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Research Article

Cerebrospinal Pharmacokinetic Analysis and Pharmacodynamic Evaluation of Ceftriaxone in Pediatric Patients with Bacterial Meningitis

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What Is Known? and Objective. Ceftriaxone has been widely used to treat bacterial meningitis in pediatric patients. Ceftriaxone dosing regimens of 80–120 mg/kg/day have been recommended for bacterial meningitis in pediatric patients, and the usual duration of therapy is 7–14 days. Although the target site for meningitis is cerebrospinal fluid (CSF), a CSF pharmacokinetic (PK) model in pediatric patients has not been reported. We aimed to develop a CSF PK model of ceftriaxone, using not only serum but also CSF concentration data, and to evaluate the appropriateness of dosing regimens for pediatric patients with bacterial meningitis. *Methods*. The population PK model was developed by simultaneously fitting serum and CSF data from pediatric patients described in nine published articles. Probabilities of attaining a pharmacodynamic target (100% $T >$ MIC, 100% of time that drug concentrations above the minimum inhibitory concentration) in CSF were estimated for some dosing regimens. *Results and Discussion*. Twenty-four pediatric patients with meningitis were the subjects for PK modeling (0.52–13 years old, and 3.5–50 kg of body weight). Sixty-eight serum concentrations and 98 CSF samples were used to develop the CSF PK model. The CSF/serum concentration ratio at the same sampling time was 0.0628 ± 0.0689. Age was not a statistically significant covariate in the PK parameter. In the CSF PK model, 40–60 mg/kg q12 h achieved a target attainment probability >90% against causative bacteria for bacterial meningitis. However, 4-h infusion (rather than 0.5-h infusion) dosing regimens were required for efficacy against antimicrobial-resistant bacteria with high MICs. *What Is New? and Conclusion*. Ceftriaxone-dosing regimens with prolonged infusion times might be reasonably effective for treating antimicrobial-resistant pathogens in empiric therapy.

1. Introduction

Bacterial meningitis is a critical disease worldwide that usually requires immediate treatment. Unless treated properly, bacterial meningitis has a very high mortality rate [1]. Accurate diagnosis and rapid treatment, including antimicrobial therapy, are necessary. Infant and pediatric mortality has been decreasing [2]; however, the rate of abnormalities in survivors remains high [3, 4]. Therefore, the appropriateness of antimicrobial therapy is important. Ceftriaxone is a third-generation cephalosporin that has been widely used for treating bacterial meningitis in pediatric patients [5]. The drug has antimicrobial activity against various pathogens causing meningitis, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. However, some bacteria resistant to ceftriaxone were recently detected in the surveillance of antimicrobial susceptibility, [6–8] which might require optimization of antibiotic selection and dosage setting. Ceftriaxone dosing regimens of 80–120 mg/kg/day have been recommended for bacterial meningitis in pediatric patients and the usual duration of therapy is 7–14 days [9–11].

Pharmacokinetic (PK)/pharmacodynamic (PD) theory has previously been used to optimize antimicrobial treatment [12, 13]. Other studies have reported population PK analysis and PD evaluation of ceftriaxone that used blood samples from pediatric patients [14–17]. However, the many bacteria that cause meningitis are present in cerebrospinal fluid (CSF), which means that drug concentrations in the CSF are important.

Furthermore, there has been insufficient blood and CSF sampling from studies in pediatric patients because of ethical issues. To overcome this problem, pooled PK analysis has been used by researchers to build PK models in populations [18, 19]. Accordingly, this study aimed to construct a PK/PD model of ceftriaxone in CSF using pooled data of pediatric patients from previous studies to enable optimization of ceftriaxone dosing regimens for bacterial meningitis.

2. Methods

2.1. PK Data Collection. Nine published reports in pediatric populations with available CSF data were selected [20–28]. In patients for whom the CSF concentration data were available, serum concentration data were also collected when possible. Information, such as ceftriaxone dosing methods, sampling time points, sex, age, body weight, dose, and clinical diagnosis (bacterial or aseptic meningitis), was collected. Cases that lacked dosing information were excluded from this PK analysis.

2.2. Calculation of the CSF/Serum Concentration Ratio. For the same sampling points of serum and CSF, the CSF/serum concentration ratio was calculated to assess the penetration into the CSF. At the same sampling points, the number of days after starting ceftriaxone administration and the time after dosing were gathered from the literature data.

2.3. Cerebrospinal PK Modeling. First, a PK model using serum samples was developed and then the cerebrospinal PK modeling, including CSF concentrations, was performed. The CSF PK model of ceftriaxone was based on the following equation (Figure 1):

$$\frac{dX(\text{central})}{dt} = -\frac{\text{CL}}{V_{\text{central}}} \times X(\text{central}),$$
$$\frac{dX(\text{CSF})}{dt} = Q_{\text{CSF}} \times \frac{X(\text{central})}{V_{\text{central}}} - Q_{\text{CSF}} \times \frac{X(\text{CSF})}{V_{\text{CSF}}/\text{KP}_{\text{CSF}}}, \quad (1)$$

where X(central) and X(CSF) are the amounts of drug (mg) in the central and CSF compartments, respectively, CL is the clearance (L/h) from the central compartment, V_{central} and V_{CSF} are the volumes of distribution (L) of the central and CSF compartments, respectively, KP_{CSF} is the CSF-to-serum partition coefficient, and Q_{CSF} is the CSF flow clearance (L/h). NONMEM 7 (ICON Development Solutions, Dublin, Ireland) was used to perform population PK modeling, and the ADVAN6 subroutine with the first-order conditional estimation method was used.

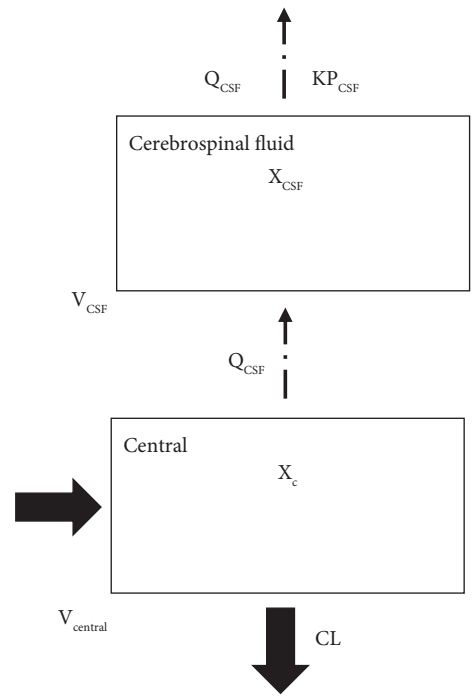

Figure 1: Cerebrospinal pharmacokinetic model of ceftriaxone. X_c and X_{CSF} are the amounts of ceftriaxone (mg) in the central and cerebrospinal fluid (CSF) compartments; CL, clearances (L/h/kg); V_{central} and V_{CSF}, distribution volumes of the central and CSF compartments (L/kg); Q_{CSF}, CSF flow clearance; KP_{CSF}, CSF to serum partition coefficient.

The interindividual variability was modeled with the following exponential error model:

$$\theta_i = \theta \times \exp(\eta_i), \quad (2)$$

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 mean zero and variance ω^2. The residual variability was modeled with a proportional-error model.

A covariate test was performed to construct the model. Covariates (age and dose) were then tested for correlation with individual PK parameters (CL and V_{central}) obtained from the basic model and were incorporated into the covariate model according to their statistical significance ($p < 0.05$).

2.4. Model Validation. A nonparametric bootstrap method was performed to test parameter robustness using Perl-speaks-NONMEM software [29]. The 95% confidence intervals of the parameters from the bootstrap method ($n = 1000$) were compared with the estimates of the final population model. Goodness-of-fit plots (observations versus predictions, conditional weighted residuals (CWRES) versus prediction) and dose-normalized visual predictive checks were performed to validate the final model. The 90% prediction interval of the drug-concentration time course, using the values from the 5%

point to the 95% point of concentrations at each time point, was obtained by performing 1000 simulations with the final parameter estimates.

2.5. Microbiological Data. The minimum inhibitory concentration (MIC) distribution data for ceftriaxone were obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [30]. Six common types of pathogenic bacteria were selected, namely, *S. agalactiae* ($n = 32$; $MIC_{50} = 0.03\,\mu g/mL$, $MIC_{90} = 0.06\,\mu g/mL$), *S. pneumoniae* ($n = 3238$; $MIC_{50} = 0.03\,\mu g/mL$, $MIC_{90} = 1\,\mu g/mL$), *N. meningitidis* ($n = 319$; $MIC_{50} = 0.002\,\mu g/mL$, $MIC_{90} = 0.002\,\mu g/mL$), *H. influenzae* ($n = 109$; $MIC_{50} = 0.004\,\mu g/mL$, $MIC_{90} = 0.008\,\mu g/mL$), *Escherichia coli* ($n = 908$; $MIC_{50} = 0.03\,\mu g/mL$, $MIC_{90} = 0.06\,\mu g/mL$), and *Klebsiella pneumoniae* ($n = 46$; $MIC_{50} = 0.03\,\mu g/mL$, $MIC_{90} = 0.25\,\mu g/mL$).

2.6. Cerebrospinal PK/PD Simulation. Five fixed-effects parameters θ_i (CL, $V_{central}$, KP_{CSF}, Q_{CSF}, V_{CSF}) were randomly generated 1000 times by the $SIMULATION command in NONMEM according to each mean estimate and interindividual variance of the developed model. The set of five θ_i values gave model equations and simulated CSF concentrations of ceftriaxone at steady state for each dosing regimen. The time point at which the CSF concentrations coincided with a specific MIC value (0.002–64 $\mu g/mL$) was determined, and the drug exposure time above the MIC for pathogens ($T > MIC$) was calculated as the cumulative percentage during 24 h for different dosing regimens. The probability of target attainment (%) at a specific MIC was defined as the proportion that achieved 100% $T > MIC$ as the PK/PD target. The total CSF concentration was not adjusted for the free fraction because the protein binding of ceftriaxone in CSF is currently unknown.

For empirical use assuming that the causative bacteria were uncertain, the probability at a specific MIC was then multiplied by the fraction of the clinical isolate population at each MIC, and the sum of the individual products was determined as the expected probability (%) of attaining the PK/PD target in CSF. The MIC distributions against common bacteria causing meningitis were derived from the MIC distributions in the EUCAST database [30].

3. Results

3.1. Patient Characteristics. The pediatric patients' demographic parameters are shown in Table 1. The subjects of this population PK analysis were 24 pediatric patients ranging in age from 0.52 to 13 years and in body weight from 3.5 to 50 kg. The subjects were administered a bolus or 1-h infusion of 10–80 mg/kg. Clinical diagnosis of bacterial meningitis was performed in 12 (50%) pediatric patients. Laboratory data such as serum albumin and creatinine clearance were not available. A total of 68 serum and 98 CSF samples after administration were used for population PK modeling.

Table 1: Summary of demographic parameters in pediatric patients with suspected bacterial meningitis.

	$N = 24$ Number (%) or mean ± S.D. (range)
Sex (male: female: not applicable)	10 : 4 : 10
Age (years)	4.0 ± 4.0 (0.52–13)[a]
Neonate (0–34 days)	3 (12.5%)
Infant (35 days-2 years)	7 (29.2%)
Child (2–11 years)	12 (50%)
Adolescent (12–16 years)	1 (4.2%)
Not applicable	1 (4.2%)
Body weight (kg)	14.8 ± 13.1 (3.5–50.0)[b]
Dose of ceftriaxone (mg/kg)	43.2 ± 16.1 (10.0–80.0)
Single dose	8 (33.3%)
Twice daily	12 (50%)
Three times daily	4 (16.7%)
Clinical diagnosis	
Bacterial meningitis	12 (50%)
Aseptic meningitis	12 (50%)

[a]One patient was excluded due to data loss; [b]ten patients were excluded due to data loss.

3.2. Calculation of the CSF/Serum Concentration Ratio. The CSF/serum concentration ratio at the same sampling point is calculated. The CSF/serum concentration ratio was 0.0628 ± 0.0689. The number of days after the start of administration and the time after dosing were 7.2 ± 7.7 days and 4.8 ± 4.7 h, respectively.

3.3. Population PK Modeling. The final parameters of ceftriaxone in this model are presented in Table 2. Incorporation of age and dose into the parameters for CL and $V_{central}$ resulted in a nonsignificant correlation. Based on the calculated CSF/serum concentration ratio, KP_{CSF} was fixed as 0.0628. All estimated parameters, including the interindividual and intraindividual variabilities, were all within the 95% confidence intervals obtained using the bootstrap method.

The goodness-of-fit plots in serum and CSF concentrations are shown in Figure 2. For both serum and CSF samples, plots of the observed concentration (DV) vs. population-predicted concentration (PRED) and plots of CWRES vs. PRED indicated no major bias. A dose-normalized visual predictive check was also performed for the observed and predicted values (based on the final model) of ceftriaxone vs. time (Figure 3). Most of the observed serum and CSF values were within the predicted 90% confidence intervals for the 5th, 50th, and 95th percentile points.

3.4. PK/PD Evaluation. Using the final model, the probabilities of target attainment in the CSF were calculated with different dosages (40–60 mg/kg q12 h or 80–120 mg/kg q24 h) and infusion time (0.5- or 4-h infusion) (Figure 4). For 100% $T > MIC$, cerebrospinal PK/PD breakpoints indicated the highest MIC at which the target attainment probability in CSF was >90%, which are represented in

Table 2: Final estimates of population pharmacokinetic parameters.

	Estimate	(RSE %)	95% CI
Fix effects parameter			
CL (L/h/kg)			
θ_1	0.0444	(18.0)	0.0310–0.0635
$V_{central}$ (L/kg)			
θ_2	0.339	(19.1)	0.217–0.469
KP_{CSF}			
θ_3	0.0628	Fixed	
Q_{CSF} (L/h/kg)			
θ_4	0.000180	(49.9)	0.0000517–0.001339
V_{CSF} (L/kg)			
θ_5	0.00484	(99.3)	0.000977–0.0298
Interindividual variability (exponential error model)			
ηCL	0.365	(53.4)	0.0389–0.720
$\eta V_{central}$	0.698	(31.4)	0.239–1.15
ηKP_{CSF}	1.01	(52.5)	0.258–2.43
ηQ_{CSF}	2.31	(48.4)	0.941–5.81
ηV_{CSF}	2.31	(41.1)	0.941–5.81
Residual variability (proportion error model)			
$\varepsilon_{proportional}$	0.0310	(39.4)	0.0131–0.0656

CI, confidence interval determined from 1000 bootstrap replicates RSE, relative standard error. θ, population mean value; η, random variable which is normally distributed with a mean of zero and variance. ε, random error which is normally distributed with a mean of zero and variance.

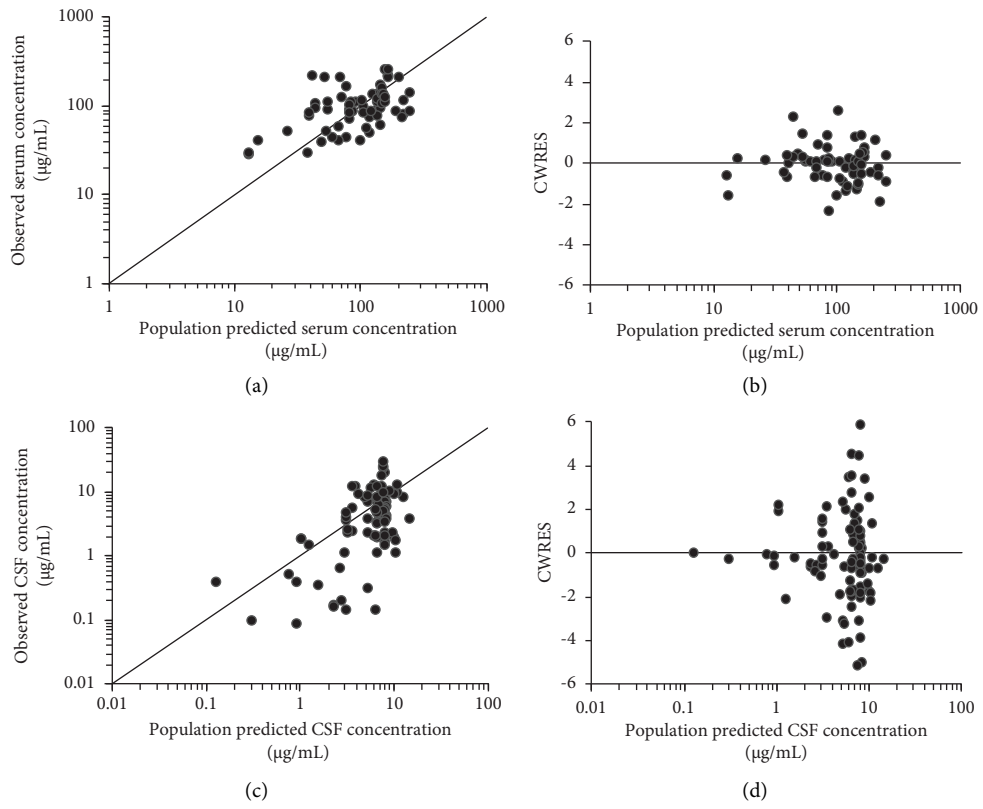

Figure 2: Diagnostic plots of the final population PK model of ceftriaxone in pediatric patients. Observed concentrations versus population-predicted concentrations in serum (a), conditional weighted residual (CWRES) versus population-predicted concentrations in serum (b), observed concentrations versus population-predicted concentrations in cerebrospinal fluid (c), and CWRES versus population-predicted concentrations in cerebrospinal fluid (d).

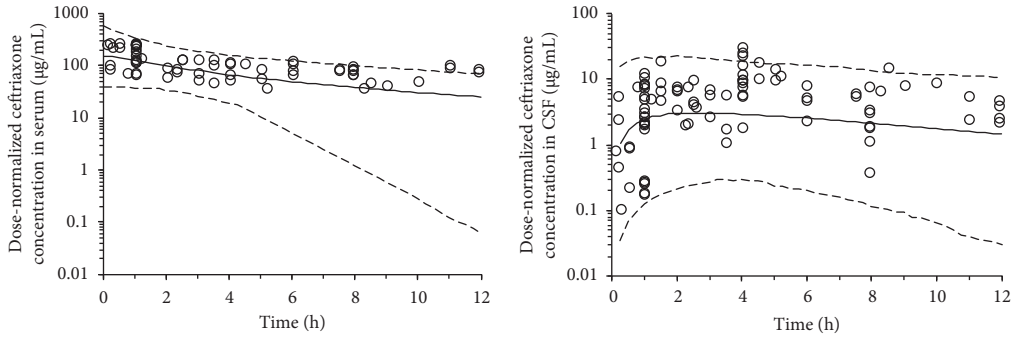

Figure 3: Visual predictive check plots representing observed serum (a) and CSF (b) concentrations normalized to 50 mg/kg of ceftriaxone the heavy and dotted line denote the median and 90% predicted intervals calculated from 1,000 simulations.

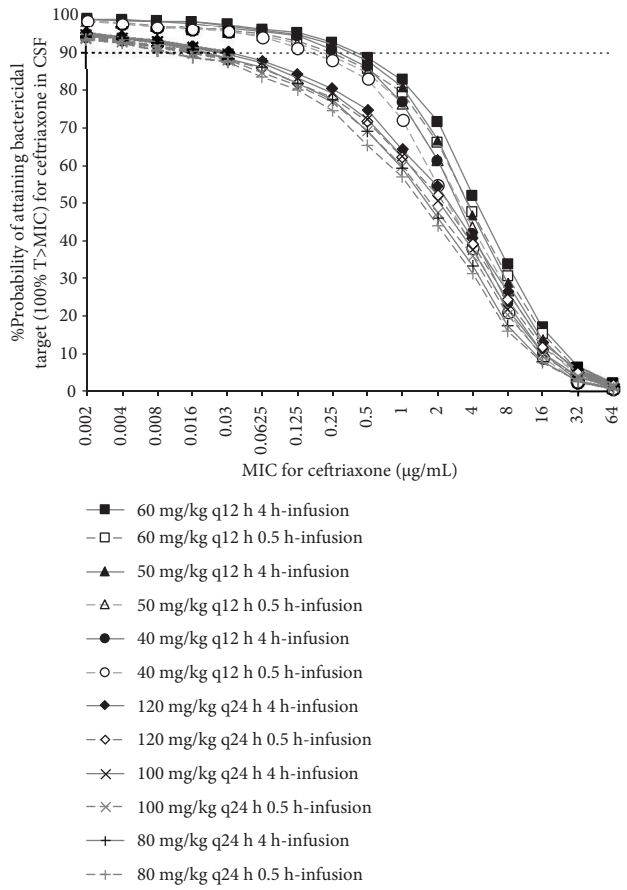

Figure 4: Probabilities of attaining pharmacokinetics (PK)/pharmacodynamics (PD) target (100% $T > \text{MIC}$) in cerebrospinal fluid (CSF) for ceftriaxone at specific MICs. The dotted lines represent 90% probability. Dosing regimens of 120 mg/kg/day are up to 4000 mg/day for pediatric patients over 33.3 kg.

Table 3. The cerebrospinal PK/PD breakpoints of 40–60 mg/kg q12 h 0.5-h infusion and 4-h infusion were 0.125 and 0.25 μg/mL, respectively. The cerebrospinal PK/PD breakpoints of 80–120 mg/kg q24 h regimens ranged from 0.008 to 0.03 μg/mL, with the highest breakpoint at 120 mg/kg q24 h 4-h infusion.

Table 3: Pharmacokinetic/pharmacodynamic breakpoints of ceftriaxone in cerebrospinal fluid (CSF).

Ceftriaxone regimen	PK/PD target in CSF (100% $T > \text{MIC}$)
40 mg/kg q12 h 0.5 h-infusion	0.125
40 mg/kg q12 h 4 h-infusion	0.25
50 mg/kg q12 h 0.5 h-infusion	0.125
50 mg/kg q12 h 4 h-infusion	0.25
60 mg/kg q12 h 0.5 h-infusion	0.125
60 mg/kg q12 h 4 h-infusion	0.25
80 mg/kg q24 h 0.5 h-infusion	0.008
80 mg/kg q24 h 4 h-infusion	0.016
100 mg/kg q24 h 0.5 h-infusion	0.008
100 mg/kg q24 h 4 h-infusion	0.016
120 mg/kg q24 h 0.5 h-infusion	0.016
120 mg/kg q24 h 4 h-infusion	0.03

Pharmacokinetic/pharmacodynamic breakpoints are defined as the largest MIC attaining more than 90% probabilities.

Furthermore, the expected probabilities (%) of attaining the PK/PD target in CSF were calculated (Table 4). All simulated dosing regimens of 40–60 mg/kg q12 h represented >90% of the expected probabilities against six pathogens (*S. agalactiae*, *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *E. coli*, and *K. pneumoniae*), whereas simulated dosing regimens of 80–120 mg/kg q24 h represented >90% of the expected probabilities against only *N. meningitidis* and *H. influenzae*.

4. Discussion

No previous reports have described studies using a CSF PK model of ceftriaxone in pediatric patients or stochastic methods to evaluate PD. This study used CSF PK/PD analysis to evaluate the efficacy of several dosing regimens for treating meningitis in pediatric patients.

Regarding the CSF/serum concentration ratio, Latif and Dajani reported a mean CSF/plasma ratio that ranged from 0.015 to 0.07 after a single 75 mg/kg dose (sampling time: 3–6 h after dose) in children with meningitis [31]. Steele et al. reported a CSF/plasma concentration ratio ranging from 0.018 to 0.246 after a single dose in pediatric patients with

Table 4: Expected probabilities of attaining PK/PD target (100% $T > MIC$) for ceftriaxone in cerebrospinal fluid (CSF), against bacterial populations (Figure 2) using different ceftriaxone regimens.

Ceftriaxone regimen	% expected probability of attaining PK/PD target (100% $T > MIC$) in CSF					
	S. agalactiae ($MIC_{90} = 0.06$)	*S. pneumoniae* ($MIC_{90} = 1$)	*N. meningitidis* ($MIC_{90} = 0.002$)	*H. influenzae* ($MIC_{90} = 0.008$)	*E. coli* ($MIC_{90} = 0.06$)	*K. pneumoniae* ($MIC_{90} = 0.25$)
40 mg/kg q12 h 0.5 h-infusion	94.8	92.1	98.4	97.4	94.4	93.8
40 mg/kg q12 h 4 h-infusion	96.2	93.9	98.8	98.4	95.7	95.4
50 mg/kg q12 h 0.5 h-infusion	95.1	92.8	98.4	97.6	94.7	94.2
50 mg/kg q12 h 4 h-infusion	96.6	94.9	98.9	98.6	96.2	96.0
60 mg/kg q12 h 0.5 h-infusion	95.5	93.4	98.4	97.8	95.0	94.6
60 mg/kg q12 h 4 h-infusion	96.8	95.4	99.0	98.7	96.6	96.4
80 mg/kg q24 h 0.5 h-infusion	85.5	82.9	93.3	91.9	85.7	84.1
80 mg/kg q24 h 4 h-infusion	87.4	84.6	94.2	93.1	87.4	86.0
100 mg/kg q24 h 0.5 h-infusion	86.3	84.1	93.6	92.4	86.5	85.2
100 mg/kg q24 h 4 h-infusion	88.4	85.8	94.6	93.3	88.3	87.1
120 mg/kg q24 h 0.5 h-infusion	87.0	84.8	94.0	92.5	87.1	85.8
120 mg/kg q24 h 4 h-infusion	88.9	86.6	95.0	93.7	88.9	87.8

meningitis (sampling time: 1–6 h after dosing) [32]. Therefore, the mean CSF/serum concentration ratio: 0.06 result of this study was similar to those of previous reports in pediatric patients. However, the CSF/serum concentration ratio in this study was measured 7.2 days after the start of administration, i.e., during the acute phase, when determining a suitable maintenance dose, it is necessary to consider the decreased CSF penetration because of the decreased inflammatory response after antimicrobial treatment.

CSF PK modeling was performed with two steps: analysis of serum concentrations, followed by analysis of CSF concentrations. PK parameters (CL and $V_{central}$) estimated from serum concentrations were similar to previous reports in pediatric patients with meningitis [33, 34]. The results of goodness-of-fit plots (Figure 2) and a dose-normalized visual predictive check (Figure 3) in serum and CSF concentrations ensured the adequacy of this model. Regarding the PK parameter covariate, previous population PK studies in pediatric patients reported that the covariates of CL and V were age and body weight [14, 15, 35]. In this study, the PK source data were all based on body weight-normalized doses, and body weight was included in the PK parameters (CL, $V_{central}$, Q_{CSF}, V_{CSF}), whereas no correlation was found between age and the PK parameters (CL and V). This result might be explained by the average age of 1 year for the subjects in the previous report, [15] whereas in the current study, the average age was 4 years, and fewer infants and neonates were included (Table 1). PK analyses that include more infants and neonates are needed since previous studies reported that the clearances of infants and neonates differ in age [36, 37].

Regarding empiric therapy, the expected probability of attaining the PK/PD target (100% $T > MIC$) in CSF against pathogens causing meningitis ($MIC_{90} = 0.002$–$1\ \mu g/mL$) was >90% (Table 4) and was good in regimens of 40–60 mg/kg q12 h, which are recommended in the guidelines [38, 39]. Meanwhile, for regimens of 80–120 mg/kg q24 h, the expected probabilities of attaining PK/PD target in CSF were >90% only against *N. meningitidis* and *H. influenzae* (Table 4). These results suggest that twice daily regimens are reasonable as the empiric therapy. However, since the MIC of penicillin-insensitive *S. pneumoniae* (PISP) with genotype *pbp2x* is high ($MIC_{90} = 0.25$) in Japan, [38] the probabilities of target attainment for 0.5-h infusion regimens were not >90% (Figure 4). Therefore, 4-h infusion regimens might be reasonable from CSF PK/PD perspectives. It has been reported that PISP with genotype *pbp2x* accounts for approximately 40% of all pneumococcal strains in Japan, [38] suggesting that 4-h infusion regimens may be appropriate for empirical therapy. Furthermore, β-lactamase nonproducing ampicillin-resistant *H. influenzae* (BLNAR) has a high MIC ($MIC_{90} = 0.25$) and is an important antimicrobial-resistant pathogen for bacterial meningitis [38]. Especially in Japanese pediatric patients, BLNAR accounts for >60%, [40] and it is necessary to choose dosing regimens covering a high MIC. However, high-dose administration to pediatric patients reportedly has risks, such as for biliary sludge and cholelithiasis [41–47]. Therefore, it may be more reasonable to extend the infusion time rather than to simply increase the dose.

There were some study limitations that should be considered when interpreting our results. First, this population included pediatric patients with aseptic meningitis, and the CSF/serum concentration ratio may have been underestimated relative to the actual patients with bacterial meningitis. However, since ethical reasons restrict CSF sampling from pediatric patients, it may be difficult to collect CSF samples only from infants with bacterial meningitis. Second, this study used antimicrobial susceptibility results from EUCAST, the database of which includes data other than CSF samples. Therefore, the MIC distributions of EUCAST and in CSF may differ. However, the EUCAST results were used because there is no database that describes details of MIC distribution only for CSF samples.

The results from this CSF PK/PD approach indicated that ceftriaxone dosing regimens with a prolonged infusion time might be reasonable for treating antimicrobial-resistant pathogens, such as PISP and BLNAR, in empiric therapy.

Data Availability

The data supporting the findings of this study were derived from the resource available in the public domain.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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