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Original Article

Pharmacokinetics, toxicity and clinical efficacy of linezolid in Japanese pediatric patients☆

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ABSTRACT

Objectives: The aims of the present study were (a) to evaluate the pharmacokinetics of linezolid, and (b) to assess the toxicity and clinical efficacy of linezolid in Japanese pediatric patients.
Patients and methods: Routine clinical data including serum linezolid total and unbound concentrations were collected from 15 pediatric patients (0–13 years old). Pharmacokinetics of linezolid was assumed to follow one-compartment with the first-order absorption model. The relationship between risk for thrombocytopenia and linezolid concentrations, and the variations in C-reactive protein (CRP) concentrations and body temperatures were evaluated as clinical efficacy assessment.
Results: Body weight (WT) and maturation of body function were significant covariates for pharmacokinetics of linezolid in pediatric patients. The elimination half-life of linezolid in a pediatric patient with a WT of 9.9 kg and age of 24 months (median of this study) was 3.0 h. Thrombocytopenia was detected in three patients (21.4%), and the minimum concentrations (C_{min}) in these patients were significantly higher than those in patients without thrombocytopenia ($P < 0.05$). The CRP concentrations decreased more than 50% in all pediatric patients after the treatment with linezolid, however body temperatures at the end of treatment were higher than 37.5 °C in 6 patients (42.9%).
Conclusions: Although dose adjustment based on body size was performed for pediatric patients, thrombocytopenia was detected in 21.4% of pediatric patients, and higher C_{min} was associated with the risk of thrombocytopenia. These results encourage the implementation of individual dose adjustment based on linezolid serum concentrations for safe and appropriate treatment with linezolid.

1. Introduction

Linezolid is the first member of the oxazolidinone antimicrobial agents used for the treatment of Gram-positive infections in adult and pediatric patients [1–3]. Linezolid inhibits protein synthesis of bacteria by preventing the formation of the 70S ribosomal complex [4], and exhibits strong antibacterial activity against Gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) [5,6]. The conventional doses of linezolid are 600 mg twice daily for patients aged >12 years old and 10 mg/kg three times daily for pediatrics [7,8]. Linezolid is administered orally or by intravenous infusion, and its oral bioavailability is approximately 100% [9]. Dose adjustment based on patient background and therapeutic drug monitoring were considered unnecessary.

The plasma protein-binding level and volume of distribution at steady state of linezolid in adults are approximately 20–30% and 40–50 L, respectively [1,10,11]. Linezolid is mainly metabolized to its inactive form by non-enzymatic oxidative reactions [12], and 30% of administered linezolid is excreted unchanged in the urine [12]. The range of elimination half-life in adults has been reported to be approximately 4.0–10.0 h [1,11,13–15]. The pharmacokinetics of linezolid was age-dependent, and the elimination half-life for children younger than 12 years old (1.8–2.9 h) was shorter than for adults [16].

The thrombocytopenia is a major adverse event in treatment with linezolid [17–20]. In pediatric clinical trials, the safety and

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tolerability of linezolid in pediatric patients has been suggested [21]. However, Bayram et al. have reported that thrombocytopenia was detected in 14.5% pediatric patients during linezolid treatment [22]. The incidence of linezolid-induced thrombocytopenia increased in patients with renal impairment [18,23–25], long-term administration of the drug [17,18], and high serum linezolid concentrations [26–29].

The clinical efficacy of linezolid is associated with the area under the drug concentration-time curve (AUC_{24})/minimum inhibitory concentration (MIC) ratio and time above MIC ratio; AUC_{24}/MIC of >100 has been recommended [7,12]. Thus, implementation of dose adjustment based on linezolid blood concentrations and therapeutic drug monitoring (TDM) for both adult and pediatric patients has been discussed [30–33]. The recommended range of minimum linezolid serum concentration is 2.0–7.0 mg/L [26].

The aims of the present study were (a) to evaluate the pharmacokinetics of linezolid using population pharmacokinetic approaches, and (b) to assess the toxicity and clinical efficacy of linezolid in Japanese pediatric patients.

2. Patients and methods

2.1. Ethics

The study was performed in conformity with the Helsinki Declaration, after approval by the Ethical Review Board of University of Toyama (approval number: clinical 24–118). A written explanation of the study was provided to parents, and written informed consent was obtained. Patient privacy and personal information were respected.

2.2. Patients and data sources

Patient data are summarized in Table 1 and details of linezolid administration and treatment for each patient are described in Table 2. Routine clinical data including serum linezolid total and unbound concentrations were collected from 15 pediatric patients (0–13 years old) who received linezolid injections or film-coated tablets (Zyvox®, Pfizer Inc., Tokyo, Japan) from October 2013 to March 2018 at Toyama University Hospital, Toyama, Japan. The usual dose of linezolid was 10 mg/kg three times daily given orally and/or by intravenous injection. Other dosage adjustments were performed according to the physicians' decisions.

2.3. Determination of linezolid concentrations

All serum samples obtained were stored at −80 °C and linezolid concentrations (total and unbound) were determined using high-performance liquid chromatography (HPLC). The bulk powder of linezolid was provided by Pfizer Inc. and all other reagents were of analytical grade and commercially available. Two hundred microliters of serum sample was centrifuged using a Centrifree® Ultrafiltration device (Merck Millipore Ltd., Cork, Ireland) for 30 min at 2000 g to extract unbound linezolid. One hundred microliters of untreated serum samples and filtrates were used for the determination of total and unbound concentrations, respectively. These samples were deproteinized using the same volume of acetonitrile and centrifuged 5 min at 14,000 g. Fifty microliters of supernatant was injected into the HPLC system (Shimadzu Corporation, Kyoto, Japan). Separation was carried out on an octadecyl silane Hypersil column (Cadenza 5CD-C18, 150 mm × 4.6 mm, 5 μm; Imtakt Co., Kyoto, Japan). As the mobile phase, a solution of 1% orthophosphoric acid, 30% methanol and 2 g/L heptane sulfonic acid (1:30:69) was used and the pH was adjusted to 5.0. The pump flow rate was 1.0 mL/min, the column temperature was maintained at 40 °C and the wavelength of UV detection was set at 254 nm. The calibration curve was linear over a concentration range of 0.1–50 mg/L, and the lower limit of quantification (LLOQ) was 0.1 mg/L (coefficient of variation < 5.0%).

2.4. Population pharmacokinetic analysis

A total of 98 total linezolid concentrations and 76 unbound linezolid concentrations were collected. Six observations of total and unbound concentrations were below the LLOQ and excluded from the data because they had been collected more than 1 day after the end of linezolid administration. Therefore, 92 observations of total and 70 points of unbound linezolid concentrations from 15 pediatric patients were used for the population pharmacokinetic analysis.

Pharmacokinetic analysis was performed using the first-order conditional estimation method with interaction (FOCE-I) according to the nonlinear mixed-effect modeling software NONMEM version 7.4.3 (ICON Development Solutions, Maryland, USA). All pharmacokinetic analyses including the executing model runs, bootstrap resampling method, and management of the results were performed with Wings for NONMEM, and graphical analyses were performed using R version 3.5.0.

The pharmacokinetics of linezolid was assumed to be one-compartment with the first-order absorption model (ADVAN2 TRANS3). Clearance (CL), volume of the central compartments (VC) and the fraction of unbound (FU) were estimated as pharmacokinetic parameters. The absorption half-life (T_{abs}) and absolute bioavailability (F) were fixed at the reported values of 3.61 h and 0.922, respectively [1]. All pharmacokinetic parameters were

Table 1
Clinical data for the study population of patients receiving linezolid.

	Number	Median	Observation Interval	
			Lower 2.5%	Upper 97.5%
Number of patients (male/female)	15 (10/5)			
Linezolid total concentration (mg/L)	92	9.4	1.1	35.1
Linezolid unbound concentration (mg/L)	70	7.5	1.2	29.1
Once dose per body weight (mg/kg, minimum-maximum)		10	8	15
Duration (day, minimum-maximum)		20	10	85
Postnatal age (year/month, minimum-maximum)		2/24	0/2	13/156
Body weight (kg)		9.9	3.0	49.7
Height (m)		0.8	0.53	1.51
Baseline values				
Platelet count (/μL)		134,000	32,750	453,050
C-reactive protein (mg/dL)		10.16	1.95	28.04
Body temperature (°C)		38.3	37.4	41.3

Table 2
Detail for linezolid administration and treatment in each patient.

Patient	Postnatal age (year/month)	Administration	Route	Duration (days)	Pathogen	Site of infection
1	5/69	10 mg/kg three times a day	IV	54	*S. mitis*	Sepsis
2	13/155	15 mg/kg twice a day	PO	20	MSSA	Wound, Skin and soft tissue
3	1/13	10 mg/kg three times a day	IV/PO	40	MRSA	Wound, Skin and soft tissue
4	8/96	10 mg/kg three times a day	IV/PO	29	MRSA	Wound, Skin and soft tissue
5	2/24	10 mg/kg three times a day	IV/PO	64	MRSA	Sepsis
6	0/7	10 mg/kg three times a day	IV	20	MRSA	Pneumonia
7	0/3	8 mg/kg three times a day	IV	19	MRSA	Wound, Skin and soft tissue
8	0/3	10 mg/kg three times a day	IV/PO	85	MRSA	Bacteremia
9	9/115	10 mg/kg three times a day	IV	14	Undetermined	Undetermined
10	2/29	10 mg/kg three times a day	IV/PO	50	MRSE	Wound, Skin and soft tissue
11	0/9	10 mg/kg three times a day	IV	10	MRSA	Wound, Skin and soft tissue
12	0/2	11 mg/kg three times a day	IV	18	MRSE	Wound, Skin and soft tissue
13	6/76	10 mg/kg three times a day	IV	37	Undetermined	Sepsis
14	12/147	10 mg/kg twice a day	IV	17	MRSE	Wound, Skin and soft tissue
15	1/20	10 mg/kg three times a day	IV	16	MRSA	Wound, Skin and soft tissue

IV, intravenous administration; PO, per os administration.
S. mitis, *Streptococcus mitis*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*.

standardized to a standard body weight (WT) of 70 kg according to the theory of allometry [34]. The between-subject variability (BSV) of CL and VC were evaluated using exponential random effects and the BSV of FU was not evaluated. The residual unidentified variability was modelled with proportional error.

2.5. Covariate model

The factor for size (F_{SIZE}) was applied to standardize the pharmacokinetic parameters, with an assumption of a standard WT of 70 kg. WT_{CHILD} and WT_{STD} in Eq. (1) represent WT of each pediatric patient and a standard value. The allometric exponent (PWR) of F_{SIZE} was fixed at 0.75 for CL and 1 for VC.

$$F_{SIZE} = \left(\frac{WT_{CHILD}}{WT_{STD}}\right)^{PWR} \quad (1)$$

The influence of age which is independent of body size in the early period of life was evaluated as the fraction of the adult value of clearance (F_{MAT}) (Eq. (2)) [34]. F_{MAT} follows the sigmoid hyperbolic model and TM_{50} represents the postnatal age (PNA) when maturation reaches 50% of the adult level.

$$F_{MAT} = \frac{PNA^{Hill}}{TM_{50}^{Hill} + PNA^{Hill}} \quad (2)$$

The covariate factors were combined to predict linezolid CL, as shown in Eq. (3). CL_i is the CL for ith individual, CL_{POP} is the population mean value of the parameters, and η_i is a normally distributed random variable with mean zero and variance ω^2.

$$CL_i = CL_{POP} \times F_{SIZE} \times F_{MAT} \times e^{\eta_i} \quad (3)$$

2.6. Model evaluation and validation

The objective function values were compared between models and the differences in OFV (ΔOFV) were evaluated according to the chi-squared test. The significance level was set at $P < 0.05$.

A bootstrap resampling method was performed for model validation. One thousand bootstrap samples were generated from the original dataset and parameters from bootstrap samples and the final estimated values were compared.

2.7. Evaluation of toxicity and efficacy

The relationship between risk for thrombocytopenia and linezolid minimum concentrations (C_{min}) was evaluated using the Mann Whitney *U* test. Patients with hematological diseases were excluded from this analysis. Linezolid-induced thrombocytopenia was defined as the condition in which platelet count decreased to less than 30% after 7 days compared to the baseline value before administration. C_{min} was defined as the total concentrations just before administration on day 7 of treatment with linezolid and was obtained by prediction using Bayesian estimation based on the final population pharmacokinetic model. The significance level was set at $P < 0.05$.

The sequential variations in serum C-reactive protein (CRP) concentrations and body temperatures during treatment with linezolid were evaluated as the indices for the clinical efficacy of linezolid. Patients for which the CRP concentrations and/or body temperature values were missing were excluded from the analysis.

3. Results

3.1. Pharmacokinetic analysis

The population pharmacokinetic model of linezolid was developed based on 92 observations of total and 70 points of unbound concentrations from 15 patients. The time after the previous dose versus observations of linezolid concentrations are shown in Fig. 1. The range for age was 2 months–13 years old and the median of one linezolid dose was 10 mg/kg (Table 1). The patients aged ≥12 years were received 600 mg of linezolid administration every 12 h, and patients younger than 12 years old were received approximately 10 mg/kg of linezolid every 8 h [8]. One patient received rifampicin treatment during administration of linezolid [35]. The summary of model building was shown in Table 3. T_{abs} and F were fixed at the value reported in the previous study. FU was estimated as the ratio of unbound concentrations to total concentrations and the estimated value in the final model was 0.811. Postnatal age (PNA) of the pediatric patients was a significant covariate of linezolid CL (ΔOFV = 9.273, degrees of freedom (df) = 2, $P < 0.05$). The PNA value when maturation reaches 50% of the adult level (TM_{50}) was estimated to be 2.06 months. The final pharmacokinetic model parameters are shown in Eq. (4), and ΔOFV between the final model and the basic model (1-compartment model without allometric scaling) was 10.416 (df = 2,

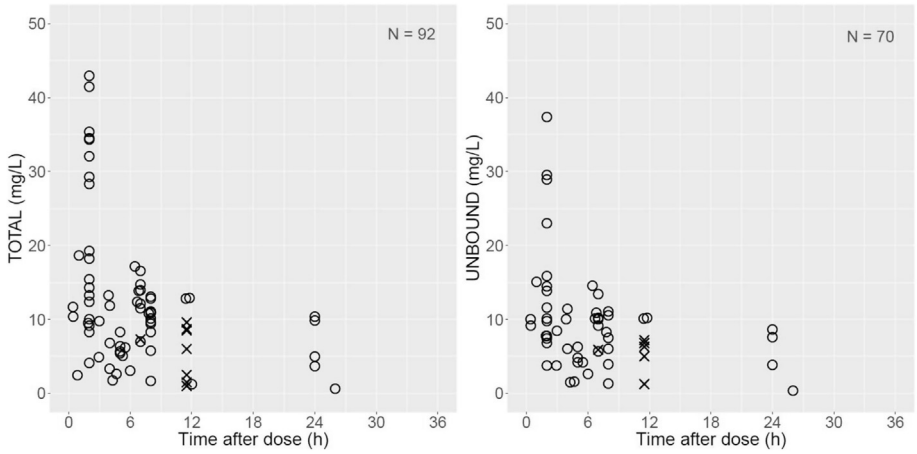

Fig. 1. Observations of total and unbound linezolid serum concentrations in 15 pediatric patients. Time after the previous dose versus observations of total (A) (n = 92) and unbound (B) (n = 70) linezolid serum concentrations plots in 15 pediatric patients. Open circles and crosses represent observations after intravenous administrations and per os administrations.

Table 3
Summary of pharmacokinetic model building.

	Model	OFV
Basic model	$CL(L/h) = \theta^1$ $VC(L) = \theta^2$	466.278
Allometric scaling	$CL(L/h) = \theta^1 \times (WT/70)^{0.75}$ $VC(L) = \theta^2 \times (WT/70)$	465.135
Final model	$CL(L/h) = \theta^1 \times (WT/70)^{0.75} \times [PNA^{\theta^3}/(\theta^{4^{\theta^3}} + PNA^{\theta^3})]$ $VC(L) = \theta^2 \times (WT/70)$	455.862

CL: clearance, VC: volume of central compartment, OFV: objective function value, WT: body weight, PNA: postnatal age.

$P < 0.05$). The parameter values from the original data and bootstrap distributions are compared in Table 4. The final estimated values of the pharmacokinetic model from the original data were within the 95% CI from the empirical bootstrap samples and the %RSEs were acceptably small for most parameters. The prediction values based on the final model and the observed linezolid concentrations for each patient are shown in Fig. 2. The predicted values were close to observed values for most patients.

$$\begin{aligned} CL(L/h) &= 5.82 \times \left(\frac{WT}{70}\right)^{0.75} \times \frac{PNA^{46.0}}{2.06^{46.0} + PNA^{46.0}}\ VC(L) \\ &= 41.3 \times \left(\frac{WT}{70}\right) \end{aligned} \quad (4)$$

Table 4
Comparison of pharmacokinetic parameters estimated from original data and 1000 bootstrap samples.

Parameter	Description	Units	Final model estimate	Bootstrap sample estimates			
				Average	95% CI		RSE%
					Lower 2.5%	Upper 97.5%	
Population mean							
CL	Clearance	L/h	5.82	5.72	3.79	7.97	18.4
VC	Volume of central compartment	L	41.3	42.2	10.0	95.3	50.0
Tabs	Absorption half-life	h	3.61 fixed	–	–	–	–
F	Absolute bioavailability		0.922 fixed	–	–	–	–
TM_{50}	Maturation half-time	month	2.06	2.05	2.02	2.07	2.13
Hill	Hill coefficient		46.0	53.3	39.1	79.8	19.2
FU	Fraction of unbound protein binding		0.811	0.812	0.784	0.841	1.87
Between-subject variability (BSV)[a]							
CL			0.523	0.469	0.180	0.687	28.5
VC			1.21	1.13	0.233	1.91	35.8
Residual unidentified variability (RUV)[b]							
RUV_{PROP_TOTAL}	Proportional residual unidentified variability of total concentration		0.289	0.289	0.217	0.358	12.5
RUV_{PROP_UNB}	Proportional residual unidentified variability of unbound concentration		0.313	0.310	0.220	0.401	15.3

CI, confidence interval; RSE%, relative standard error.
[a] BSV calculated from Square root (sqrt) (NONMEM OMEGA).
[b] RUV estimated using THETA.

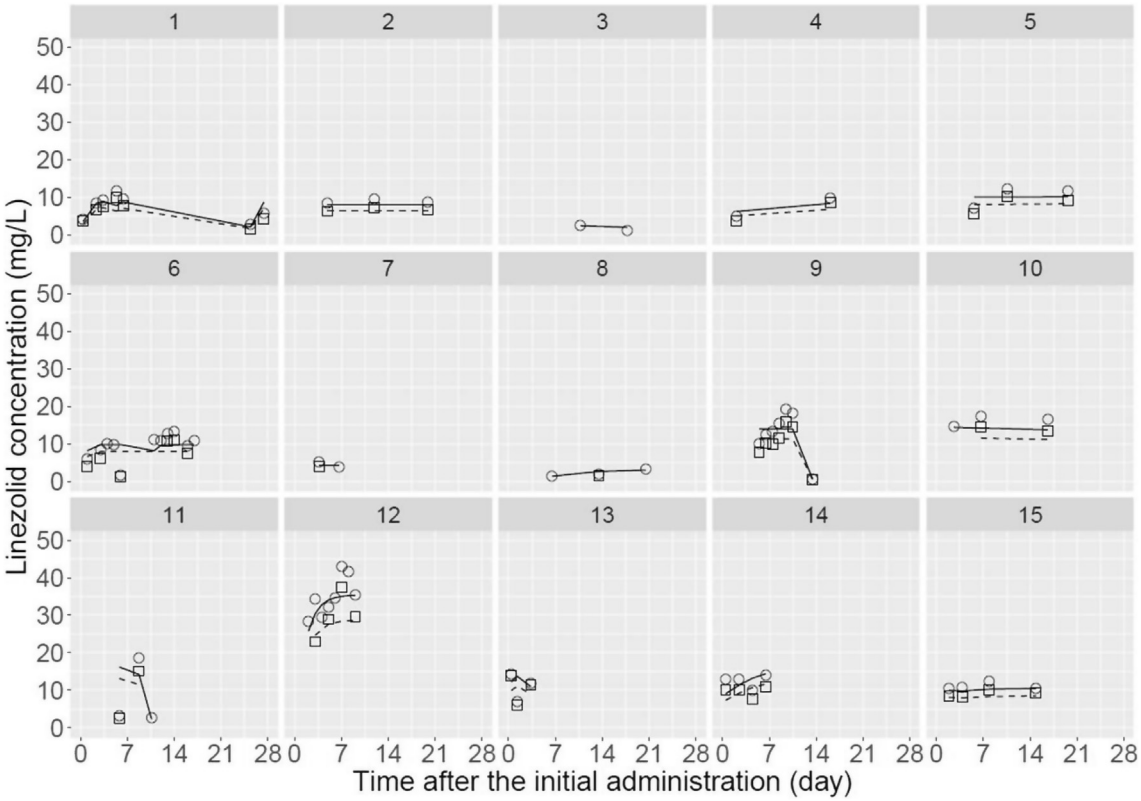

Fig. 2. Predicted values and observed linezolid concentrations in each individual patient. Time after the initial administration versus linezolid serum concentrations plots in each individual patient. Open circles and open squares represent observations total and unbound concentrations, and solid and dashed lines represent predictions of total and unbound concentrations.

3.2. Toxicity and clinical efficacy

Thrombocytopenia occurred in 3 of 14 patients (21.4%) during the treatment with linezolid. C_{min} was significantly associated with inducing thrombocytopenia ($P = 0.0176$) (Fig. 3), and the average of C_{min} in patients with or without thrombocytopenia was 19.9 mg/L (standard division (SD) = 13.0 mg/L) or 6.97 mg/L (SD = 3.65 mg/L).

Time course values of CRP concentrations and body temperatures are shown in Fig. 4. CRP concentrations decreased more than 50% from the baseline values after the treatment with linezolid in all patients and decreased more than 90% in 11 patients (73.3%). Body temperatures at the end of treatment with linezolid were lower than 37.5 °C for 8 patients (53.3%).

4. Discussion

Pharmacokinetics of linezolid in pediatric patients have been evaluated in previous studies [2,3,33,36]. In this study, pharmacokinetics of total and unbound linezolid, and toxicity and clinical efficacy were in Japanese pediatric patients aged 3 months to 13 years.

Although only unbound concentrations are responsible for clinical efficacy and side effects, no studies evaluating pharmacokinetics of unbound linezolid in pediatric patients have been reported [2,3,33,36]. To evaluate variations in unbound linezolid and consider the utility of measuring unbound linezolid in pediatric patients, pharmacokinetics of both unbound and total linezolid were modelled in this study. The final estimated value of protein binding ratio was 18.9%, and significant variations of protein binding ratio between patients were not detected. These results did not differ from the results in adult patients [1,10], and suggested that it was not necessary to measure unbound linezolid concentrations in clinical.

The pharmacokinetics of linezolid was explained by one-compartment with the first-order absorption model. Both the one-compartment model and the two-compartment model were used to explain the pharmacokinetics of linezolid in previous studies [1,2,11,13,14,37–39]. In the present study, only the one-compartment model was evaluated because there were not enough observations to apply the two-compartment model (Fig. 1).

To consider the variations depending on growth of body size, the pharmacokinetic parameters were standardized to a standard WT of 70 kg according to the theory of allometry [34]. WT was used for the allometric size predictor and other size predictors considering that body composition could not be applied because of insufficient information on these predictors for pediatric patients younger than 3 years old [40]. The OFV of the allometry model decreased compared with the basic model ($\Delta OFV = 1.143$), and model fitting was improved. Higher blood concentrations of linezolid in adult patients with renal impairment have been reported in several studies [18,23–25]. The influence of renal function on clearance in pediatric patients was evaluated, but considering renal function did not improve model fitting (data not shown). The drug interaction between linezolid and rifampicin has been reported [35]. The influence of rifampicin coadministration on pharmacokinetics of linezolid was not evaluated in this study because only 1 patient received rifampicin treatment during linezolid administration.

In previous studies, the clearance of linezolid in pediatric patients was age-dependent [2,16]. The difference in maturation of body function between babies and adults was considered using F_{MAT} (Eq. (2)) [34]. Instead of postmenstrual age, which is a good predictor of maturation, postnatal age (PNA) was used to evaluate

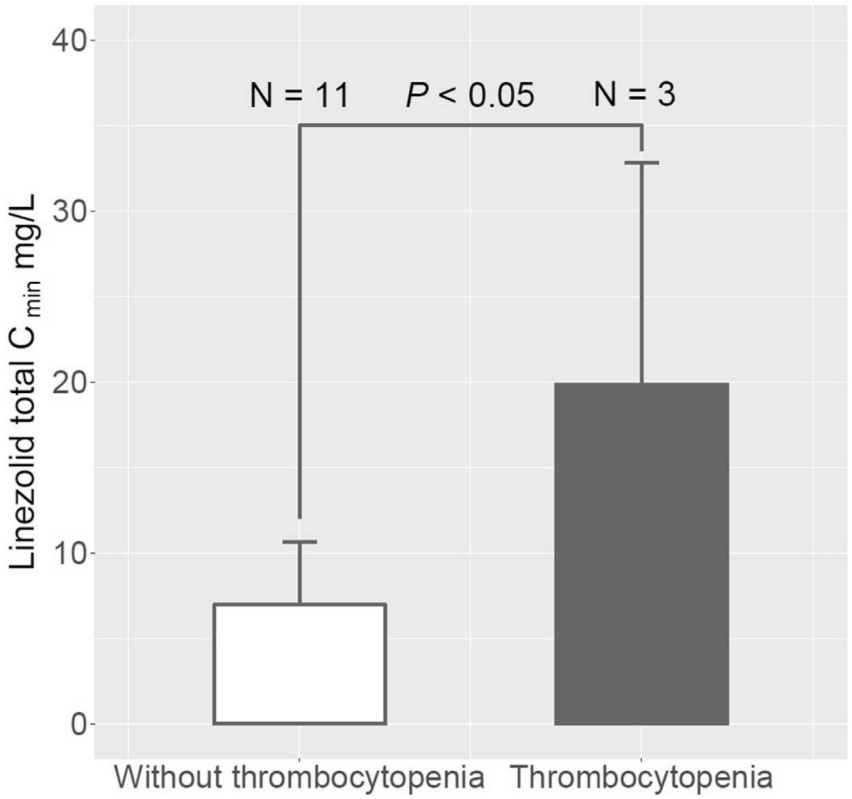

Fig. 3. Linezolid total concentration in pediatric patients with or without thrombocytopenia.

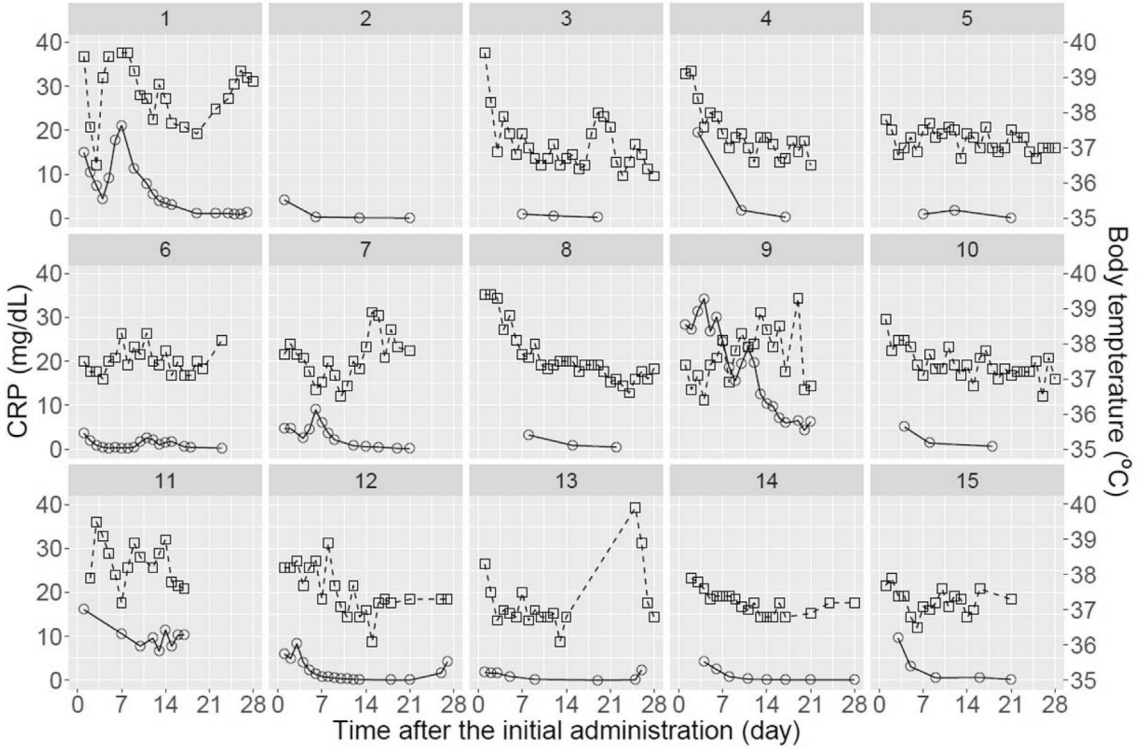

Fig. 4. Observations of C-reactive protein concentrations and body temperatures. Time after the initial administration versus C-reactive protein (CRP) concentrations or body temperatures. Open circles and solid lines represent observed CRP concentrations in 15 pediatric patients, and open squares and dashed lines represent observed body temperatures of 14 pediatric patients.

the influence of maturation because both postmenstrual age and gestational age were not obtained. Maturation half-time (TM_{50}) was estimated to be 2.06 months, and the Hill coefficient was estimated to be 46.0. These values suggest that linezolid clearance significantly increases with age in infants, and a large variability of clearance in these patients should be considered in linezolid administration. Thibault et al. also reported that PNA was a significant covariate of clearance in premature infants [2].

Comparing each pharmacokinetic parameter between present and previous studies is difficult because few studies have evaluated the pharmacokinetics of linezolid in pediatric patients. The elimination half-life of linezolid calculated using CL and VC in a patient with a WT of 9.9 kg and age of 24 months (median of this study) was 3.0 h. This value did not differ from previous values for pediatric cases (1.8–2.9 h) [3,16,36].

Thrombocytopenia, which is a major serious concern in linezolid administration, was detected in three patients (21.4%), and C_{min} in these patients (average: 19.8 mg/L) were significantly higher than those in patients without thrombocytopenia (average: 6.84 mg/L). This suggested that linezolid serum concentrations could also be associated with inducing thrombocytopenia in pediatric patients. Thus, dose adjustment based on linezolid serum concentrations is recommended for the safe treatment.

The C-reactive protein (CRP) concentration is a useful index to assess the clinical efficacy of pediatric patients with acute infection [41]. CRP concentrations decreased more than 50% in all pediatric patients after the treatment with linezolid. This indicated that the inflammatory response inducing acute infection was alleviated by approximately 10 mg/kg of linezolid administration. Although CRP concentrations significantly decreased, body temperatures at the end of treatment were higher than 37.5 °C in 6 patients (42.9%). Body temperatures varied according to various factors including other diseases, injuries, surgery and circadian rhythm. These may have been causes of this finding.

The lack of robustness of the estimated VC value was a limitation of this study. The %RSEs from the empirical bootstrap samples were acceptably small (<30%) for most parameters, however the %RSE for the population mean value of VC was 50.0%. The observations of linezolid concentrations in this study were not complete but sparse, and this was a cause for the lack of robustness of the VC estimation. Therefore, a simple one-compartment model was selected to describe the pharmacokinetics of linezolid in pediatric patients.

Enough microbiological data were not obtained, and thus, the microbiological assessment such as evaluating bacteriological response which was categorized by bacterial cultures as either eradication or persistence were not performed in the present study. Instead, variations in CRP concentrations and body temperatures which have been widely used as the convenient indices for clinical efficacy were evaluated in pediatric antimicrobial therapy. To assess microbiological efficacy of linezolid in pediatric patients is our next objective.

We performed population PK analyses and assessment of toxicity and clinical efficacy of linezolid. Body size and maturation of body function were significant covariates of linezolid pharmacokinetics in pediatric patients. Although dose adjustment based on body size was performed for pediatric patients, thrombocytopenia which is a serious concern in linezolid treatment was detected in 21.4% of pediatric patients, and C_{min} values of linezolid were associated with inducing thrombocytopenia. These results suggest that implementation of individual dose adjustment based on linezolid serum concentrations and therapeutic drug monitoring should be used for safe and appropriate treatment with linezolid.

Conflicts of interest

The authors have no conflicts of interest to declare.

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