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Note

Linezolid dosage in pediatric patients based on pharmacokinetics and pharmacodynamics

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ABSTRACT

Linezolid pharmacokinetic profile in pediatric patients has not been fully characterized, and the dose needed to achieve a pharmacokinetic-pharmacodynamic (PK-PD) target has yet to be established because its efficacy is associated with the area under the plasma drug concentration–time curve (AUC_{24})/minimum inhibitory concentration (MIC) ratio. The present study aimed to define the pharmacokinetic parameters of intravenous linezolid in pediatric patients and assess the rationale for the approved dosage recommendations. Linezolid was safe, tolerated well, and clinically effective for treating Gram-positive bacteria in five pediatric patients (3–11 years). The mean values for the volume of distribution and total clearance (CL) in a one-compartment model were estimated to be 0.646 ± 0.239 l/kg and 0.171 ± 0.068 l/h/kg, respectively (mean ± S.D.). Based on this analysis, the AUC_{24} and trough drug concentration in plasma (C_{min}) for linezolid doses were predicted to be 175.4 μg h/ml and 3.4 μg/ml for 30 mg/kg/day, 204.7 μg h/ml and 4.3 μg/ml for 35 mg/kg/day, and 263.2 μg h/ml and 6.2 μg/ml for 45 mg/kg/day, respectively. Taking into account that AUC_{24} should be ≥200 μg h/ml for MIC of 2.0 μg/ml (to achieve an AUC_{24}/MIC ratio of ≥100) and C_{min} should be approximately 7 μg/ml (to avoid thrombocytopenia), we consider the approved dosage of 30 mg/kg/day to be fundamentally rational, but can be underdosed against bacteria with MIC of 2.0 μg/ml; therefore, a dose of 35–45 mg/kg/day is more appropriate to ensure the efficacy and safety of linezolid in pediatric patients.

Linezolid is a member of the oxazolidinone class of synthetic antibacterial agents, and exhibits a broad spectrum of activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci. Age-dependent variability has been associated with the pharmacokinetics of linezolid. Children younger than 12 years of age have been shown to have a faster clearance and shorter elimination half-life than adults [1]. The pharmacokinetic-pharmacodynamic (PK-PD) index associated with efficacy for linezolid is the area under the plasma drug concentration–time curve (AUC_{24})/minimum inhibitory concentration (MIC) ratio of ≥100 [2]. The MICs of linezolid for 50% and 90% of MRSA (MIC_{50} and MIC_{90}) isolated from surgical site infections and respiratory tract infections were found to be 2 and 2 μg/ml, respectively, in a Japanese nationwide survey [3,4]. An AUC_{24} of 200 μg h/ml is required to achieve an AUC_{24}/MIC ratio of ≥100 when MIC is 2.0 μg/ml. It is important to apply this index to pediatric patients. Although several studies have examined the pharmacokinetics of linezolid in pediatric patients, its pharmacokinetic profile has not been fully characterized, and the dose of linezolid needed to achieve an AUC_{24}/MIC ratio of ≥100 for a favorable response has not yet been established.

The present study aimed to define the pharmacokinetic parameters of linezolid in pediatric patients and assess the rationale for the approved dosage recommendations for this population.

This study was approved by the Ethics Review Board of Kagoshima University Hospital (#20–35). Written informed consent was obtained from five pediatric patients who received linezolid between September 2010 and October 2013 at Kagoshima University Hospital.

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Table 1
Characteristics of the 5 patients included in this study.

Patient no.	Age (years)	Gender	Height (cm)	Weight (kg)	Linezolid regimen	Duration of the treatment (days)	eGFR (ml/min/1.73 m^2)	Infection	Linezolid MIC (μg/ml)
1	11	Female	146.6	63.3	600 mg every 12 h (19.0 mg/kg/day)	13	84.9	MRSA pneumonia	<2
2	8	Female	118.7	22.3	220 mg every 8 h (29.6 mg/kg/day)	22	125.5	MRSA soft tissue infection	No data
3	4	Female	104	19.0	200 mg every 8 h (31.6 mg/kg/day)	11	146.7	MRSE bacteremia	<2
4	3	Male	95.5	12.3	120 mg every 8 h (29.3 mg/kg/day)	28	128.1	MRSE bacteremia	<2
5	6	Male	103	20.7	200 mg every 8 h (29.0 mg/kg/day)	15	108.9	MRSA pneumonia	2

eGFR, estimated glomerular filtration rate; MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MIC, minimum inhibitory concentration.

On days 4–21 after the initial intravenous administration (under steady-state conditions), venous blood samples were drawn just before the next administration (observed trough drug concentration in plasma: C_{min}) and just after the end of the 1 h infusion.

Linezolid plasma concentrations were measured by high-performance liquid chromatography [5]. The analytical column was Mightysil RP-18, 5 μ, 250 × 4.6 mm, the UV wavelength for linezolid was 251 nm, and the mobile phase consisted of 0.1 M acetate buffer (pH 3.5):acetonitrile:water = 2.5:1:6.5. The lowest detectable concentration of linezolid was 0.2 μg/ml. Intra- and inter-day accuracies (as absolute values of the relative errors of the means) and precision (as coefficients of variations) were within 10%.

The MICs of linezolid for MRSA and methicillin-resistant *Staphylococcus epidermidis* (MRSE) strains from patients were determined by the broth microdilution method as described by the Clinical and Laboratory Standards Institute.

We used the formula developed by Schwartz et al. [6] to estimate GFR: eGFR = K*height (cm)/serum creatinine (mg/dl). Serum creatinine values as measured by the Jaffe assay were used. Serum creatinine was measured using an enzymatic assay in the present study. Because creatinine measured by the enzymatic assay is 0.2 mg/dl lower than creatinine measured by the Jaffe assay, serum creatinine in the equation was calculated as the actual measured value +0.2. The K factor was 0.55 for children aged 2–12 years.

A pharmacokinetic analysis of linezolid was performed using the nonlinear least squares program MULTI (Yamaoka et al., 1981) [7]. For each individual patient, the drug concentration data were fit to a standard one-compartment model with zero-order input and first-order elimination. The pharmacokinetic parameters used were total clearance (CL, l/h) and volume of distribution (V, l). The area under the plasma linezolid concentration–time curve for 24 h (AUC_{24}) was estimated using pharmacokinetic parameters as daily dose/CL.

The correlation between linezolid CL and eGFR, or between linezolid AUC_{24} and observed C_{min} was investigated by Pearson's correlation coefficient test because the distribution patterns of their data were regarded as normal distributions. Statistical analysis was performed using Excel 2010 (Microsoft Corporation, Redmond, WA, USA) with the add-in software Statcel 3.

Patient characteristics are shown in Table 1. Two males and three females, with a mean age of 6.4 ± 3.2 years (mean ± S.D.) and eGFR 118.8 ± 23.2 ml/min/1.73 m^2, were evaluated in the study. The duration of the linezolid treatment was 11–28 days (mean ± S.D. 17.8 ± 7.0 days). All patients improved clinically in response to the treatment with linezolid. Platelet counts decreased from 340,000/mm^3 to 153,000/mm^3 in patient No. 2 receiving high-dose methotrexate during linezolid treatment, but platelet counts changed slightly in the other four patients. No other severe adverse events were observed that required drug discontinuation.

The pharmacokinetic parameters of the five patients receiving the intravenous multiple-dose administration of linezolid are shown in Table 2. The mean values for V and CL were estimated as 0.646 ± 0.239 l/kg and 0.171 ± 0.068 l/h/kg, respectively. A strong positive correlation with a correlation coefficient of 0.883 was found between linezolid CL and eGFR ($P < 0.05$) (Fig. 1a). A positive correlation with a correlation coefficient of 0.828 was also found between linezolid AUC_{24} (116.5–231.2 μg h/ml) and observed C_{min} (1.4–4.7 μg/ml) ($P = 0.08$) (Fig. 1b). The correlation equation was C_{min} = 0.0325* AUC24 − 2.3104.

The PK-PD index associated with efficacy for linezolid is an AUC_{24}/MIC ratio of ≥100. An AUC_{24} of 200 μg h/ml is required to achieve this target value when MIC is 2.0 μg/ml. Using the correlation equation in Fig. 1b, C_{min} for AUC_{24} of 200 μg h/ml was predicted as 4.2 μg/ml. The daily dose to achieve AUC_{24} of 200 μg h/ml in pediatric patients was calculated as follows: daily dose = AUC_{24} (μg h/ml)*CL (l/h/kg) = 200*0.171 (the mean CL value, Table 2) = 34.2 mg/kg/day. Furthermore, when the daily dose was 30, 35, 40, 45, and 50 mg/kg/day, AUC_{24} was calculated using the following formula: AUC_{24} = daily dose/CL. Based on this calculation, AUC_{24} and C_{min} were predicted as 175.4 μg h/ml and 3.4 μg/ml for 30 mg/kg/day, 204.7 μg h/ml and 4.3 μg/ml for 35 mg/kg/day,

Table 2
Estimated pharmacokinetic parameters and observed trough plasma concentrations for intravenous linezolid in pediatric patients.

Patient no.	V (l/kg)	CL (l/h/kg)	k_e (1/h)	$t_{1/2}$ (h)	AUC_{24} (μg*h/ml)	C_{min} (μg/ml)
1	0.500	0.082	0.165	4.201	231.2	4.6
2	1.026	0.164	0.160	4.332	180.5	4.7
3	0.739	0.271	0.366	1.894	116.5	1.4
4	0.497	0.157	0.316	2.194	186.4	4.4
5	0.470	0.180	0.383	1.810	161.1	1.8
Mean ± S.D.	0.646 ± 0.239	0.171 ± 0.068	0.278 ± 0.109	2.891 ± 1.278	175.1 ± 41.6	3.4 ± 1.6

V, volume of distribution; CL, total clearance; k_e, elimination rate constant; $t_{1/2}$, elimination half-life; AUC_{24}, area under the plasma drug concentration–time curve for 24 h; C_{min}, observed trough drug concentration in plasma.