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Research Paper

Indications for a ceftriaxone dosing regimen in Japanese paediatric patients using population pharmacokinetic/pharmacodynamic analysis and simulation

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Abstract

Objectives The objective of this study was to build a ceftriaxone population pharmacokinetic model for Japanese paediatric patients and to examine the dosing regimen of ceftriaxone based on pharmacokinetic/pharmacodynamic (PK/PD) analysis.

Methods The population pharmacokinetic analysis using NONMEM was based on published serum concentrations of ceftriaxone. A Monte Carlo simulation was examined to evaluate the time above the minimum inhibitory concentration (TAM) in 20 and 60 mg/kg body weight dose regimen using the population pharmacokinetic parameters.

Key findings The time course of the serum concentration of ceftriaxone in paediatric patients was fitted to a two-compartment model and body weight was incorporated to pharmacokinetic parameters as the covariate. Based on the percent TAM estimated from the final population pharmacokinetic model and the minimum inhibitory concentration (MIC) of ceftriaxone in 2004, we have predicted that the once daily administration of 20 mg/kg ceftriaxone would be effective on various infecting organisms.

Conclusions A population pharmacokinetic model of ceftriaxone was built for Japanese paediatric patients based on the available data. The estimated PK/PD result confirmed the appropriateness of once daily dose of 20 mg/kg. In some patients for whom no efficacy was observed at 20 mg/kg, an increase to 60 mg/kg may be required.

Keywords ceftriaxone; Japanese paediatric patients; pharmacodynamics; population pharmacokinetics

Introduction

Ceftriaxone is a 'third generation' cephalosporin possessing broad spectrum antimicrobial activity, which was launched by Hoffman-La Roche in 1978 and belongs to the family of β-lactam antibiotics.[1] Ceftriaxone is an active agent against Gram-negative and Gram-positive microorganisms. The half-life of ceftriaxone is 7–8 h and the plasma concentration after 24 h intravenous dosing is approximately 12 μg/ml at a dose of 1 g in adult patients. This plasma concentration level makes a once daily dose regimen of ceftriaxone to be efficacious against many infectious diseases. The relationship between blood concentration of antibiotics and efficacy has been elucidated and it is clear that the time above minimum inhibitory concentration (TAM) is related to efficacy of β-lactam antibiotics such as ceftriaxone.[2] Craig[2] reported that maximal efficacy of cephalosporins was attained when TAM was held for 60–70% of the time before the next dosing. According to published reports and since the minimum inhibitory concentration (MIC) generally varies among different regions and time spans, it is important to estimate TAM using precise pharmacokinetics of ceftriaxone based on local MIC values.[3,4] Thus, serum ceftriaxone concentration and MIC against infecting bacteria are important parameters for prediction of efficacy in a ceftriaxone regimen.

Several studies have reported that there is a specific protein binding site for ceftriaxone on human serum albumin (HSA).[5,6] This means that the protein binding ratio of ceftriaxone to HSA depends on the drug concentration. When serum ceftriaxone concentration is extremely high (e.g. the value immediately after intravenous dosing), binding ratio decreases along with the increase of free ceftriaxone; resulting in high tissue distribution of free ceftriaxone from blood. As a result, dose proportionality is not observed at the initial serum

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concentration and if the initial serum ceftriaxone concentration is predicted using a model to which changes due to HSA binding are not incorporated, the predicted value becomes higher than that observed. On the basis of this thought, a model to which the change of protein-binding ratios is incorporated is essential for the pharmacokinetic model of ceftriaxone.

According to United States and European Union guidelines, the ceftriaxone dosing regimen in paediatric patients of those countries is once daily. On the other hand, the regimen for paediatric patients in Japan is twice daily, which is written on the ceftriaxone package insert for political reasons. Recently, a ceftriaxone once daily dosing regimen in paediatric patients has gradually become the requirement even in Japan, in conjunction with the popularization of outpatient parenteral antimicrobial therapy (OPAT). Also, the uniform dose is used for adult patients while the body weight normalized dose is used for paediatric patients. We need to confirm which regimens are appropriate for paediatric patients.

We have investigated population pharmacokinetics in Japanese paediatric patients based on published data, because no indication based on pharmacokinetic/pharmacodynamic (PK/PD) exists for a paediatric dosing regimen. We have used a population pharmacokinetic analysis approach and determined appropriate once daily ceftriaxone dose for paediatric patients, based on TAM. This is the first report describing a once daily dosing regimen of ceftriaxone for Japanese paediatric patients, established using a population pharmacokinetic model in which volume of distribution associated with protein binding has been included and MIC of infecting organisms in 2004.

Materials and Methods

Analysis object

Data on 531 point blood samples from published pharmacokinetic analyses of ceftriaxone were collected from 78 subjects (Table 1).[7–14] The method of ceftriaxone administration was intravenous bolus injection or infusion. All serum concentrations of ceftriaxone were measured by a bioassay.[15] Observations lacking information on age, weight or administration time were excluded from the analysis. When information on infusion time was missing for an intravenous bolus injection, 1 min was set as the infusion time.

Outlier

No specific examination was performed for the outliers, and all the data that satisfied the criteria of the analysis object were used for analysis.

Population pharmacokinetic model building

The population pharmacokinetic model was built according to the following procedure. The number of compartments in the pharmacokinetic model was assessed at first so as to be able to select a model with the minimum objective function value (OFV) and without bias in the goodness of fit plot. An error model with the minimum OFV was examined to determine the base model. The effect of body weight was examined as a covariate, each OFV of the base model was compared, and the model with the lowest OFV was selected as the final model. The details of the model used at each step are described below.

Pharmacokinetic model

We investigated one- and two-compartment pharmacokinetic models to which protein binding was incorporated as a factor. In each model, we predicted that ceftriaxone was eliminated from the central compartment and the measured serum ceftriaxone concentration was total concentration. The parameters of unbound ceftriaxone were calculated by incorporating an equation by which the concentrations of unbound form was calculated from the protein unbinding rates (eqn 1). The binding parameters of ceftriaxone with serum protein have been reported by McNamara *et al*.[5]:

$$C_{total} = C_f + C_b = C_f + \frac{C_f \cdot nPK}{1 + C_f \cdot K} \quad (1)$$

where C_f is the concentration of free ceftriaxone, C_b is the concentration of bound ceftriaxone, n is the number of protein binding sites, P is the concentration of protein in serum and K is the association constant of ceftriaxone to serum protein.

Error model

As the error model of intra-individual variation, a model with the smallest OFV was selected and examined for equations 2–4. The inter-individual variation of pharmacokinetic parameters was to be a logarithm error expressed by equation 5:

Table 1 List of source data and number of patients for population pharmacokinetic analysis

Author	Title	Number of patients
Nagamatsu *et al*.[7]	Ceftriaxone therapy for paediatric infections	5
Satoh *et al*. [8]	Fundamental and clinical evaluation of ceftriaxone in the field of paediatrics	22
Meguro *et al*. [9]	Clinical and pharmacokinetic study of ceftriaxone in paediatric bacterial infections	13
Toyonaga *et al*.[10]	Fundamental and clinical evaluation of ceftriaxone in the paediatric field	7
Nakazawa *et al*.[11]	Evaluation of ceftriaxone in the paediatric field	10
Motohiro *et al*.[12]	Fundamental and clinical evaluation of ceftriaxone in the paediatric field	8
Fujita *et al*.[13]	Clinical and pharmacokinetic evaluation of ceftriaxone in children	11
Minamitani *et al*.[14]	Clinical evaluation of ceftriaxone in the paediatric field	2
Total		78

$$C_{ij} = \hat{C}_{ij} + \varepsilon_{ij} \quad (2)$$

$$C_{ij} = \hat{C}_{ij} \times e^{\varepsilon_{ij}} \quad (3)$$

$$C_{ij} = \hat{C}_{ij} \times e^{\varepsilon_{1ij}} + \varepsilon_{2ij} \quad (4)$$

$$\theta_j = \theta_{pop} \cdot e^{\eta_j} \quad (5)$$

where C_{ij} represents the serum concentration of drug, ε_{ij} is the intra-individual variation, θ_j is the individual parameter, θ_{pop} is the population mean value, and η_j the inter-individual variation.

Covariate effects

Body size was considered in relation to body weight.[16] Consequently, we compared the renal/metabolism maturation model (eqns 6 and 7) proposed by Holford[17] and Tod *et al*.[18] for which the effect of body weight on pharmacokinetic parameters is taken into account with the base model:

$$CL_j = CL_{pop} \cdot \left(\frac{WT_j}{70}\right)^{3/4} \cdot e^{\eta_{CL,j}} \quad (6)$$

$$V_j = V_{pop} \cdot \left(\frac{Wt_j}{70}\right) \cdot e^{\eta_{V,j}} \quad (7)$$

The difference in OFV was used to compare alternative models. A model with the lowest OFV was selected as a final model. Goodness-of-fit from the final model was evaluated with visual inspection of diagnostic scatter plots, including observed versus predicted concentrations.

Calculation of population pharmacokinetic parameters by the bootstrap method

A nonparametric bootstrap method ($n = 1000$) was used to evaluate the uncertainty of all PK parameter estimates from the final model.[19] The 95% confidence interval of population pharmacokinetic parameters was determined by selecting the values from the 2.5% point to the 97.5% point.

Validation of pharmacokinetic model by visual predictive checks

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 implementing 1000 Monte Carlo simulations with the final model and its parameter estimates. By visually comparing the measured values with this estimation interval, we judged the appropriateness of the final population pharmacokinetic model.

Evaluation of dosing regimens

To compare the pharmacokinetics of ceftriaxone in uniform dose (dose per body) and body weight normalized dose, area under the curve (AUC) was simulated 1000 times according to two different dosing regimens. The route of administration for the simulation was rapid infusion in 5 min, which corresponded to a bolus injection. A 60 mg/kg dose was used for the analysis. The median of the body weight from the population was used for the uniform dose and individual body weight was used for the normalized dose. The dosing regimen was evaluated with the distribution of estimated AUC value.

Estimation of pharmacodynamics

Serum total concentration (sum of free and bound concentrations) was calculated from estimated PK parameters using Monte Carlo simulation; antibiotic activity was estimated from the TAM of serum total concentration. The simulation was performed 1000-times at each dose of 20 and 60 mg/kg, between 0 and 24 h after bolus injection. The TAM was calculated from simulated serum concentration. TAM for each bacterium was calculated as the time when serum concentration was above MIC90.[15] Percent TAM was calculated by dividing TAM by 24 h, the predicted dose interval.

Analysis software

Ceftriaxone serum concentration data were analysed by a nonlinear mixed effects modelling approach using NONMEM (Version V, Level 1.1, GloboMax LLC, MD, USA) with the Compaq Visual FORTRAN compiler (Version 6.6, Compaq, NH, USA) under double precision. The NONMEM executions were done with Wings for NONMEM (WFN 408b). First-order conditional estimation with interaction (FOCEI) was applied to pharmacokinetic parameter estimation.

Results

Analysis object

Demographic characteristics of Japanese paediatric patients used in the analysis are shown in Tables 1 and 2. Serum concentration–time profiles in each observation are shown in Figure 1. The number of patients for evaluation was 78. Age ranged from 0.05 to 17 years, body weight from 3.0 to 51 kg, and doses from 9.6 to 80 mg/kg. The administration method was intravenous bolus injection or infusion.

Population pharmacokinetic analysis

The fit between predicted and observed values with the two-compartment model was better than that with the one-compartment model. OFV analysed by the one-compartment and two-compartment models were 3879.489 and 3255.278, respectively. The lowest OFV was obtained with the two-compartment model. Among the error models of intra-individual variation, the mixed error model (eqn 4) resulted in the minimum OFV (OFV of the model with the proportional error and mixed error were 3255.278 and 3250.688, respectively). Since the mixed error model (eqn 4) had the lowest OFV value, this model was chosen as the base model. The renal/metabolism maturation model was compared with the base model. The renal/metabolism maturation model was selected as the final model because the OFV value was further lowered with this model.

The bootstrap method was applied to estimate precise final population pharmacokinetic parameters with the final model. The results are shown in Table 3.

Table 2 Summary of patient characteristics

	Weight (kg)	Age (year)	Dose		Dosing rate	
			Body weight normalized (mg/kg)	Uniform (mg)	Body weight normalized (mg/kg/h)	Uniform (mg/h)
Minimum	3.0	0.05	9.6	59.8	9.6	59.8
Median	21.5	8.00	20.0	400.0	232.8	4 557.8
Maximum	51.0	17.00	80.0	2001.0	2880.0	80 040.0

The average of body-weight normalized dose and dosing rate were 23.3 mg/kg and 592.8 mg/kg/h, respectively.

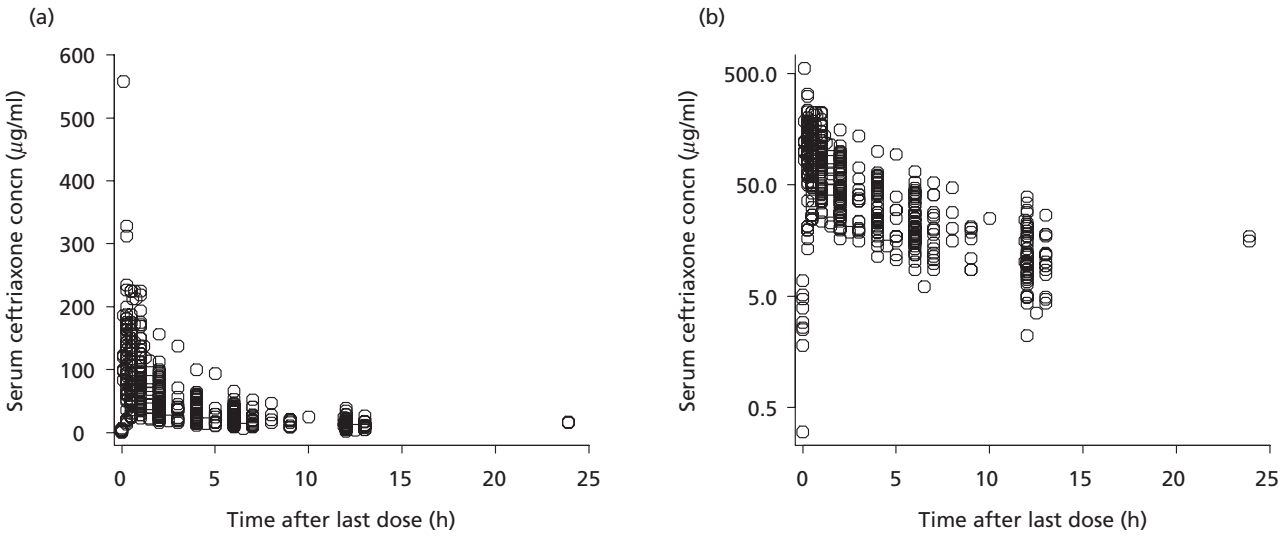

Figure 1 Serum ceftriaxone concentration in Japanese paediatric patients after intravenous injection or infusion. (a) Normal axis plot; (b) semi-logarithmic axis plot. No missing value in this observation.

Goodness-of-fit plots of the final model are shown in Figure 2 and the results of visual predictive checks are shown in Figure 3. The plots showed that the fitting of the model was sufficiently good enough to examine further simulations.

Evaluation of dosing regimen

Ceftriaxone AUC distribution with each dosing regimen, administering the uniform dose or body weight normalized dose, was simulated using the final model. The values of AUC simulated based on the uniform dose and the body weight-normalized dose were 514–3609 and 618–1528 μg/ml, respectively. The AUC distribution at uniform dose was broader than that of body-weight normalized dose.

Dosing simulations to estimate time above the minimum inhibitory concentration

Ceftriaxone serum concentration was simulated 1000-times at the doses of 20 and 60 mg/kg by bolus injection over low (3 kg), medium (21.5 kg), and high (51 kg) body weights. The percent TAM against various bacteria at each body weight was obtained by the simulation (Table 4).

The median percent TAM was approximately 100% regardless of body weight. When paediatric patients had a lower body weight, the lower limit of 95% predicted interval was 50% or less at the dose of 20 mg/kg in *Streptococcus pneumoniae* (penicillin insensitive/penicillin sensitive). On the other hand, the lower limit of 95% predicted interval was 60% or less at the dose of 60 mg/kg in any infecting organisms.

In patients whose body weights were in the range of middle or heavy, the percent TAM was more than 70% even at the dose of 20 mg/kg; the result suggesting enough efficacy could be obtained even at this dose.

Discussion

When pharmacokinetic analysis of ceftriaxone concentration was carried out using a model including a protein binding effect, a good fit to the observed concentration was obtained. Thus, such an analysis was thought to reflect precise ceftriaxone pharmacokinetics.

Schaad and Stoeckel[20] reported that the clearance of ceftriaxone in paediatric patients was affected by body weight. Contrary to this, it had been reported that body weight did not affect the pharmacokinetics of other drugs in a retrospective population pharmacokinetic analysis.[21] Thus, the renal/metabolism maturation model was evaluated to estimate the variance of clearance and distribution volume. The results showed that the renal/metabolism maturation model better described ceftriaxone serum concentration than other models.

Table 3 Parameter estimates with the final model by the bootstrap method for Japanese paediatric patients

Parameter	Units	Median	CV (%)	95% CI	
				Lower	Upper
Fixed effects					
Clearance (CL)	l/h/70 kg	29.4	4.44	26.8	31.9
Central distribution volume (V1)	l/70 kg	88.6	7.09	75.9	101.0
Inter-compartment clearance (Q)	l/h/70 kg	50.2	11.00	39.3	61.9
Peripheral distribution volume (V2)	l/70 kg	157.0	6.82	137.0	180.0
Random effects					
Between subject variability					
BSV CL		0.358	13.29	0.277	0.461
BSV V1		0.545	19.55	0.356	0.764
BSV Q		0.666	16.18	0.455	0.896
BSV V2		0.437	14.81	0.291	0.548
Correlation of CL and V1 R12		0.552	26.69	0.277	0.851
Correlation of CL and Q R13		0.173	67.45	–0.077	0.365
Correlation of V1 and Q R23		0.572	25.83	0.306	0.889
Correlation of CL and V2 R14		0.485	24.01	0.249	0.693
Correlation of V1 and V2 R24		0.560	20.66	0.348	0.809
Correlation of Q and V2 R34		0.615	33.89	0.090	0.836
Random error					
CV		0.146	9.50	0.120	0.817
SD	μg/ml	0.179	99.18	0.000	0.817

BSV means inter-subject variability; CI, confidence interval; CV, coefficient of variation.

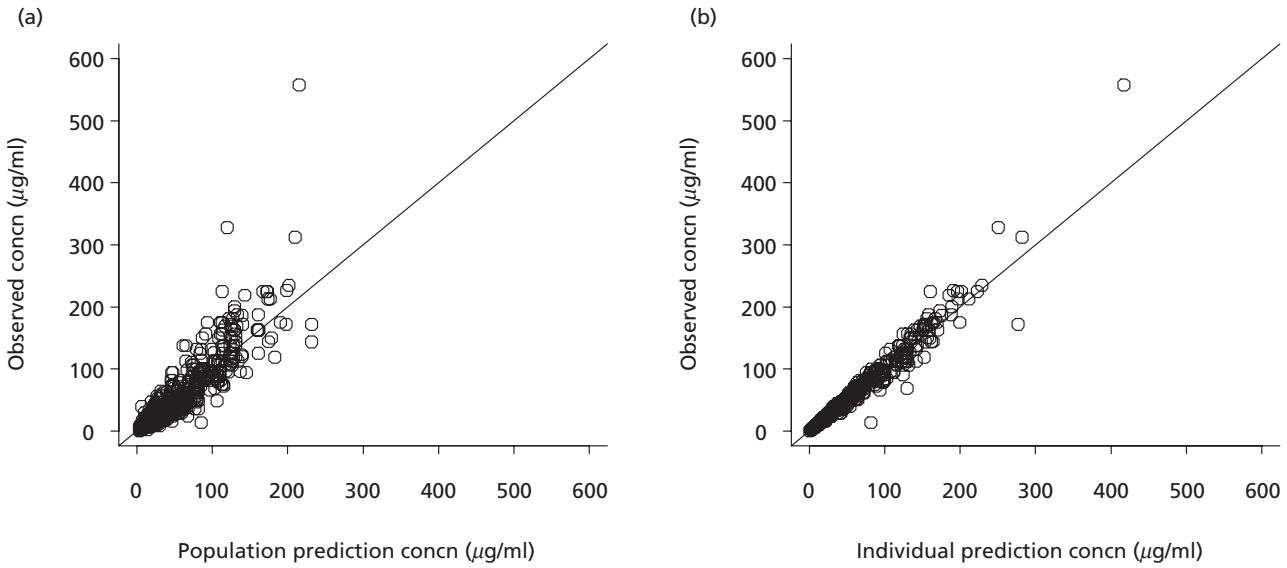

Figure 2 Goodness-of-fit plots of final pharmacokinetic model. (a) Observed vs population predicted serum concentration of ceftriaxone; (b) observed vs individual predicted serum concentration of ceftriaxone. The solid line in each panel shows y = x.

The present population had a broad distribution of body weight, because the target population was paediatric patients. Ceftriaxone was administered intravenously. Our result that body weight affected the pharmacokinetic parameters of ceftriaxone was ascribed to: a highly broad distribution of body weights because the target population in this analysis was paediatric patients; and no influence of bioavailability variations because the dosing route of ceftriaxone was intravenous.

At the median body weight of 21.5 kg, clearance (CL) was calculated as 11.9 l/h. The typical CL from the adult patients, as reported by Iida *et al*.[22], was 12.0 l/h and the CL values from both paediatric and adult patients were similar. The pharmacokinetic model for both paediatric and adult patients was two-compartment. The result suggested that the CL of ceftriaxone in paediatric patients was approximately the same as that of adults when the dose was adjusted by body weight. Further analysis is needed to clarify where the difference

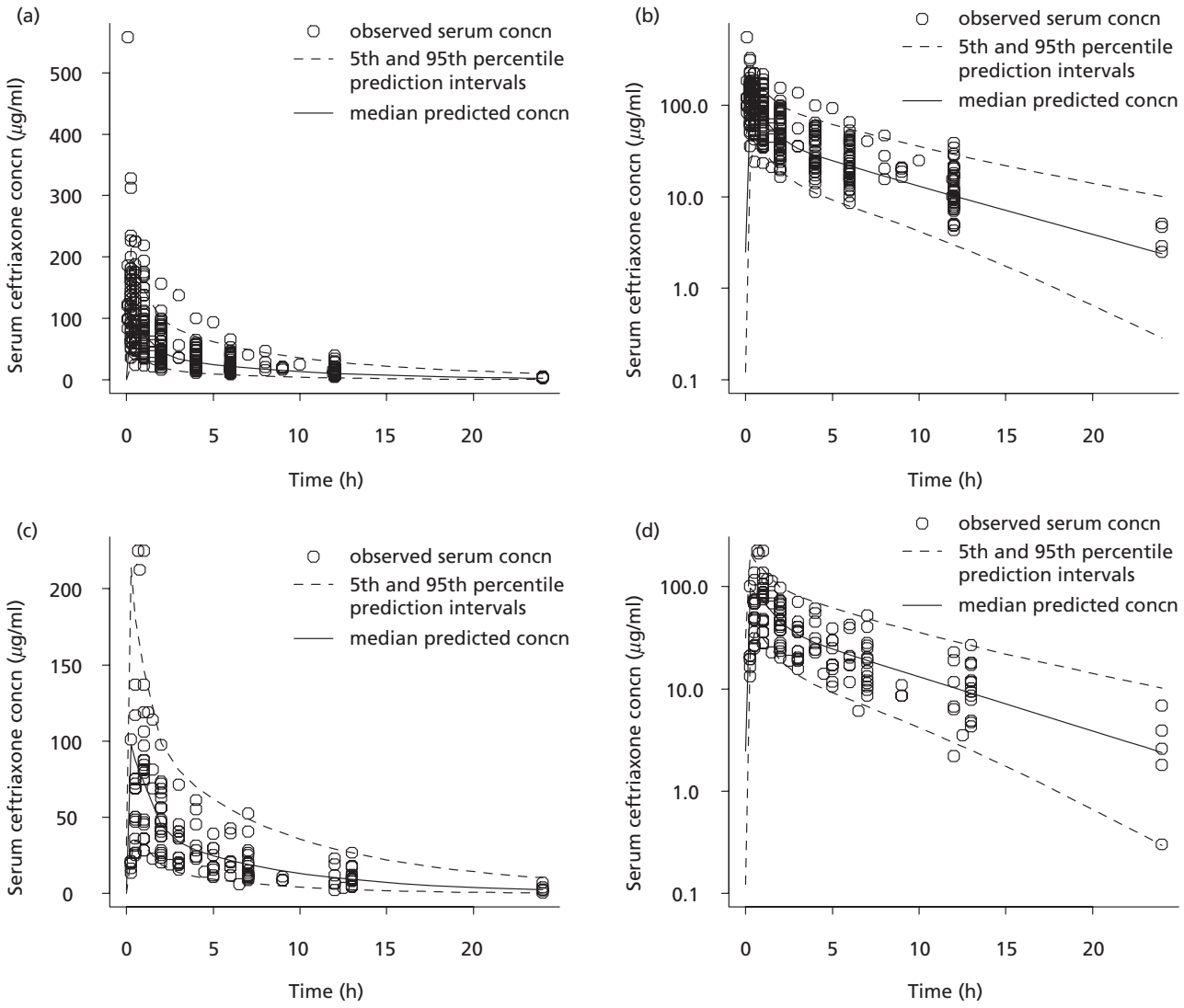

Figure 3 Visual predictive checks of the final population pharmacokinetic model for injection and infusion of ceftriaxone. Injection (a) and (b); infusion (c) and (d). (a) and (c) show normal axis plots, and (b) and (d) show semilogarithmic axis plots.

Table 4 Percent time above the minimum inhibitory concentration against each bacterium after ceftriaxone administration to Japanese paediatric patients

Bacterium	MIC (μg/ml)	Low body weight		Medium body weight		High body weight	
		20 mg/kg dose	60 mg/kg dose	20 mg/kg dose	60 mg/kg dose	20 mg/kg dose	60 mg/kg dose
Escherichia coli	0.06	100 (82.9–100)	100 (96.7–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
Haemophilus influenzae (ABPC sensitive)	0.06	100 (82.9–100)	100 (96.7–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
H. influenzae (BLNAR)	0.25	100 (65.8–100)	100 (79.2–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
H. influenzae (β-lactamase +)	0.12	100 (75–100)	100 (88.3–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
Klebsiella pneumoniae	0.06	100 (82.9–100)	100 (96.7–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
Neisseria gonorrhoeae	0.06	100 (82.9–100)	100 (96.7–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
Streptococcus pneumoniae	0.25	100 (65.8–100)	100 (79.2–100)	100 (100–100)	100 (100–100)	100 (100–100)	100 (100–100)
S. pneumoniae (PISP / PRSP)	1	84.2 (49.2–100)	100 (62.5–100)	100 (75–100)	100 (95.8–100)	100 (96.2–100)	100 (100–100)

BLNAR, β-lactamase-negative ampicillin resistant; MIC, minimum inhibitory concentration; PISP, penicillin insensitive *S. pneumoniae*; PRSP, penicillin sensitive *S. pneumoniae*. Data show median and 95% confidence interval. Body weight was regarded as 3 kg for low, 21.5 kg for medium, and 51 kg for high weight.

between the parameters for paediatric and adult patients comes from.

The body weight-normalized dose of ceftriaxone is used for paediatric patients. The two regimens, uniform dose and body weight-normalized dose were next applied to calculate AUC using the final model. The AUC calculated using the per total body weight regimen showed much less variability than the AUC derived from the uniform dose regimen. It was concluded from this result that the current regimen i.e. body weight-normalized dose, was the more reasonable.

Ceftriaxone is not metabolized but is excreted in the urine (40% in 48 h).[23] This implies that the renal function affects ceftriaxone elimination and the half-life of ceftriaxone is longer in patients with impaired renal function.[24] The data used in this analysis did not, however, give any information about the renal function parameters (e.g. creatinine clearance). As a result, an analysis to elucidate the relationship between ceftriaxone pharmacokinetics and such functions has yet to be undertaken. Such analyses are considered necessary in the future.

As described above, the efficacy of β-lactam antimicrobials is related to percent TAM. Thus, 1000 Monte Carlo simulations were used to calculate percent TAM for prediction of efficacy, based on analysis with intravenous doses of 20 and 60 mg/kg. The simulation results showed efficacy against all bacteria when ceftriaxone was administered to paediatric patients with low body weight using the once daily regimen.

The 20 mg/kg dose may not result in enough efficacy in patients with lower serum ceftriaxone concentration. When this occurs, an increase of the dose up to 60 mg/kg may cause the elevation of blood concentrations, resulting in sufficient efficacy.

Conclusions

The population pharmacokinetic model of ceftriaxone was built using Japanese paediatric patients. We had thought that sufficient efficacy may be obtained by the once daily 20 mg/kg dose regimen of ceftriaxone based on PK/PD estimation. However, it was simultaneously shown that the 20 mg/kg dose may not give enough efficacy to patients with low body weight. In such cases, a dose increase up to 60 mg/kg should give good results in efficacy.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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