

# Population pharmacokinetic analysis of linezolid in patients with different types of shock: Effect of platelet count

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Received January 8, 2019; Accepted May 24, 2019

DOI: 10.3892/etm.2019.7747

**Abstract.** Linezolid was approved by the Food and Drug Administration for the treatment of serious infections. However, patients with serious frequently develop shock, and it is currently elusive whether shock affects the pharmacokinetics of linezolid. The aim of the present study was to explore whether the pharmacokinetics of linezolid are different among patients with various types of shock or patients without shock and whether potential confounders are involved in their outcomes. A population pharmacokinetic analysis using a non-linear mixed-effects model was performed to examine the pharmacokinetics of patients with different types of shock or patients without shock. The pharmacokinetics of linezolid in patients with different types of shock or patients without shock was described by a one-compartment model. In our results, the patients with different types of shock or patients without shock demonstrated no differences in pharmacokinetics, whereas the platelet count was identified as a significant influencing factor. The results demonstrated that the pharmacokinetics of linezolid exhibited no significant differences among patients with different types of shock or patients without shock, whereas the platelet count significantly affected the clearance rate of linezolid.

## Introduction

Linezolid is a unique synthetic antimicrobial agent of the oxazolidinone class of antibiotics with activity against all gram-positive microorganisms, including certain mycobacteria

and various gram-negative anaerobes (1-4). This drug was approved by the Food and Drug Administration in April 2000 for the treatment of serious infections caused by gram-positive microorganisms, including those with known multidrug resistance, namely methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* (4). In addition, linezolid has been used as a second-line agent for treating tuberculosis (5-7) and exhibited no cross-resistance with other anti-tuberculosis drugs (8-10).

Pharmacokinetic studies of linezolid have been previously performed (11-13). It has been indicated that linezolid is used to treat patients with serious infections and in patients that develop frequent shock (14-17). To date, it has remained elusive whether the different types of shock affect the pharmacokinetic parameters of linezolid. In the present study, a population pharmacokinetic (PPK) analysis was performed to explore whether the pharmacokinetics of linezolid differ among patients with different types of shock or patients without shock and to explore the potential influencing factors.

## Methods

**Patients and data collection.** The data used in the present study were obtained from clinical routine diagnostic examinations and treatments of shock patients treated between January 2016 and August 2018 at the Zhongda Hospital affiliated to Southeast University (Nanjing, China). The clinical information available from the database was retrospectively reviewed. The retrospective inclusion criteria were as follows: Subjects (patients without shock, septic shock, hemorrhagic shock, neurogenic shock and cardiogenic shock) treated with linezolid (600 mg linezolid every 12 h, intravenously). Regarding the different types of shock, the patients were treated with different therapeutic regimens. In order to avoid the influence of drug interactions from different therapeutic schemes on linezolid pharmacokinetics, the following exclusion criteria were set: Combined use of drugs, which may have affected the pharmacokinetics of linezolid. Blood concentrations were obtained from the records of therapeutic drug monitoring. The associated clinical data were from medical log information. Prior to the present study, the data (blood parameters and medical log information) were already

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**Key words:** linezolid, shock patients, population pharmacokinetics, platelet

available, no organized collection or biological detection was required, and the information was retrospectively collated and analyzed. Using the already recorded and available blood concentrations and medical log information, the PPK model was built. The present study was approved by the Research Ethics Committee of the Zhongda Hospital affiliated to the Southeast University (Nanjing, China). The present study is a retrospective study and the analysis was approved by the affiliated ethics committee without any requirement for written informed consent.

The medical information included the following parameters: Sex, age, albumin (ALB), globulin (GLB), ALB/GLB (A/G), alanine transaminase (ALT), aspartate transaminase (AST), serum creatinine (SCR), urea, total protein (TP), total bile acid (TBA), total bilirubin (TBIL), hematocrit (HCT), hemoglobin (HGB), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC). In addition, the platelet count (PLT) was measured. Furthermore, the patient status (patients without shock, septic shock, hemorrhagic shock, neurogenic shock and cardiogenic shock) was also recorded.

**PPK modeling.** The data were analysed using the non-linear mixed-effects model (NONMEM) computer program (version VII; ICON Development Solutions). A one-compartment model with clearance (CL) and volumes of distribution (V) was used to describe the pharmacokinetic parameters of linezolid in the population of the present study.

**Random-effects model.** The inter-individual variabilities were evaluated by the exponential error model, according to the following equation:

$P_i = T(P) \times \exp(\eta_i)$  (a), where  $P_i$  is the individual parameter value,  $T(P)$  is the typical individual parameter value and  $\eta_i$  is the symmetrical distribution, which includes zero-mean chance variables with a variance.

The variabilities of the residual error variability were estimated as follows:

$OB = IP \times (1 + \varepsilon_i)$  (b), where OB is the observation and IP represents the individual predicted concentration.  $\varepsilon_i$  represents the symmetrical distribution, which includes zero-mean chance variables with a variance.

**Covariate model.** The following two equations describe the correlation of the parameters between continuous and categorical covariates, respectively.

$P_i = T(P) \times (\text{Cov}_i / \text{Cov}_{\text{constant}})^{\theta}$  (c)  $P_i = T(P) \times (1 + \theta \times \text{Cov}_i)$  (d), where  $P_i$  is the individual parameter value and  $T(P)$  is the typical individual parameter value.  $\theta$  is the estimated parameter and  $\text{Cov}_i$  is the covariate of the  $i$ -th individual.  $\text{Cov}_{\text{constant}}$  was fixed at a value similar to the population median of the covariate.

The potential covariates were sex, age, ALB, GLB, A/G, ALT, AST, SCR, UREA, TP, TBA, TBIL, PLT, HCT, HGB, MCH and MCHC levels, as well as the different types of shock. The stepwise-way set-up covariate model and likelihood ratio were used to compare the hierarchical models. The alterations in the objective function values (OFV) were produced by covariate inclusions and a decrease of OFV to  $>3.84$  ( $P < 0.05$ )

was deemed as the inclusion standard of the covariates into the basic model (18,19). Following the establishment of a full regression model, the assessment was performed by deleting covariates from each parameter one by one in order to obtain the final model. An increase in OFV to  $>6.64$  ( $P < 0.01$ ) was considered as a standard for significant associations in the final model (18,19).

**Model validation.** The final model was evaluated using bootstrap, an internal validation method, which was generated by repeated random sampling with replacement from the raw database. The process was performed by the software Wings for NONMEM, which performed 1,000 repetitions with different random sampling. The medians and percentiles (2.5-97.5) from bootstrap consequences were used for comparison of these values with those derived from the final model. Visual inspection of routine diagnostic plots included observations vs. individual predictions and absolute value of weighted residuals (iWRES) vs. individual predictions. The prediction-corrected visual predictive check (VPC) plots were used to assess the predictive performance of the final model.

## Results

**Data collection.** The data of 37 Chinese patients treated with linezolid were analyzed, and their demographic and laboratory data are provided in Table I. The pharmacokinetic profiles of linezolid in patients with different types of shock are provided in Fig. 1A-E. The results revealed that the concentration-time relation from patients with different types of shock or patients without shock demonstrated certain differences. However, whether the differences were a result of patient status or other potential influencing factors requires further study in future research. The population included 18 patients without shock, 11 septic shock patients, 1 hemorrhagic shock patient, 4 neurogenic shock patients and 3 cardiogenic shock patients (Fig. 1F).

**Modeling.** All potential covariates were analysed in the present study, and only the PLT on CL covariate exhibited statistical significance. The changes in the OFV are presented in Table II and the final model was constructed as follows:

$CL = \theta_{CL} \times (PLT/200)^{\theta_{PLT}} \times \omega_{CL}$  (e)  $V = \theta_V \times \omega_V$  (f), where CL, V,  $\theta_{CL}$ ,  $\theta_V$ ,  $\theta_{PLT}$ ,  $\omega_{CL}$  and  $\omega_V$  are the clearance, volume of distribution, typical value of CL, typical value of V, the coefficient of the platelet, inter-individual variability of CL and inter-individual variability of V, respectively. The platelet count was included in the covariates and the clearance rate of linezolid was increased in parallel with an increase in the platelet count.

**Validation.** The routine diagnostic plots that were visually inspected are provided in Fig. 2. They included the following comparison of the variables: Observations vs. individual predictions and iWRES vs. individual predictions. The parameter estimates in the final model and internal validation are provided in Table III. From 1,000 bootstrap runs, 992 runs were minimised with a successful covariance step and were included in the bootstrap analysis. The bootstrap median values were approximate to the estimate values in the final model, and the absolute value of all bias was  $<6\%$ , indicating

Table I. Demographic and laboratory data of the patients (n=37).

Characteristic	Mean±SD	Median (range)
Sex (male/female)	27/10	/
Age (years)	59.49±16.25	62.00 (29.00-89.00)
Albumin (g/l)	32.57±3.40	32.40 (25.40-43.80)
Globulin (g/l)	30.50±5.87	30.10 (15.40-40.40)
Albumin/globulin	1.12±0.34	1.01 (0.67-2.30)
Alanine transaminase (IU/l)	69.43±85.99	48.00 (3.00-525.00)
Aspartate transaminase (IU/l)	57.89±41.92	41.00 (11.00-181.00)
Serum creatinine ( $\mu$ mol/l)	126.03±113.64	85.00 (16.00-499.00)
Urea (mmol/l)	12.03±6.30	11.10 (2.40-29.90)
Total protein (g/l)	62.76±7.00	62.80 (45.90-75.10)
Total bile acid ( $\mu$ mol/l)	7.20±13.06	3.80 (1.00-81.50)
Total bilirubin ( $\mu$ mol/l)	25.04±65.96	11.10 (2.00-414.70)
Platelets ( $10^9$ /l)	246.54±187.20	213.00 (11.00-895.00)
Hematocrit (%)	27.14±5.32	26.50 (19.00-44.80)
Hemoglobin (g/l)	89.84±17.68	87.00 (63.00-140.00)
Mean corpuscular hemoglobin (pg)	29.78±1.93	29.90 (25.30-35.00)
Mean corpuscular hemoglobin concentration (g/l)	321.84±16.45	321.00 (277.00-355.00)

SD, standard deviation.

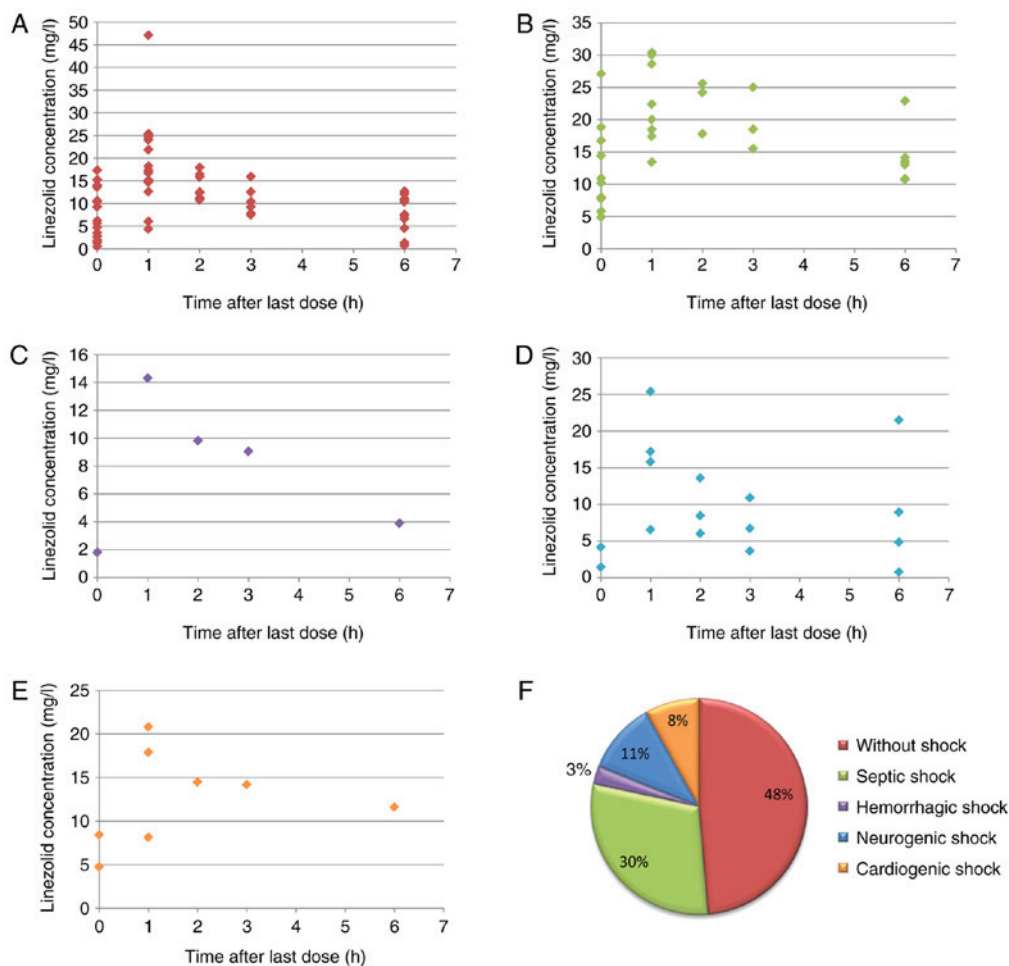


Figure 1. (A-E) Plasma Linezolid concentration in different types of shock patient following the last administration. (A) Patients without shock, (B) patients with septic shock, (C) patients with hemorrhagic shock, (D) patients with neurogenic shock and (E) patients with cardiogenic shock. (F) Constituent ratio of different types of shock patient.

Table II. Change of objective function value of covariate analysis.

Model description	OFV	$\Delta$ OFV	P-value
Inclusion step 1			
Basic model	1080.738	/	/
Influence of sex on CL	1075.476	-5.262	<0.05
Influence of age on CL	1079.979	-0.759	>0.05
Influence of absence of shock on CL	1080.620	-0.118	>0.05
Influence of septic shock on CL	1078.700	-2.038	>0.05
Influence of hemorrhagic shock on CL	1079.133	-1.605	>0.05
Influence of neurogenic shock on CL	1080.613	-0.125	>0.05
Influence of cardiogenic shock on CL	1080.393	-0.345	>0.05
Influence of ALB on CL	1078.277	-2.461	>0.05
Influence of GLB on CL	1080.727	-0.011	>0.05
Influence of A/G on CL	1080.354	-0.384	>0.05
Influence of ALT on CL	1080.723	-0.015	>0.05
Influence of AST on CL	1080.719	-0.019	>0.05
Influence of SCR on CL	1080.727	-0.011	>0.05
Influence of urea on CL	1080.508	-0.230	>0.05
Influence of TP on CL	1080.678	-0.060	>0.05
Influence of TBA on CL	1077.249	-3.489	>0.05
Influence of TBIL on CL	1077.598	-3.140	>0.05
Influence of PLT on CL	1069.637	-11.101	<0.05
Influence of HCT on CL	1079.774	-0.964	>0.05
Influence of HGB on CL	1080.241	-0.497	>0.05
Influence of MCH on CL	1077.168	-3.570	>0.05
Influence of MCHC on CL	1080.212	-0.526	>0.05
Inclusion step 2			
Influence of PLT on CL	1069.637	/	/
Influence of PLT and sex on CL	1067.456	-2.181	>0.05
Elimination			
Full model	1069.637	/	/
Elimination of PLT on CL	1080.738	11.101	<0.01

OFV, objective function values; CL, clearance; ALB, albumin; GLB, globulin; A/G, ALB/GLB; ALT, alanine transaminase; AST, aspartate transaminase; SCR, serum creatinine; TP, total protein; TBA, total bile acid; TBIL, total bilirubin; PLT, platelets; HCT, hematocrit; HGB, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

that the final model was dependent on specific parameters. The VPC plots for the final model are presented in Fig. 3, revealing that the most frequently observed concentration data were included in the 95% prediction intervals produced by the simulation data. Overall, the data suggested that the final model was able to predict drug concentrations with optimal efficiency.

## Discussion

Linezolid is currently used for the treatment of severe infections caused by gram-positive microorganisms, including vancomycin-resistant *Enterococcus*, vancomycin-sensitive *Enterococcus* and *Staphylococcus* infections (20-22). Since linezolid has a time-dependent activity, the percentage of time during which plasma concentrations exceed the minimal inhibitory concentration (MIC) represents its efficacy.

Furthermore, the area under the concentration-time curve (AUC) over 24 h may be divided by the MIC ( $AUC_{0-24}/MIC$ ) and used for evaluating the pharmacokinetics of linezolid (23). A higher success rate was reported when plasma concentrations remained above the MIC for the entire dosing interval and when the  $AUC_{0-24}/MIC$  values were between 80 and 120 (24,25). This showcases the importance of studying the pharmacokinetics of linezolid for evaluating its efficacy. However, severe infections are frequently accompanied by shock (14-17), and whether different types of shock affect the pharmacokinetics of linezolid has remained elusive.

The application of PPK may provide useful information from limited data of patients. Furthermore, PPK analysis differentiates between inter-individual and intra-individual variabilities. Therefore, PPK is more reliable for confirming the effects of various factors with regard to pharmacokinetic parameters compared with the traditional use of

Table III. Parameter estimates of final model and bootstrap validation.

Parameter	Estimate	SE	Bootstrap (n=992)		Bias (%)
			Median	95% CI	
CL (l/h)	11.8	0.23	11.2	[3.110, 16.625]	-5.085
V (l)	209	0.20	197	[53.850, 308.000]	-5.742
$\theta_{PLT}$	0.261	0.33	0.254	[0.052, 0.425]	-2.682
$\omega_{CL}$	0.299	2.15	0.287	[0.212, 0.359]	-4.013
$\omega_V$	0.299	2.15	0.287	[0.211, 0.356]	-4.013
$\sigma_1$	1.020	0.08	1.015	[0.864, 1.179]	-0.490

95% CI is displayed as the 2.5th, 97.5th percentile of bootstrap estimates. CL, clearance; V, volume of distribution;  $\theta_{PLT}$ , was the coefficient of the platelet;  $\omega_{CL}$ , inter-individual variability of CL;  $\omega_V$ , inter-individual variability of V;  $\sigma_1$ , residual variability (proportional error); bias, prediction error [Bias=(Median-Estimate)/Estimate x100%].

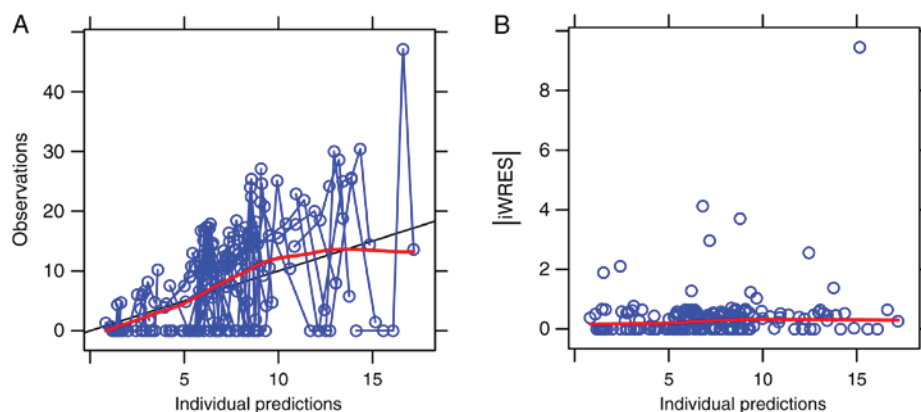


Figure 2. Visual inspection of routine diagnostic plots of the final population model. (A) Observations vs. individual predictions. (B) Absolute value of iWRES vs. individual predictions. iWRES, weighted residuals.

pharmacokinetics (18,19,26-33). In the present study, it was investigated whether the pharmacokinetics of linezolid are different in patients with different types of shock or patients without shock and the effects of several potential confounders on its metabolic profile were assessed. Among these groups, the population characteristics and biological features were screened as covariates.

In the present study, the pharmacokinetics of linezolid in patients with different types of shock or patients without shock was described by a one-compartment model with the parameters CL and V. The typical values of CL and V in the final PPK model were 11.8 l/h and 209 liters, respectively. Plock *et al* (34) reported on the population pharmacokinetics of linezolid of 10 healthy volunteers and 24 septic patients and the typical value of CL was estimated to be 11.1 l/h, which was similar to the results obtained in the present study. Of note, the present study determined that patients with different types of shock or patients without shock exhibited no differences in pharmacokinetics, suggesting that patient status (patients without shock, septic shock, hemorrhagic shock, neurogenic shock and cardiogenic shock) was not an influencing factor. However, when the platelet count was included in the covariates, the clearance rate of linezolid increased with the increase of the platelet

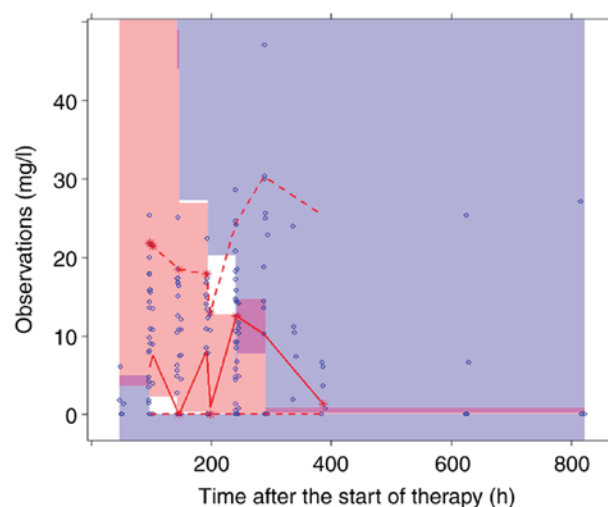


Figure 3. Prediction-corrected visual predictive check for the final model. The middle solid line represents the median of the prediction-corrected concentrations. The lower and upper dashed lines represent the 2.5 and 97.5th percentiles of the prediction-corrected concentrations, respectively.

count. Therefore, the data suggested that adjustment of a patient's linezolid regimen is possible, provided that the



platelet count is measured and the linezolid concentration values are adjusted accordingly.

The present study has a limitation: The analysis and patient inclusion were performed at a single center. Therefore, further multicenter and prospective studies with a larger number of patients are required.

In conclusion, the pharmacokinetics of linezolid were not different among patients without shock, as well as patients with septic shock, hemorrhagic shock, neurogenic shock and cardiogenic shock. However, the platelet count significantly influenced the clearance rate of linezolid.

## Acknowledgements

Not applicable.

## Funding

The current study was supported by AOSAİKANG pharmaceutical foundation (grant no. A201826), The Young Medical Talents of Wuxi (grant no. QNRC020), Young Project of Wuxi Health and Family Planning Research (grant no. Q201706) and the Wuxi Science and Technology Development Guidance Plan (medical and health care; grant no. CSZON1744).

## Availability of data and materials

The datasets used and/or analysed during the present study are available from the corresponding author on reasonable request.

## Authors' contributions

XC and DW conceived and designed the study. XZ collected the data. DW, XZ and YY built the model. DW wrote the manuscript. XZ and YY reviewed and edited the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

The present study was approved by the Research Ethics Committee of the Zhongda Hospital affiliated to Southeast University (Nanjing, China). The retrospective analysis was approved by the ethics committee without the requirement for written informed consent, since the data were collected without patient identifiers.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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