic parameters in order to avoid a collinearity effect. None of the covariates examined had a significant effect on Q. During the backward deletion process, every covariate and coefficient remained in the model, causing a significant OBJ increase. Therefore, the final model was as follows:

$Cl\ (l/h)=0.674\times BW^{0.538}$, $V_c\ (l)=0.00233\times BW^{2.25}+1.85$, $Q\ (l/h)=1.46$, and $V_p\ (l)=0.0964\times BW$.

The estimates (mean and variability), their standard errors and 95% confidence intervals of the population pharmacokinetic parameters of the final model are summarized in Table 1. Diagnostic scatter plots indicated that the final model accurately reflected the data (Fig. 1).

Based on the final model, three typical patients, with a BW of 10, 20 or 30 kg, were supposed.

Table 1. Final population pharmacokinetic parameters of cefozopran in pediatric patients.

Parameter	Estimate	Standard error	95% Confidence interval
Fixed-effects parameter			
$Cl\ (l/h) = \theta_1 \times BW^{\theta 2}$			
θ_1	0.674	0.0857	0.506–0.841
θ_2	0.538	0.0513	0.437–0.638
$V_c\ (l) = \theta_3 \times BW^{\theta 4} + \theta_5$			
θ_3	0.00233	0.000584	0.00118–0.00347
θ_4	2.25	0.140	1.97–2.52
θ_5	1.85	0.432	1.00–2.69
$Q\ (l/h) = \theta_6$			
θ_6	1.46	0.282	0.907–2.01
$V_p\ (l) = \theta_7 \times BW$			
θ_7	0.0964	0.00801	0.0807–0.112
Interindividual variability			
η_{Cl}	0.120 (ω_{Cl} = 35.7%)	0.0231	0.0747–0.165
η_{Vc}	0.187 (ω_{Vc} = 45.3%)	0.0399	0.108–0.265
η_{Q}	0.623 (ω_{Q} = 93.0%)	0.242	0.148–1.09
η_{Vp}	0.0418 (ω_{Vp} = 20.7%)	0.0118	0.0186–0.0649
Residual variability			
ε	0.00392	0.00143	0.00111–0.00672

As shown in Fig. 2, the probabilities of target (70% T>MIC) attainment for six different cefozopran regimens in the three patients generally increased in the following order: (20 mg/kg, 10 mg/kg, 10 mg/kg) three times a day (t.i.d.)<10 mg/kg four times a day (q.i.d.)≒(40 mg/kg, 20 mg/kg, 20 mg/kg) t.i.d.<20 mg/kg q.i.d.≒(80 mg/kg, 40 mg/kg, 40 mg/kg) t.i.d.<40 mg/kg q.i.d.

Table 2 lists the expected population probabilities of target attainment against common pathogenic bacteria. For all patients, 10 mg/kg q.i.d. achieved 93.6～94.3% probability against *E. coli* isolates and 20 mg/kg q.i.d. achieved 88.7～99.7% probability against *S. pneumoniae* isolates. However, the probability values were lower against *H. influenzae* and *P. aeruginosa* isolates. A regimen of 20 mg/kg q.i.d. achieved only 83.5～84.3% probability in a patient with a BW of 30 kg, and 40 mg/kg q.i.d. was required to achieve a probability >80% in a patient with a BW of 20 kg.

Discussion

We have employed pharmacokinetic analysis to develop a population model for cefozopran in pediatric patients and have identified BW as the most significant covariate that affects cefozopran pharmacokinetics. Pharmacodynamic assessment using this model showed that administration of cefozopran at 20 mg/kg q.i.d. and 40 mg/kg q.i.d. achieved a high probability of target attainment

Fig. 1. Diagnostic scatter plots of the final population pharmacokinetic model of cefozopran.

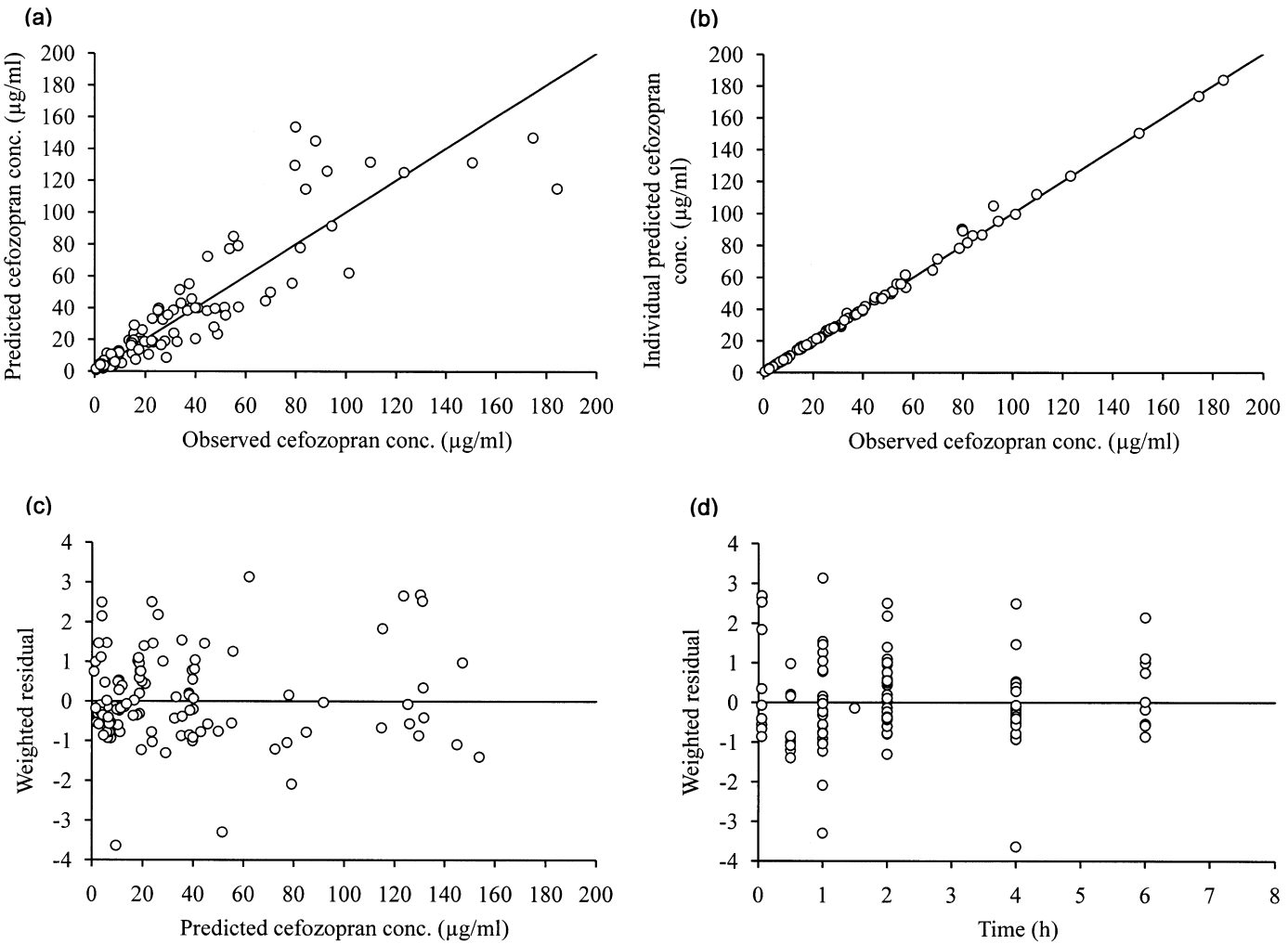

Fig. 2. Probabilities of 70% T>MIC attainment using different cefozopran regimens (0.5-h infusions) in patients of differing body weight (BW).
t.i.d., three times a day; q.i.d., four times a day

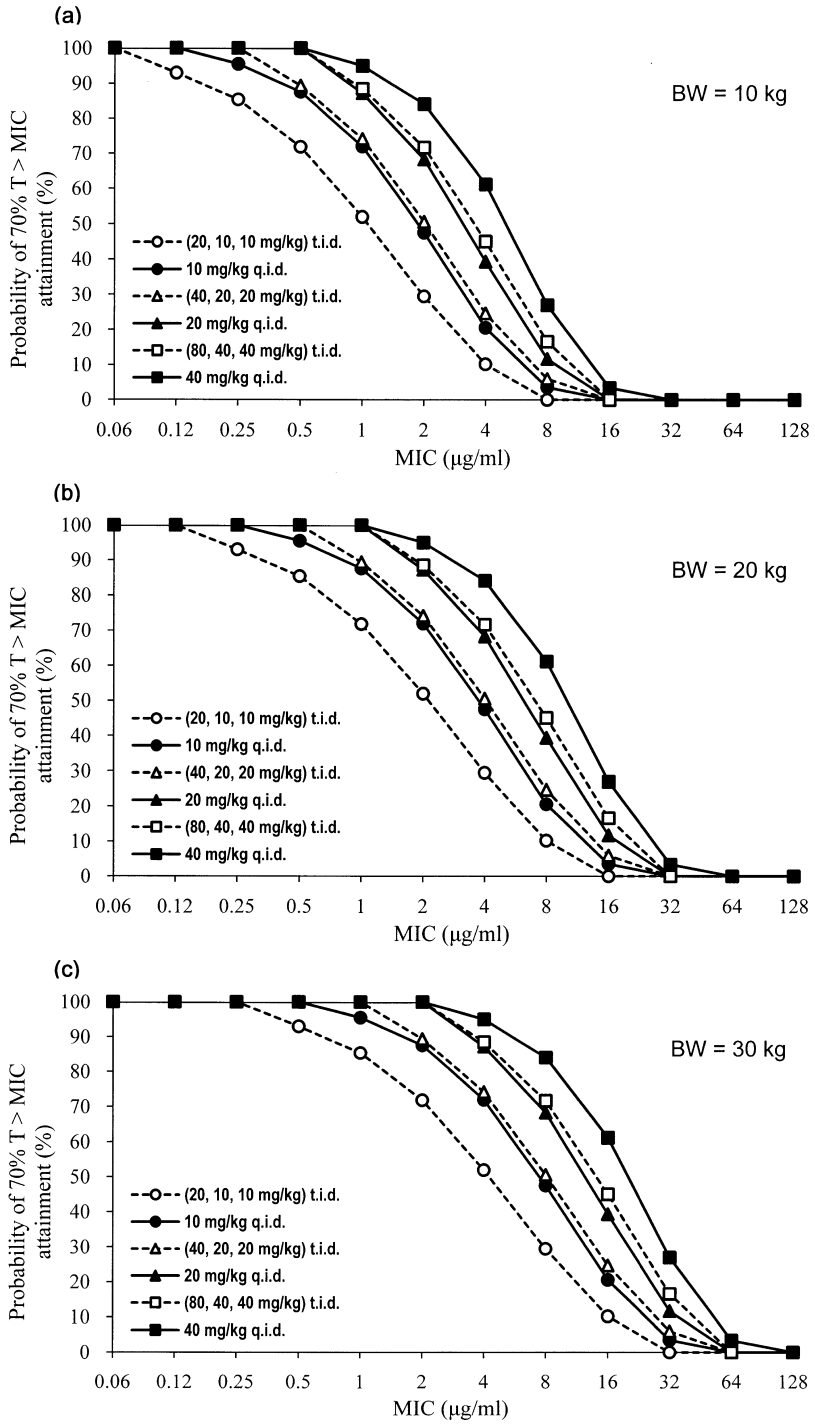

Table 2. Expected population probabilities of 70% T>MIC attainment (%) in three typical patients (body weight (BW): 10, 20 or 30 kg) against *Escherichia coli*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* isolates using cefozopran regimens (0.5-h infusions) of three times a day (t.i.d.) or four times a day (q.i.d.).

Cefozopran regimen	Probability of 70% T > MIC attainment (%)		
	BW = 10 kg	BW = 20 kg	BW = 30 kg
E. coli			
(20 mg/kg, 10 mg/kg, 10 mg/kg) t.i.d.	92.7	93.6	94.0
10 mg/kg q.i.d.	93.6	93.9	94.3
(40 mg/kg, 20 mg/kg, 20 mg/kg) t.i.d.	93.7	94.0	94.4
20 mg/kg q.i.d.	93.8	94.2	94.7
S. pneumoniae			
(20 mg/kg, 10 mg/kg, 10 mg/kg) t.i.d.	62.5	77.0	88.1
10 mg/kg q.i.d.	76.9	89.0	95.6
(40 mg/kg, 20 mg/kg, 20 mg/kg) t.i.d.	79.6	90.7	97.0
20 mg/kg q.i.d.	88.7	96.4	99.7
H. influenzae			
(40 mg/kg, 20 mg/kg, 20 mg/kg) t.i.d.	59.8	67.9	77.3
20 mg/kg q.i.d.	64.0	73.3	83.5
(80 mg/kg, 40 mg/kg, 40 mg/kg) t.i.d.	65.4	75.0	85.0
40 mg/kg q.i.d.	69.4	80.1	89.6
P. aeruginosa			
(40 mg/kg, 20 mg/kg, 20 mg/kg) t.i.d.	49.8	65.5	78.0
20 mg/kg q.i.d.	61.0	74.9	84.3
(80 mg/kg, 40 mg/kg, 40 mg/kg) t.i.d.	63.1	76.3	85.3
40 mg/kg q.i.d.	70.4	81.2	88.5

against common pathogenic bacteria in most typical patients. This is the first report of the population pharmacokinetics and pharmacodynamics of cefozopran in a pediatric patient population.

Previous population pharmacokinetic analysis of cefozopran in adults (23～82 years old)[2] indicated that cefozopran followed a two-compartment model and that body weight had the greatest influence on drug distribution. Population pharmacokinetic modeling of cefozopran in neonates (1～27 days old)[14] also showed that body weight was the covariate that had the greatest influence on cefozopran clearance. The results of our study (Table 1) are consistent with these earlier findings of the importance of body weight. Thus, although age often plays an important role in pharmacokinetics, especially in pediatrics, BW appears to have a more direct effect than age on cefozopran pharmacokinetics.

The final population pharmacokinetic model lacked any bias, regardless of the drug concentration (Fig. 1c) or the time (Fig. 1d), and the observed drug concentration was almost identical to the individual predicted concentration after the Bayesian step (Fig. 1b). Therefore, the final model is

considered to have a good predictive performance.

In this study, the population pharmacokinetic model was developed not only for descriptive purposes but also for pharmacodynamic assessment and practical use. The results of the Monte Carlo simulation (Fig. 2) showed that the probabilities of target attainment for 10 mg/kg q.i.d. (40 mg/kg/day regimen) and 20 mg/kg q.i.d. (80 mg/kg/day regimen) were comparable to those for (40, 20, 20 mg/kg) t.i.d. (80 mg/kg/day regimen) and (80, 40, 40 mg/kg) t.i.d. (160 mg/kg/day regimen), respectively. This result suggests that the dosing interval is more important than the daily dosage for dosing of cefozopran, which exhibits time-dependent killing. From a cost-effective viewpoint, q.i.d. regimens would be preferable to t.i.d. regimens, unless frequent drug administration is unacceptable due to an increase in the patient's burden and in the medical workload.

The observed differences in the expected population probability of target attainment among the bacteria tested (Table 2) resulted from their varying specific susceptibilities to cefozopran. Based on the differences, a regimen of 20 mg/kg q.i.d. would be sufficient against high-susceptibility bacteria such as *E. coli* and *S. pneumoniae*. However, if infection with cefozopran-resistant bacteria such as *H. influenzae* and *P. aeruginosa* is suspected then a regimen of 40 mg/kg q.i.d. is recommended, especially for a patient with a low BW. We should note that susceptibility of clinical isolates (especially resistance of *S. pneumoniae*) can vary with patient factors such as children/adults and in-/outpatients. Therefore, our results have a limitation in that we could neither obtain MIC distributions exclusively from children nor extract the MIC distributions for pediatric patients from the surveillance data[11]. Nevertheless, the profiles of the probability of target attainment versus MIC (Fig. 2) are useful when the MIC value for a bacterium is given, regardless of its susceptibility pattern.

Conclusions

The present study developed a population model for cefozopran in pediatric patients and identified BW as the most significant covariate that affected cefozopran pharmacokinetics. The pharmacodynamics of approved cefozopran regimes were assessed based on this model. The Monte Carlo simulation showed that 20 mg/kg q.i.d. and 40 mg/kg q.i.d. regimens, which were more effective than the corresponding t.i.d. regimens, had sufficient bactericidal effects against common bacteria in most typical patients. These results provide a better understanding of the pharmacokinetics of cefozopran. They are also useful in the choice of a cefozopran regimen based on the BW of the pediatric patient and the susceptibility of the causative bacteria (either suspected because of the patient's symptoms or identified by MIC data). The implications of our findings and proposals need to be confirmed in a clinical setting.

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