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ORIGINAL RESEARCH

Physiologically Based Pharmacokinetic Modeling and Dose Optimization of Linezolid in Pediatric Patients With Renal Impairment

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Objective: Linezolid (LZD), a commonly used antimicrobial agent in clinical practice, has not undergone adequate pharmacokinetic (PK) assessment in pediatric populations with renal impairment (RI). Physiologically based pharmacokinetic (PBPK) modeling provides unique benefits for investigating drug pharmacokinetics in specific patient groups. This study aimed to employ the PBPK model to refine and optimize the therapeutic dosing protocol of LZD for RI pediatric patients.

Methods: The model was developed and validated for both healthy adults and RI adults, which was subsequently adapted for pediatric applications. Upon verification of the pediatric Based on clinical PK data and real-world study findings, the PBPK model demonstrated precise prediction of LZD exposure in pediatric populations with varying degrees of RI, encompassing weight- and age-associated PK variations.

Results: The PBPK modeling simulations exhibited robust agreement with observational data for LZD across both oral and intravenous delivery routes under diverse dosing protocols, as evidenced by the fold error (FE) always between 0.5 and 2 times, geometric mean fold error (GMFE) was less than 2.0 and mean absolute prediction error (MAPE) was within 100%. Pediatric populations with severe or end-stage RI exhibited 1.21-fold and 1.28-fold elevations in plasma concentration-time curve (AUC) values, respectively, relative to healthy pediatric counterparts when administered equivalent 10 mg/kg LZD doses. Pharmacodynamic analysis confirmed that the proposed dosing regimens—8 mg/kg every 8 hours for children with severe or end-stage RI —were effective in achieving the target $AUC_{0\text{-}24}$/MIC ratio of ≥80 at a susceptible inhibitory concentration of ≤ 2 mg/L.

Conclusion: Our model provides a predictive instrument to enhance precision in determining therapeutic LZD dosage regimens for pediatric populations through systematic integration of developmental PK parameters.

Keywords: pediatric, physiologically based pharmacokinetic model, renal impairment, linezolid, pharmacodynamics

Introduction

Linezolid (LZD), a first-in-class synthetic oxazolidinone antimicrobial agent, is clinically indicated for the management of multidrug-resistant Gram-positive bacterial pathogens, including methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), and Mycobacterium tuberculosis infections.[1,2] LZD can be administered either intravenously or orally owing to its absolute bioavailability of close to 100%.[3] Sadahiro et al's research shows that age and body weight (BW) were influential covariates on clearance.[4] The pharmacokinetic (PK) parameters of LZD in adolescents aged 12–18 were shown to be similar to those of adult patients, for children younger than 12 years old, the clearance of LZD increased in an age-dependent manner.[5] The established dosage protocol specifies distinct administration schedules based on patient age demographics. For patients aged ≥12 years, a twice-daily regimen of 600 mg per dose is recommended. In contrast, pediatric populations encompassing neonates and children under 12 years require a weight-adjusted regimen of 10 mg/kg administered three times daily.[6]

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LZD is predominantly metabolized through the oxidation of its morpholine ring to an inactive form by nonenzymatic oxidative reactions, namely aminoethoxy acetic metabolite (PNU-142300) and hydroxyethyl glycine metabolite (PNU-142586), which is unrelated to the cytochrome P450 system. This non-enzymatic metabolic pathway circumvents the influence of liver development, so individual differences related to liver metabolic regulation have a weaker impact on the in vivo processes of LZD. Nonrenal clearance accounts for approximately 65% of the total clearance of LZD. Under steady-state conditions, approximately 30% of the dose appears in the urine as LZD, 40% as metabolite PNU-142586, and 10% as metabolite PNU-142300.[7] Previous studies have shown that as renal function declines in patients, the clearance rate of LZD and its two main metabolites decreases, resulting in an increased rate of metabolite accumulation and elevated plasma concentrations in patients with renal impairment. Therefore, although the parent drug accounts for only 35% of renal clearance, the renal-dependent excretion of metabolites results in total body exposure that is highly correlated with renal function.[8] Consequently, caution is warranted regarding the risk of accumulation in cases of severe renal impairment.

While current LZD prescribing information states that dosage adjustments are not indicated for renally impaired patients, this recommendation is primarily derived from an early PK study involving only 18 renal impairment (RI) patients,[9] and subsequent research have demonstrated the clinical necessity of therapeutic drug monitoring (TDM) in LZD regimens[10] Clinical investigations have identified a significant correlation between renal function parameters and the incidence of LZD-induced thrombocytopenia (LIT) in treated patients,[11] and it could be arise from the altered exposure of the drug. Prior PK investigations revealed significantly elevated risks of systemic overexposure in renally impaired patients (creatinine clearance ≤40 mL/min), demonstrating a 4.27-fold increase in plasma exposure in comparison with cohorts with preserved renal function (eGFR >80 mL/min),[12] while the median LZD concentration in RI patients was 1.46-fold that of patients with normal function.[13]

The PK of the majority of drugs vary between pediatric and adult populations, necessitating the use of distinct, age-appropriate dosing regimens. Additionally, in cases of renal impairment or renal failure when renal function has a significantly influences in-vivo exposure of the drug.[14] According to the expert consensus statement on therapeutic drug monitoring and individualization of LZD, for RI patients who are not undergoing hemodialysis, the LZD dosage can be adjusted to a regimen of 300 mg administered q12h,[6] however, there is no research and recommendation for the dose adjustment for RI pediatric patients.

Considering the physiological distinctions between adults and pediatric populations, research has illustrated the benefits of PBPK modeling in predicting and simulating drug exposure across various age groups,[15–18] recognized by the FDA and the European Medicines Agency (EMA), to explore and quantitatively predict the PK of drugs, to evaluate drug–drug interactions (DDIs), and to support clinical study design, dose selection.[19,20] Consequently, our study constructed PBPK models tailored for children and RI pediatric patients, aiming to using validated PBPK models to predict changes in drug exposure in children with renal impairment, thereby guiding dose information when clinical trials are not feasible.

Methods

PK Data

A systematic review of published literature was conducted to aggregate intravenous LZD PK parameters across distinct populations, encompassing healthy adult and pediatric cohorts as well as adult subjects with renal impairment.[7,9,21] Using the digitizing software GetData Graph Digitizer version 2.26, the observational concentration–time curves were extracted directly from the graphs.

Establishment of the PBPK Model

The models were developed with the processes shown in Figure S1. The PBPK model for LZD was constructed using GastroPlus version 9.9 (Simulations Plus Inc., Lancaster, CA, USA) and utilized for whole simulations involving both healthy individuals and RI patients. Grounded in the physiological, biochemical, and anatomical principles of the human body, the PBPK model incorporates 13 non-eliminative compartments, including the brain, lungs, heart, muscle, adipose tissue, pancreas, liver, skin, skin, spleen, stomach, intestines, bone, and thymus, along with one eliminative compartment, the kidneys. These organs and tissues are interconnected by arterial and venous blood, each exhibiting its own

hemodynamic flow rates, compartmental volumes, tissue-plasma partition coefficients, and transvacuolar permeability characteristics in accordance with the principle of mass conservation. In the present investigation, LZD, exhibiting properties such as a low molecular weight, high lipid solubility, and excellent tissue penetrability,[22–24] was employed within a perfusion-limited to constructing a PBPK model. The basic physicochemical and biopharmaceutical parameters for LZD are listed in Table S1.

Estimation of Clearance

LZD is not considered as a substrate for any known major renal transport system, despite the fact that renal reabsorption plays a role in its overall renal clearance (CL_R).[25] According to the drug label of LZD, the mean total clearance following intravenous administration is roughly 8.76 L/h. It has been reported that the CL_R subsequent to tubular reabsorption falls within the range of 1.8–3.0 L/h.[7] When the CL_R is 1.8 L/h, the predicted alteration in the plasma concentration–time curve (AUC), which is obtained by comparing the RI adults (creatinine clearance <30 mL/min) to the healthy adults, is 1.3-fold. This predicted value is in close proximity to the clinical observation of a 1.2-fold change.[7,9] Therefore, a CL_R value of 1.8 L/h was established as the foundational PK parameter in this investigation. Given that the intricate and detailed mechanism underlying the liver metabolism of the substance in question remains unknown,[25] in the current research, the hepatic intrinsic clearance (Hep C_{Lint}) was estimated through the application of the retrogressive approach within the GastroPlus software. The estimated value of Hep C_{Lint} was determined to be 0.996 μL/min/mg protein.

Healthy Adults' LZD PBPK Model

We developed PBPK models for both oral and intravenous administration in healthy adult populations. Utilizing available PK data, we conducted simulations for single-dose and multiple-dose regimens in healthy adults. The experimental design incorporated both single-dose intravenous regimens (250 and 500 mg) and a single 600 mg oral administration,[7] alongside multi-dose intravenous protocols delivering 500 mg and 625 mg doses at 12-hour intervals (q12h).[21] The PBPK model for LZD was verified using clinical PK data from previous PK studies.

Pediatric Patients' LZD PBPK Model

We developed PBPK models based on injection administration in pediatric patients. The simulation in pediatric patients with 13–17, 7–12, 3–6, 1–2, 0.25–1 years included a LZD single-dose injection administration of 10 mg/kg according to the previous PK studies.[7] The PBPK model for LZD was verified using clinical PK data from previous PK studies.

Hospitalized Pediatric Populations Individualization LZD PBPK Model

We retrospectively collected 16 pediatric inpatients receiving intravenous LZD therapy, with systematic quantification of post-administration plasma drug concentrations were performed using HPLC-MS. Patient-individualized PBPK models were developed by integrating demographic covariates (age, gender, body mass index), clinical parameters (kidney and hepatic function), and pharmacotherapeutic variables (administration frequency, dose, and route), and we used the calculated concentrations obtained from the models to compare with the measured concentrations to complete validation of the models. Moreover, we further used a *t*-test to analyze the predicted plasma concentrations.

PBPK Model of LZD for Adult and Pediatric Populations Across a Spectrum of RI Severity

Specific differences in physiological parameters, including glomerular filtration rate (GFR), hematocrit, plasma protein levels, and blood pressure, between healthy and RI populations were incorporated into the GastroPlus model. The software follows the renal function classification of the FDA guidance (FDA/CDER 2010, accessible via www.accessdata.fda.gov/scripts/cder/daf/) using the GFR ranges 60–90, 30–59, 15–29, and <15mL/min/1.73m^2, which represent mild, moderate, and end-stage RI, respectively.

Model Validation

The simulations were executed under conditions mirroring those of actual clinical trials, encompassing demographic data and dosing regimens. According to the EMA guidelines for PBPK modelling and simulation assessment and reporting,[20] quantitative metrics evaluate model predictive performance as follows: the fold error (FE) and geometric mean fold error (GMFE) of PK parameters (AUC and C_{max}) representing exposure levels were utilized to evaluate the predictive capability of the model. Prediction error (PE) and mean absolute prediction error (MAPE) are derived by comparing predicted and literature-reported meaning plasma drug concentrations. If FE is between 0.5 and 2 times, GMFE was less than 2.0 and MAPE is within 100%, indicating that the model's predictive performance is good.[26–28]

$$FE = \frac{Pred\ PK\ parameter}{Obs\ PK\ parameter} \tag{1}$$

$$GMFE = 10^{\left(\sum_{i=1}^{n}\left|\lg\left(\frac{Pred\ PK\ parameter}{Obs\ PK\ parameter}\right)\right|\right)/n} \tag{2}$$

$$PE = \frac{predicted - observed}{observed} \times 100\% \tag{3}$$

$$MAPE(\%) = \frac{1}{n}\sum_{i=1}^{n}|PE_i| \tag{4}$$

Population Simulation

To evaluate covariate effects arising from interindividual variability in physiological parameters and compound-specific determinants on the physiological characteristics of the population and compound variables, population simulation for LZD was performed with a sample size of 100. The simulation incorporated the following population traits: virtual adult individuals ranging in the age range of 18 to 65 years, and pediatric individuals classified into age brackets of 13–17, 7–12, 3–6, 1–2, and 0.25–1 years. The virtual cohort consisted of 100 subjects, with an equal gender distribution (50% male). The dosing regimen aligned with prior PK studies.[15]

Prediction of LZD PK and Dose Adjustment Strategies for Pediatric Populations Across a Spectrum of RI Severity

The PBPK model for LZD disposition in pediatric cohorts with preserved renal function underwent development and validation prior to its extrapolative application in simulating PK at a 10 mg/kg dosing regimen for RI pediatric populations. The software's embedded parameters were utilized to simulate pediatric populations across a spectrum of RI severity. Observational and predicted PK parameters, involving AUC and the maximum plasma concentration (C_{max}), were paralleled, with the normal population serving as the reference group. The dosage optimization for RI pediatrics was determined by multiplying the geometric mean ratio of the normal population to the RI population by the standard dose used in healthy individuals, calculated as:

$$\text{Recommended Dose} = \left(\frac{\text{Geometric Mean AUC}_{\text{Healthy}}}{\text{Geometric Mean AUC}_{\text{RI}}}\right) \times \text{Standard Pediatric Dose} \tag{5}$$

Pharmacodynamic Evaluation

LZD has a time-dependent killing effect on susceptible bacteria,[29] and the PK/PD target of $AUC_{0\text{-}24}$/MIC ≥80 has been established.[30] The minimum inhibitory concentration (MIC) of LZD is 0.5–2.0 mg/L for most common clinical isolates of gram-positive bacteria.[31] Consequently, we employed the population simulation feature of GastroPlus, in conjunction with human physiological parameters, to assess the pharmacodynamics (PD) when the MIC values were set at 0.5, 1, 1.5, and 2 mg/L, respectively. For each of the recommended doses, the simulation was carried out 10,000 times. We obtained blood concentration data, and a statistical analysis was performed on the PD metrics associated with the recommended LZD dosages for various

degrees of renal function. Leveraging these PK/PD data, the LZD's PBPK model was utilized to make predictions regarding the efficacious dosing regimens for RI pediatric patients.

Results

Development, Verification and Population Simulation of Healthy Adults' LZD PBPK Model

The average Plasma Concentration–Time curves, which were both simulated and observational, for single and multiple intravenous doses of LZD in adult individuals with normal renal activity are illustrated in Figures 1 and 2. As presented in Table 1, for the dosing regimens with different doses in healthy adults, the FE values are between 0.8 and 1.4, the GMFE values were found to be less than 2.0. The outcomes of the population simulations are depicted in Figure 3. It was noted that the concentration values following the administration of LZD all fell within the 95% simulated probability range.

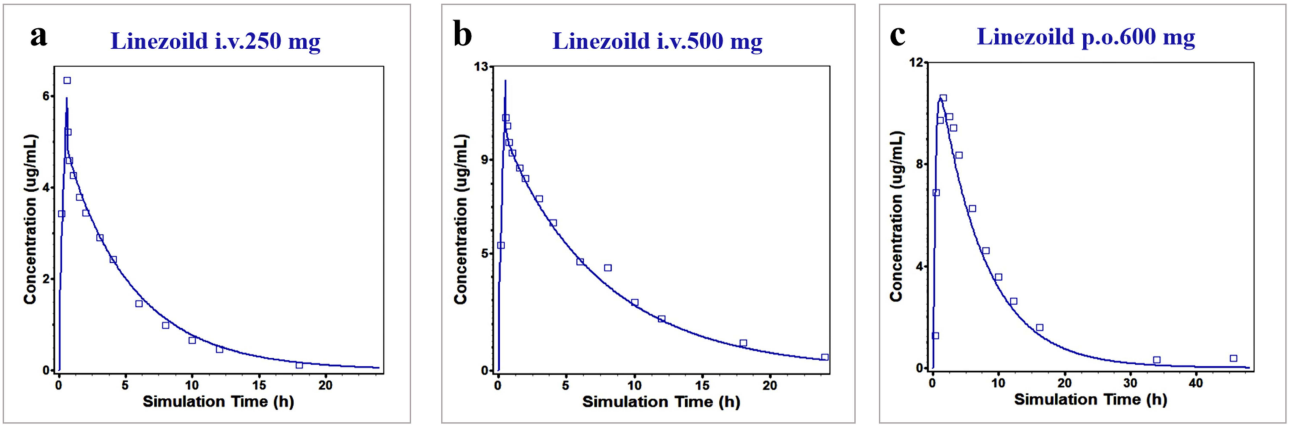

Figure 1 Average plasma concentration–time curve of healthy adult subjects after single dose of LZD. (**a** and **b**) Intravenous Injection, (**c**) Oral Administration, squares are observed values and blue lines are predicted values for LZD.

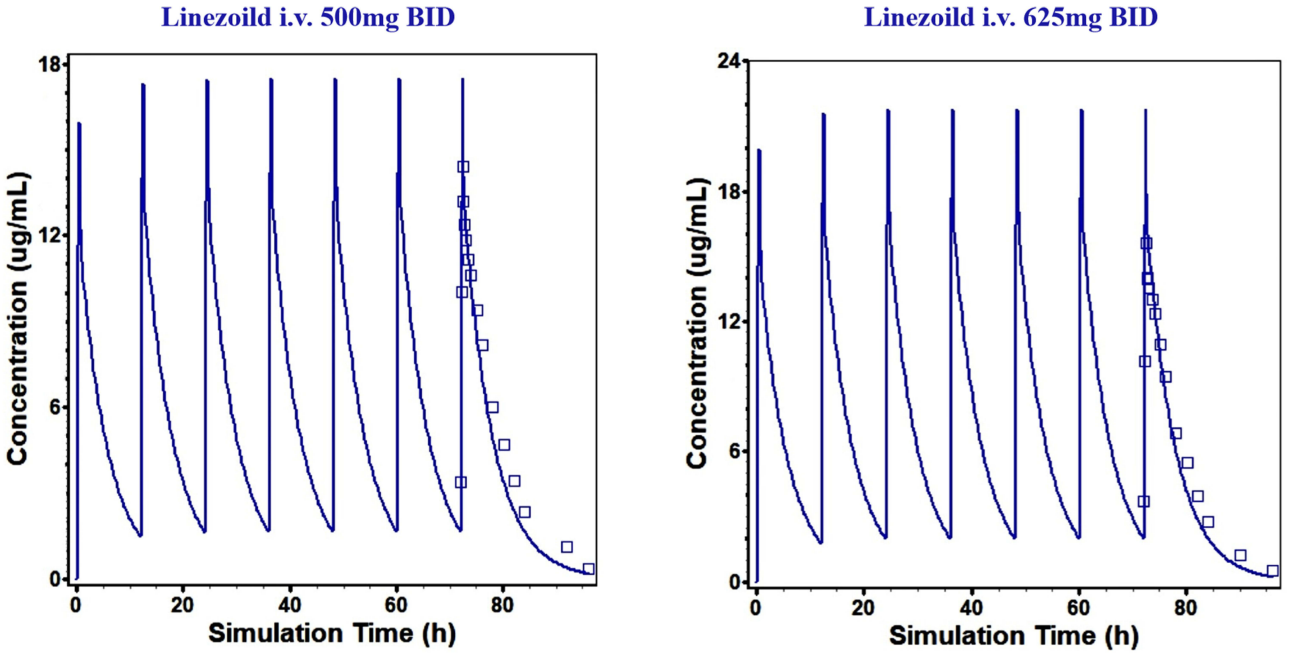

Figure 2 Average plasma concentration–time curves following twice-daily oral administration of 500 mg and 625 mg LZD in healthy subjects. Squares are observed values and blue lines are predicted values for LZD.

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Table 1 Observational and Modeled PK Parameters of Intravenous Linezolid in Adult Populations

Population	Dose	AUC_{0-t}(μg·h/mL)				C_{max}(μg/mL)			
		Observed	Predicted	FE	GMFE	Observed	Predicted	FE	GMFE
Healthy adult	I.v. 250mg (n=16)	24.792	26.342	1.062	1.130	6.331	5.958	0.941	1.165
	I.v. 500mg (n=16)	79.334	74.799	0.943		10.816	12.405	1.147	
	P.O.600mg (n=16)	104.130	85.955	0.825		10.615	10.590	0.998	
	I.v.500mg BID (n=6)	94.847	78.962	0.833		14.393	18.166	1.262	
	I.v.625mg BID (n=6)	109.846	97.639	0.889		15.622	21.768	1.393	

Development, Verification and Population Simulation of Pediatric Patients' LZD PBPK Model

The average Plasma Concentration–Time curves, encompassing both the simulated and observational data, for a single intravenous dose of LZD in pediatric patients are presented in Figure 4. Additionally, as evidenced in Table 2, for the single-dose regimens administered to children, the FE values are between 0.8 and 1.4, the GMFE values were found to be less than 2.0. The results of the population simulation are depicted in Figure 3. Notably, the concentration values of LZD following its administration all fell within the 95% simulation probability range.

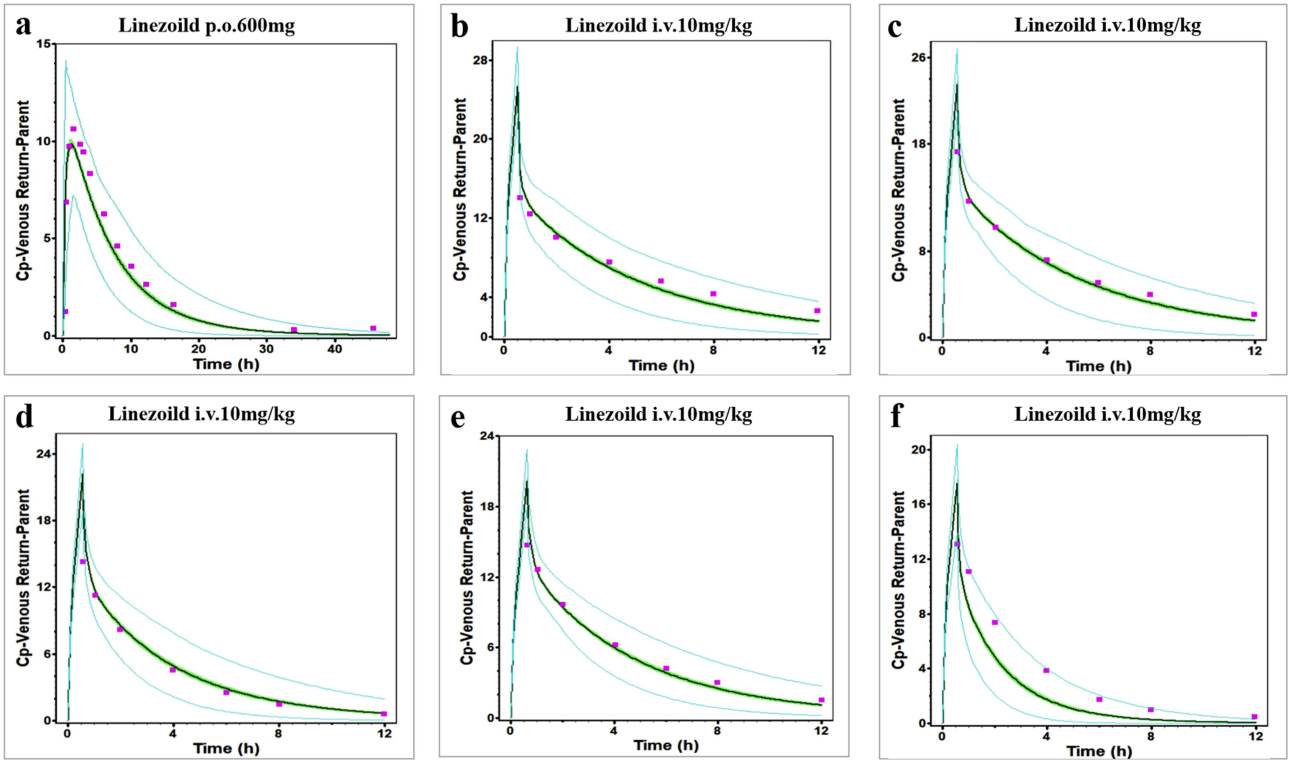

Figure 3 Population simulation of LZD after a single intravenous infusion in adults and children. (**a**) 18–65yrs, (**b**) 13–17yrs, (**c**) 7–12yrs, (**d**) 3–6yrs, (**e**) 1–2yrs, (**f**) 0.25–1yrs, population simulation results are shown as a black line, plasma concentration-time profiles with a 95% probability are shown as blue line, and observational values are shown as red squares.

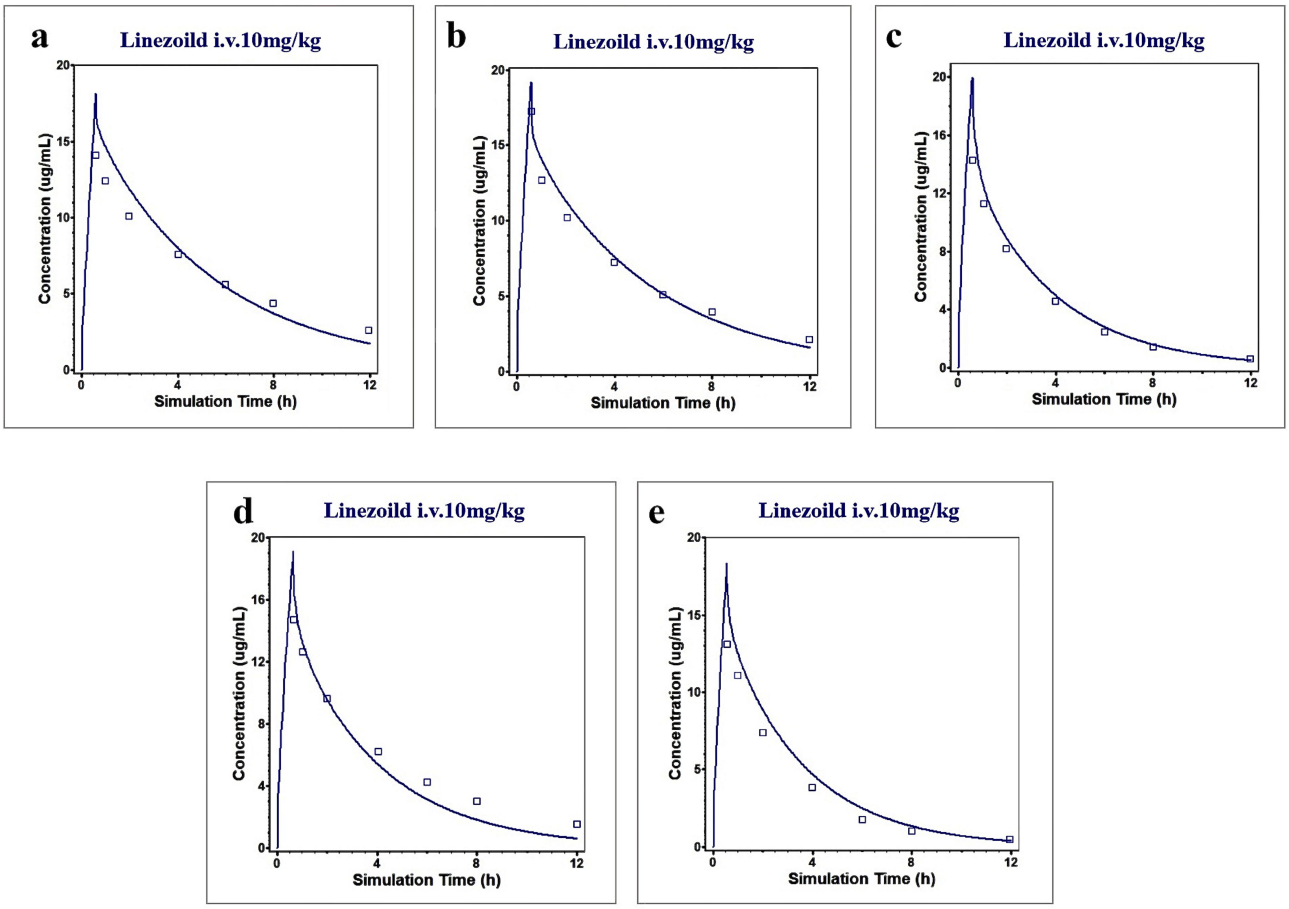

Figure 4 Average plasma concentration–time curves following a single intravenous dose of 10 mg/kg LZD in pediatric age subgroups. (**a**) 13–17yrs, (**b**) 7–12yrs, (**c**) 3–6yrs, (**d**) 1–2yrs, (**e**) 0.25–1yrs, squares are observed values and blue lines are predicted values for LZD.

Development and Verification of Hospitalized Pediatric Patients' Individualization LZD PBPK Model

The Plasma Concentration–Time curves, which include both the simulated and measured data, for intravenous administration of LZD in 16 hospitalized pediatric patients are illustrated in Figure 5. Table 3 demonstrated that the MAPE

Table 2 Observational and Modeled PK Parameters of Intravenous Linezolid Across Pediatric Age Subgroups

Population	Dose	Age	$AUC_{0\text{-}t}$ (μg·h/mL)				C_{max} (μg/mL)			
			Observed	Predicted	FE	GMFE	Observed	Predicted	FE	GMFE
Paediatric patients	I.v. 10mg/kg	13-17 yrs (n=12)	75.365	77.691	1.031	1.101	14.093	18.146	1.288	1.293
		7-12 yrs (n=15)	73.830	74.855	1.012		17.272	19.171	1.110	
		3-6 yrs (n=14)	47.114	52.791	1.120		14.310	19.952	1.394	
		1-2 yrs (n=12)	63.766	55.980	0.878		14.717	19.104	1.298	
		0.25–1yrs (n=10)	40.707	49.495	1.216		13.122	18.308	1.395	

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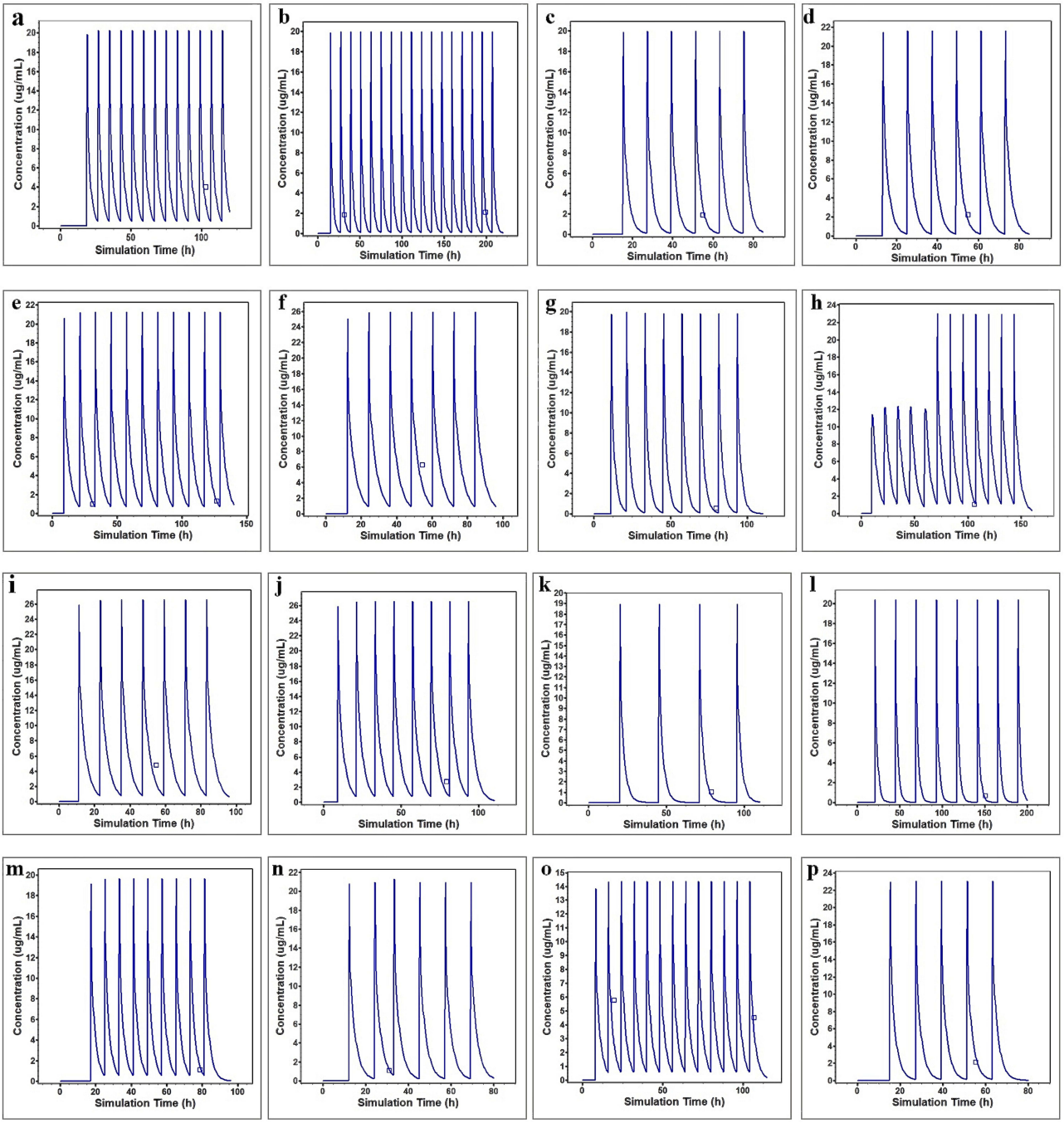

Figure 5 Plasma concentration–time curves of LZD in hospitalized pediatric patients. (**a–p**) 16 patients numbered a~p in Table 3 respectively, squares are observed values and blue lines are predicted values for LZD.

value of 35.4% for simulated and measured blood concentrations under different dosing regimens and the P-value of 0.292 showed no statistically significant differences.

Development and Verification of the PBPK Model of LZD in RI Adults

Table 4 showed the FE values are between 0.6 and 1.0, the GMFE values were found to be less than 2.0 for simulated and observational single doses of intravenous LZD in RI adults. The predicted values indicated a 20–30% decrease in complete LZD elimination in RI adults, resulting in an increase in the AUC linked to RI. Specifically, the AUC is 1.16-fold and 1.20-fold higher in patients with severe and end-stage RI, respectively, in comparison with healthy adults.

Table 3 Observational and Modeled Blood Concentrations of Intravenous Linezolid in Hospitalized Pediatric Patients

Pediatric Patient Number	Age	Weight (kg)	Dosage	Frequency of Administration	Blood Sampling Point (h)	Plasma Concentration (μg·h/mL)			
						Observed	Predicted	MAPE	P_value
a	3.0	12.0	I.v. 120mg	q8h	131.00	4.05	2.23	35.4%	0.292
b	3.0	12.0	I.v. 120mg	q12h	31.22	1.84	2.47		
	3.0	12.0	I.v. 120mg	q12h	199.23	2.13	2.62		
c	3.0	12.0	I.v. 120mg	q12h	54.88	1.91	2.81		
d	5.5	14.5	I.v. 150mg	q12h	54.82	2.25	1.85		
e	5.6	22.5	I.v. 200mg	q12h	30.95	0.97	1.26		
	5.6	22.5	I.v. 200mg	q12h	126.67	1.33	1.40		
f	7.9	28.0	I.v. 300mg	q12h	54.42	6.28	3.80		
g	11.2	15.0	I.v. 150mg	q12h	79.37	0.55	0.29		
h	11.8	31.5	I.v. 300mg	bid	106.00	1.07	1.48		
i	12.0	26.0	I.v. 300mg	q12h	54.65	4.83	2.52		
j	12.0	26.0	I.v. 300mg	q12h	79.12	2.74	1.42		
k	12.7	28.0	I.v. 260mg	qd	78.92	1.04	0.70		
l	12.8	28.0	I.v. 280mg	qd	150.33	0.71	0.43		
m	13.2	26.0	I.v. 250mg	q8h	78.65	1.10	1.53		
n	13.3	30.0	I.v. 300mg	bid	31.00	1.11	1.20		
o	13.4	30.0	I.v. 200mg	q8h	19.78	5.77	3.78		
	13.4	30.0	I.v. 200mg	q8h	107.00	4.52	5.09		
p	13.6	26.0	I.v. 300mg	q12h	55.33	2.16	2.79		

Table 4 PK Parameters of Linezolid: Observational Versus Simulated Data Following Oral Administration in Adults with Renal Impairment

Group	$AUC_{0-\infty}$(μg·h/mL)				C_{max}(μg/mL)			
	Observed	Predicted	FE	GMFE	Observed	Predicted	FE	GMFE
Moderate RI (n=6)	128±53	98.763	0.772	1.263	15.5±7.1	10.412	0.672	1.365
Severe RI (n=6)	127±66	105.32	0.830		10.8±3.1	9.913	0.918	
End-stage RI (n=6)	141±45	109.22	0.775		15.4±5.0	9.808	0.637	

Predicting of the PK of LZD and Developing Dose Adjustment Regimens in Pediatric Patients Across a Spectrum of RI Severity

The simulated PK changes in RI pediatric patients are presented in Table 5. While no significant alterations were observed in the volume of distribution at steady state (V_{ss}) or half-life (T_{half}) in children, the AUC increased by 20–30% in those with severe and end-stage RI in comparison with healthy children. Based on these AUC variations, appropriate dose adjustments for LZD are recommended for children with severe and end-stage RI, as detailed in Table 6.

Pharmacodynamic Evaluation

The dose was adjusted to 8 mg/kg every 8 hours (q8h), and the PD evaluation results for children with severe and end-stage RI are summarized in Table S2. At a MIC of 1.5 mg/L, 98.7% and 98.9% of children with severe and end-stage RI, respectively, achieved the PK/PD target at the recommended dose. At a MIC of 2 mg/L, the target achievement rate (PTA) for AUC_{0-24}/MIC ≥80 at the recommended dose exceeded 85% in both severe and end-stage RI children, as illustrated in Figure 6.

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Table 5 Simulated PK Profiles of Intravenous Linezolid Administration in Pediatric Age Subgroups Across a Spectrum of Kidney Function

Group	Condition	$AUC_{0-\infty}$ (μg·h/mL)	C_{max} (μg/mL)	CL (L/h)	GFR (mL/s)	$CL_{non-renal}$ (L/h)	CL_{renal} (L/h)	V_{ss} (L)	T_{half} (h)
13–17yrs	Normal[a]	346.47	20.367	7.347	1.897	5.101	2.246	36.883	3.479
	Mild RI	361.25	27.749	7.046	1.580	5.152	1.894	37.197	3.658
	Moderate RI	396.18	28.220	6.424	0.948	5.261	1.163	37.847	4.083
	Severe RI	427.73	28.403	5.950	0.474	5.358	0.592	38.367	4.468
	End-stage RI	451.95	28.389	5.630	0.157	5.431	0.199	38.712	4.765
7–12yrs	Normal[a]	497.5	23.736	4.685	1.575	3.242	1.443	22.783	3.370
	Mild RI	518.89	29.826	4.491	1.312	3.274	1.217	22.976	3.545
	Moderate RI	569.8	30.692	4.089	0.788	3.342	0.747	23.237	3.961
	Severe RI	616.02	31.258	3.782	0.394	3.402	0.380	23.692	4.341
	End-stage RI	651.61	31.553	3.575	0.131	3.447	0.128	23.907	4.634
3–6yrs	Normal[a]	341.88	25.508	3.523	1.021	2.794	0.730	11.706	2.302
	Mild RI	350.7	25.708	3.335	0.851	2.807	0.615	11.803	2.453
	Moderate RI	370.35	25.868	3.252	0.511	2.875	0.377	11.998	2.557
	Severe RI	386.37	25.865	3.117	0.255	2.925	0.192	12.154	2.702
	End-stage RI	397.74	25.731	3.028	0.085	2.964	0.064	12.260	2.806
1–2yrs	Normal[a]	364.65	25.855	2.120	0.677	1.601	0.519	7.389	2.416
	Mild RI	376.58	26.039	2.052	0.564	1.615	0.437	7.448	2.515
	Moderate RI	403.58	26.409	1.915	0.338	1.647	0.268	7.569	2.739
	Severe RI	426.79	26.893	1.811	0.169	1.675	0.136	7.665	2.934
	End-stage RI	443.66	26.545	1.742	0.056	1.696	0.046	7.730	3.076
0.25–1yrs	Normal[a]	304.09	23.03	1.853	0.439	1.334	0.519	5.489	2.053
	Mild RI	316.12	23.223	1.782	0.366	1.346	0.436	5.533	2.152
	Moderate RI	343.54	23.627	1.640	0.219	1.372	0.268	5.626	2.378
	Severe RI	368.13	23.871	1.530	0.110	1.394	0.136	5.698	2.581
	End-stage RI	386.59	23.971	1.457	0.036	1.411	0.046	5.748	2.734

Note: [a]Normal renal function.

Table 6 Recommended Dose Adjustments for Linezolid in RI Pediatrics

	Normal[a]	Mild RI	Moderate RI	Severe RI	End-stage RI
$fAUC_{0-24h}$ (μg·h/mL)	128.29	136.90	146.76	155.28	164.12
Geometric mean ratio (RI/healthy)		1.07	1.14	1.21	1.28
Proposed recommended dose	10mg/kgq8 h	10mg/kgq8 h	10mg/kgq8 h	8mg/kg q8 h	8mg/kg q8 h

Note: [a] Normal renal function.

Abbreviations: $fAUC_{0-24h}$, free area under the concentration vs. time curve from 0 to 24h calculated by trapezoidal rule, which was based on children aged 6 years with different levels of renal function; RI, renal impairment.

Discussion

Pediatric drug development is faced with many difficulties, such as ethical problems, low consent rates from neonate parents, and limited blood volume availability.[32] The PBPK model functions as a robust framework for synthesizing diverse data streams, encompassing in vitro, preclinical, and clinical data, to elucidate PK variations in pediatric populations. Consequently, it offers significant advantages in predicting PK of adult and extrapolating these findings to pediatric cohorts,[33] which has been extensively utilized as a critical tool in determination-making processes, study design optimization, and data analysis within academic research, pharmaceutical development, and supervising evaluations of pediatric drug therapies,[34–36] numerous modeling reports have been either published or formally submitted to health supervising agencies, serving to optimize clinical trial designs or to support requests for clinical research waivers.[37–39]

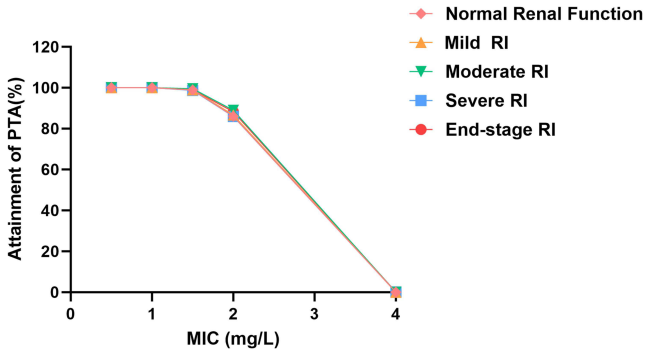

Figure 6 The probability of achieving PK goals in children with mild and moderate RI receiving 10 mg/kg LZD, q8h, and in children with severe RI receiving the recommended dose of LZD 8mg/kg, q8h, respectively.

A comprehensive PBPK model incorporating physiological variability was initially established and rigorously validated for intravenous LZD administration in both healthy populations and RI adults, based on which a PBPK model for RI patients can be developed and adequately evaluated. Computational analyses of multi-age cohorts (pediatric and adult subjects) with varying degrees of renal impairment demonstrated a statistically 10–30% reduction in systemic drug clearance relative to age-matched controls with preserved renal function. The analysis of PK parameters showed that values for T_{half}, V_{ss}, and total clearance almost no change with decrease in creatinine clearance. In pediatric patients with renal impairment, with the decrease in renal clearance, the nonrenal clearance increased, the observed compensatory increase in nonrenal LZD clearance may arise from declining renal function. This reduction diminishes renal excretion, leading to metabolite accumulation and decreased plasma protein binding.[40] The resultant elevation of free plasma drug concentrations accelerates non-enzymatic oxidation rates, thereby compensating for the loss of renal clearance.

To advance the practical application of this model in our hospital, we further analyzed data from our hospital patients. Since the number of patients with measured LZD plasma concentrations in our hospital is limited, we currently have data from only 16 patients. The results with MAPE within 100% further validate the model's estimation performance. For the 16 patients, we collected data from, we further used a *T*-test to analyze the predicted plasma concentrations, and the results showed no statistically significant differences. In the future, we will further validate and optimize the model through practical application in a larger population of patients with diverse characteristics.

Previous research showed that LZD may be the substrate of P-glycoprotein (P-gp) and the AUC over the dosing interval and C_{max} for LZD were reduced by approximately 32% and 21% when LZD was co-administered with rifampin,[41] in comparison with the monotherapy group, the combined use of 500 mg clarithromycin increased the AUC of LZD by 44%.[42] However, Madin-Darby canine kidney cells transfected with the human multidrug resistance 1 gene cell-based assay indicated that LZD was not a substrate of P-gp.[41] The idea that LZD acts as a P-gp substrate is likewise a subject of debate. Consequently, the parameters of P-gp have not yet been incorporated into our model, the verification results demonstrated acceptable predictive accuracy, so further additional studies are warranted to ascertain whether the inclusion of P-gp would enhance the model's predictive capabilities.

Previous research has indicated that RI patients experienced LIT more frequently during constant-dose therapy.[43–45] Specifically, the proportion of males was 76.5% of 221 patients (20–98yrs) receiving LZD, examination based on the patients' renal function showed that compared with patients with normal renal function (n=44) LIT occurs twice, 8times, and 9times as often in patients with mild (n=54), moderate (n=56), and severe (n=43) renal impairment, respectively, and 8 times more often in patients undergoing hemodialysis (n=24).[46] The results of a retrospective cohort study of children showed that 57% of the 37 children with baseline renal impairment developed LIT.[47] RI has been identified as a crucial risk factor for increased LZD C_{min} in real-world clinical studies.[12,48] Nevertheless, current therapeutic guidelines maintain a uniform 10 mg/kg q8h dosing regimen across all pediatric cohorts, despite documented instances of overexposure and LIT in cases of RI.[9] TDM and dose-adjustment strategies have been advocated by multiple researchers to enhance the safety and efficacy of LZD therapy in RI adult

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patients,[44,49,50] whereas our research can provide reference for the formulation of drug administration scheme for RI children in clinical.

Based on our research findings, age demonstrates a significant correlation with drug clearance, clearance rates were observed to increase with age, which in turn influences drug exposure, ie, drug concentration. Clinically, since children's body weight typically increases with age, pediatric dosages have primarily been determined based on weight. However, beyond body weight, renal function emerges as another critical factor affecting exposure to LZD. The appropriate LZD dosage in RI pediatric patients could theoretically achieve the same free AUC (fAUC) as in healthy children when multiplied by the correction factor for total drug in the indicated category of renal impairment. Based on changes in AUC in RI children in comparison with healthy children, we can draw some conclusions. For children aged 12 years and older, the recommended dosage aligns with that for adults, consistent with prescribing guidelines; for pediatric patients aged 3 months to 11 years, modification is not required for those with mild or moderate RI. However, in cases of severe and end-stage RI, the recommended dosage should be adjusted to 8 mg/kg administered every 8 hours (q8h)., supported by PD analyses.

There were several limitations to this study. First, the conduct of pediatric clinical trials is inherently constrained by numerous practical considerations, such as ethical limitations and difficulties in participant recruitment,[51] PK data for LZD in RI pediatric patients are not available to verify the model; therefore, it will be necessary to accumulate relevant clinical data to further optimize and verify future studies of the model. Second, our assumptions may not be appropriate for children with overweight or underweight suffering from renal impairment because we only considered children at the normal level of development. Further studies on children with abnormal development states should be conducted in the future.

Conclusion

In summary, the present study was conducted with the objective of developing, optimizing, and validating PBPK models for LZD in pediatric patients with impaired renal function in order to predict LZD exposure to RI children and to complete PD assessments. The study proposed available optimized dosage regimens for pediatric patients with severe and end-stage RI, respectively. Our model has the potential to serve as a tool for predicting LZD PK and facilitating dose modifications or other further applicable therapeutic decisions.

Ethical Approval

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University with an informed consent exemption considering the observational and retrospective nature of the study, and the data were collected without identifiers. (Approval No. 2020–282).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors affirm that this research was carried out without any commercial or financial affiliations that might be perceived as potential conflicts of interest.

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