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Population pharmacokinetics of linezolid and its major metabolites PNU-142300 and PNU-142586 in adult patients

A short running title: Population pharmacokinetics of linezolid and its metabolites

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Conflict of interest

The authors declare no conflict of interest.

Abstract

Purpose:

Only a few reports are available on the population pharmacokinetic (PK) analysis of linezolid and its main metabolites. Therefore, we investigated the population PK of linezolid and its metabolites, and evaluated the relationship between them.

Methods:

Population PK analysis was performed using medical data collected from patients who were treated with intravenous linezolid (600 mg twice daily). We examined the impact of covariate candidates such as demographic characteristics and laboratory parameters. Simulations using the final model were investigated and used to estimate the plasma concentrations, trough concentrations (C_{min}) and area under the curve (AUC) of linezolid and its metabolites, and the C_{min} and AUC ratios were used to assess the accumulation of metabolites over linezolid.

Results:

A total of 82 plasma concentrations from 23 patients were analyzed. The volume of distribution was estimated to be 47.1 L, assuming that linezolid and its metabolites were the same. The total clearance (CL) of linezolid, and CLs of PNU-142300 and PNU-142586 were influenced by creatinine clearance (CL_{cr}), with population mean CLs of 3.86, 7.27, and 13.54 L/h, respectively. The C_{min} and AUCs of linezolid and its metabolites and the ratios of metabolites per linezolid were predicted to increase exponentially with decreasing renal function.

Conclusion:

We developed the first population PK model in which CL_{cr} was incorporated as a covariate in the CL of linezolid and its metabolites. Using the final model, it was possible to predict the plasma concentration, C_{min} and AUC appropriately. The model was found to be a potentially useful tool for future studies on optimal dosing and toxicity analysis.

Keywords: linezolid, PNU-123400, PNU-142586, population pharmacokinetics

Introduction

Linezolid is an oxazolidinone antibiotic with a broad spectrum of activity against gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci.¹⁻³ Linezolid is characterized by high bioavailability and good tissue penetration⁴ and is used for the treatment of severe infections such as pneumonia and skin and soft tissue infection.^{5, 6} Unlike other anti-MRSA drugs, linezolid does not require therapeutic drug monitoring (TDM), and dosage adjustment based on renal or hepatic function is also not necessary.^{7,}

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However, myelosuppression (thrombocytopenia, anemia, leukopenia, and pancytopenia), typically an adverse event associated with linezolid, has been reported to correlate with trough concentrations (C_{min}) and/or area under the curve (AUC).^{9, 10} Furthermore, in recent years to reduce adverse events, the need for TDM has been highlighted.^{9, 11-13} In addition, renal dysfunction has been reported to be an important risk factor for linezolid-related myelosuppression.^{14,}

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Linezolid is primarily metabolized by oxidation of the morpholine ring, resulting in two microbiologically inactive ring-opened carboxylic acid metabolites, namely aminoethoxyacetic acid metabolite (PNU-142300) and hydroxyethyl glycine metabolite (PNU-142586).^{16, 17} Recently, it has been reported that similar to its parent compound, these major metabolites also accumulate in the blood of patients with renal dysfunction.^{18, 19} To date, the mechanism of myelosuppression that develops during linezolid treatment has not been fully elucidated. Therefore, the accumulation of metabolites may be associated with an increased risk of myelosuppression and other adverse events,¹⁹ and elucidation of the main metabolite pharmacokinetics may lead to a reduction in adverse events owing to linezolid treatment. Thus, our group has recently developed a method for the simultaneous quantification of linezolid and its metabolites, PNU-142300 and PNU-142586, in human plasma using ultra-performance liquid chromatography (UPLC) to contribute to the optimization of linezolid therapy and toxicity studies.²⁰

Population pharmacokinetic (PK) analysis is a method of simultaneously analyzing the average pharmacokinetic and pharmacodynamic parameters and multiple factors that affect these parameters based on drug concentrations and clinical indices obtained from a large number of subjects with a wide range of backgrounds.²¹ Several population PK

analyses of linezolid have been reported, and body weight, renal functions, including creatinine clearance (CLcr), and liver functions, including cirrhosis and prothrombin activity (PTA), have been identified as factors influencing linezolid pharmacokinetics.^{10,22-24} However, research on population PK analysis including linezolid and its metabolites is limited.

Therefore, we aimed to characterize the pharmacokinetic parameters of the parent compound and the main metabolites in patients treated with intravenous linezolid and to identify the causative factors affecting pharmacokinetics in order to provide useful information on linezolid toxicity in future studies. In addition, we evaluated the relationship between the parent compound and metabolites, and we estimated the plasma concentrations, C_{min} and AUC from 0 to 24 h for each compound using a Monte Carlo simulation approach.

Methods

Patients and study design

We prospectively enrolled patients who were treated with intravenous linezolid (600 mg twice daily) at Osaka City University Hospital. This study was carried out in compliance with the ethical guidelines for clinical research and was approved by the Ethics Review Committee of Osaka City University Hospital (Ethics Committee approval number: 2982). Patients who provided consent were included in the present study. Blood samples were collected under steady-state conditions for three or more days after the administration of linezolid. Patients were sampled once or multiple times randomly in the interval between a single dose to the next dose. The infusion and sampling time were recorded precisely. The exclusion criteria were as follows: 1) patients receiving renal replacement therapy and 2) patients aged < 18 years.

Measurement of linezolid and metabolite concentrations

Following venous blood sample collection, plasma samples were extracted by centrifugation at $3,000 \times g$ for 10 min at 4°C and stored at -80°C until further analyses. The measurement of linezolid and its metabolites using UPLC has been detailed in our previous report.²⁰ Linearity of the assay was exhibited over a concentration range of 0.20–50.0

µg/mL for linezolid and 0.20–20.0 µg/mL for PNU-142300 and PNU-142586. The intra- and inter-assay accuracies of linezolid were 92.9–103.6 and 93.6–111.5%, respectively, and the corresponding intra- and inter-assay precisions (RSD%) were <4.1 and <15.8%. Similarly, the intra- and inter-assay accuracies of PNU-142300 were 93.6–106.9 and 89.5–109.5%, respectively, and the corresponding intra- and inter-assay precisions (RSD%) were <1.7 and <3.8%, respectively. The intra- and inter-assay accuracies of PNU-142586 were 96.9–101.5 and 92.8–97.3%, respectively, and the corresponding intra- and inter-assay precisions (RSD%) were <4.9 and <7.1%, respectively.

Population PK analysis

Population PK analysis of linezolid and its metabolites was performed using Phoenix NLME™ (Certara, USA) with the first-order conditional estimation-extended least squares method. The population PK modeling process was performed using the following procedure: (1) structural and statistical model, (2) covariate model, and (3) model validation.

Structural and statistical model

One- and two-compartment PK models with first-order elimination of linezolid and its metabolites were tested using the structural model. As PNU-142300 and PNU-142586 are non-enzymatically formed from linezolid and were not directly administered, the volumes of distribution for both metabolites were assumed to be comparable with that of linezolid. In addition, since the levels of linezolid and its metabolites in urine could not be measured, we chose to fix the fraction eliminated through each pathway based on a previous report,¹⁶ that is, the formational clearances of PNU-142300 and PNU-142586, and the elimination clearance of unchanged linezolid were defined as 0.11, 0.50, and 0.30 of the total elimination linezolid clearance, respectively.¹⁶

The optimal structural model was comprehensively evaluated using the goodness-of-fit criteria, the improvement of the objective function value (OFV; $-2 \log$ -likelihood, $-2LL$), and Akaike Information Criterion.

The interindividual variability of the PK parameters was described using an exponential model:

$$P_i = \theta \times \exp(\eta_i)$$

where P_i represents the estimated pharmacokinetic parameter value of the i -th individual, θ is the typical population

value of the parameter, and η_i is a random variable for the i -th individual, which is assumed to follow a normal distribution with a mean of zero and a variance of ω^2 .

The residual variability models were performed as follows:

$$\text{Additive error model: } C_{\text{obs},ij} = C_{\text{pred},ij} + \varepsilon_{ij}$$

$$\text{Proportional error model: } C_{\text{obs},ij} = C_{\text{pred},ij} \times (1 + \varepsilon_{ij})$$

$$\text{Combined error model: } C_{\text{obs},ij} = C_{\text{pred},ij} + \varepsilon_{ij} \times \text{sqrt} [1 + C_{\text{pred},ij}^2 \times (\text{Cmultstdev}/\sigma)^2]$$

where $C_{\text{obs},ij}$ represents the j -th measured concentration in the i -th individual, $C_{\text{pred},ij}$ is the individual predicted concentration, Cmultstdev is the multiplicative component of the residual, and ε_{ij} is proportional and additive residual variability term which are assumed to follow a normal distribution with a mean of zero and a variance of σ^2 .

Covariate model

To screen for covariates that affect PK parameters, demographic characteristics (sex, age, body weight, and body mass index), renal function (serum creatinine, CLcr, eGFR, blood urea nitrogen), and hepatic function (aspartate aminotransferase, alanine aminotransferase, total bilirubin, and albumin) were evaluated as covariate candidates. CLcr was calculated using the Cockcroft-Gault equation. Covariates were examined using a stepwise forward inclusion and backward elimination procedure. During the forward stepwise inclusion process, a covariate was considered significant and included in the basic model if the OFV decreased by more than 6.635 points with a P value of < 0.01 (χ^2 distribution with one degree of freedom). All significant covariates were incorporated into the basic model to construct a full model. Then, a backward elimination process was used to exclude covariates from the full model with an increase in the OFV of < 10.827 (χ^2 distribution with one degree of freedom) at the statistical level of $P < 0.001$.

For continuous covariates, the exponential model was performed based on the following equation:

$$P_i = \theta \times (\text{COV}_i / \text{COV}_{\text{median}})^{\theta_{\text{cov}}} \times \exp(\eta_i)$$

Covariates were normalized by the median, where P_i is the value of parameter P for the i -th individual, θ is the typical value of P , COV_i represents the i -th covariate, $\text{COV}_{\text{median}}$ is the median of the covariate, and θ_{COV} is the estimated parameter describing the fixed effect of covariates on the PK parameters.

Model validation

The validity of the final model was verified using goodness-of-fit (GOF) plots. GOF plots were used to examine the correlation between the observed concentrations (DV) and population-predicted concentrations (PRED), the correlation between DV and individual-predicted concentrations (IPRED), and the conditional weighted residuals (CWRES) versus time after dose. The reliability and stability of the final model were evaluated using nonparametric bootstrap analysis. The median and 95% confidence interval (CI) of the parameters from 1,000 bootstrap replicates were calculated and compared with the estimated parameters obtained from the final model.

Evaluating the plasma concentration, C_{min} and AUC of linezolid and its metabolites

Based on the final population PK model, the plasma concentrations, C_{min} and AUCs of linezolid and its metabolites in patients with several CL_{cr} (15, 30, 60, and 90 mL/min) who were treated with standard dose linezolid (600 mg twice daily) were simulated using the Monte Carlo method. Additionally, the C_{min} and AUC ratios (metabolites over linezolid) for each renal function were simulated to assess metabolite accumulation over the parent compound. These simulations using Phoenix NLME™ were performed in 10,000 simulated patients. To evaluate the outcomes of the simulations for plasma concentrations of linezolid and its metabolites, we plotted the population median of the simulated plasma concentration versus time. The AUCs and AUC ratios of linezolid and its metabolites from 0–24 h at a steady state were calculated based on the CLs of linezolid and its metabolites, drug dose, and the formation clearances of metabolites.

AUCs were derived as follows²⁵:

$$\text{AUC}_{\text{linezolid}} = \text{dose} / \text{CL}_{\text{linezolid}}$$

$$\text{AUC}_{\text{PNU142300}} = 0.11 \times \text{dose} / \text{CL}_{\text{PNU142300}}$$

$$\text{AUC}_{\text{PNU142586}} = 0.50 \times \text{dose} / \text{CL}_{\text{PNU 142586}}$$

Results

Patient characteristics and measurement of linezolid and metabolite concentrations

A total of 23 patients who were administered 600 mg of linezolid twice daily were enrolled in this study, and their characteristics are shown in Table 1. One-to-five blood samples per patient could be collected between 1–15 h after the administration of linezolid, and the total number of blood samples was 82. The median age and CL_{cr} were 64 (26–87) years and 78.9 (16.4–207.4) mL/min, respectively. Critically ill patients, including those with suspected sepsis, were not included in this study. None of the plasma concentrations of LZD or metabolites were below the lower limit of quantification (BLQ), and linezolid, PNU-142300, and PNU-142586 concentrations within the ranges of 0.34–37.03, 0.20–10.31, and 0.38–10.99 µg/mL, respectively, were obtained for population PK modeling.

Population PK analysis

The one-compartment models for linezolid and its metabolites best fit the data (Fig. 1). The results of a stepwise search for covariates and the estimated parameters of the final model are listed in Table 2 and Table 3. In the residue error model analysis, the combined error model was the best fit for linezolid and PNU-142300, and the proportional error model was the best fit for PNU-142568. In the covariate model analysis, CL_{cr} was extracted as an influencing factor on the total CL of linezolid, CLs of PNU-142300 and PNU-142586 with population mean CLs of 3.86, 7.27, and 13.54 L/h, respectively. The volume of distribution was estimated to be 47.1 L, assuming that the values of linezolid and its metabolites were the same. Model validation was performed, and the median values, coefficient of variation (CV), and 95% CI of each estimated parameter in the bootstrap sample were consistent with those of the original data, thus confirming the validity of the estimates (Table 3). Figure 2 shows a GOF plot of the final model. The prediction accuracies of PRED for both linezolid and its metabolites were good, with no bias against the baseline. IPRED was almost perfectly correlated with DV. The CWRES versus time after the dose plot showed no concentration- or time-dependent prediction bias, confirming the validity of the final model.

Plasma concentration, C_{min} and AUC, and ratio (metabolites/linezolid) for renal functioning

The plasma concentration, C_{min}, and AUCs 0–24 h along with ratios of linezolid and its metabolites at a steady state

when administered at the standard dose (600 mg twice daily) are shown in Figure 3. Plasma concentrations of linezolid and its metabolites were expected to increase with a decline in renal function. The C_{min} of linezolid, PNU-142300, and PNU-142586 in patients with normal renal function (CL_{cr} : 90 mL/min) were estimated to be 6.2, 0.3, and 0.7 $\mu\text{g/mL}$, respectively, and the corresponding AUCs were 233.2, 9.3, and 25.7 $\text{mg}\cdot\text{h/L}$. On the other hand, in patients with severe renal dysfunction (CL_{cr} : 15 mL/min), the C_{min} were estimated to be 17.3, 2.2, and 4.5 $\mu\text{g/mL}$, respectively, while the corresponding AUCs were 488.7, 50.8, and 107.1 $\text{mg}\cdot\text{h/L}$. The C_{min} and AUCs of linezolid and its metabolites were predicted to increase exponentially with declining renal function. The C_{min} ratios of metabolites to linezolid were 0.047 for PNU-142300/linezolid and 0.127 for PNU-142586/linezolid in patients with normal renal function (CL_{cr} : 90 mL/min), while the AUC ratios were 0.039 and 0.113, respectively. In contrast, among patients with severe renal dysfunction (CL_{cr} : 15 mL/min), the C_{min} ratios of PNU-142300/linezolid and PNU-142586/linezolid were 0.133 and 0.268, while the AUC ratios were 0.106 and 0.222, respectively, which were predicted to increase with declining renal function.

Discussion

This study is the first to construct a population PK model to quantitatively represent the pharmacokinetics of linezolid and its main metabolites. To evaluate the effects of renal function on the pharmacokinetics of linezolid and its metabolites, we simulated the plasma concentration, C_{min} and AUC_{0-24h} of linezolid and its metabolites under steady-state conditions based on the final model constructed in this study. Furthermore, we evaluated the C_{min} and AUC ratios of metabolites to linezolid and characterized the pharmacokinetics of linezolid and its metabolites.

There have been reports on population PK analysis of linezolid using the one-compartment model^{10, 24} or the two-compartment model.^{22, 26} In this study, the one-compartment model was a suitable fit for the final model of linezolid. The one-compartment model also fitted the metabolites as well as linezolid. With respect to the covariates model research, CL_{cr} was extracted as a factor that significantly affected the total CL of linezolid and CLs of its metabolites, and each CL was shown to decrease with decreasing renal function. Since the excretion rate of linezolid in the urine is approximately 30%, the impact of renal function on plasma concentrations is generally limited. In contrast, among

patients with renal dysfunction, the plasma concentration of linezolid increased and was reported to be associated with the occurrence of adverse events, including thrombocytopenia.^{14, 15} In addition, our results are in line with those of previous reports, wherein CL_{cr} was selected as a covariate for CL of linezolid.^{10, 23, 24} Furthermore, recent reports have shown that plasma concentrations of PNU-142300 and PNU-142586, the two main metabolites of linezolid, increased with declining renal function,^{18, 19} thus supporting our results that CL_{cr} is associated with CLs of PNU-142300 and PNU-142586 as factors that significantly affect their pharmacokinetics. Four patients with moderate renal dysfunction ($30 \leq \text{CL}_{\text{cr}} < 60$ mL/min) and two patients with severe renal dysfunction ($\text{CL}_{\text{cr}} < 30$ mL/min) were included in this population PK analysis. Therefore, we believe that the selected CL_{cr} as a covariate can be evaluated appropriately. Further, we believe that the impact of renal function should be considered in linezolid treatment in the future. There have been previous reports showing that liver function (cirrhosis or PTA) was a significant covariate.^{23, 24} However, since the patient background of this study included few patients with cirrhosis or hepatic dysfunction, this model cannot be applied to those with hepatic dysfunction.

To accurately estimate the volume of distribution in population PK analysis, it is generally necessary to administer the target compound and measure its concentration in the blood. However, in the present study, the concentrations of linezolid and its metabolites were measured in plasma obtained from patients treated with linezolid in clinical setting. Therefore, we believe that it was not possible to accurately estimate the volume of distribution of the metabolites because the metabolites themselves were not administered to the patients. In addition, since the two metabolites are formed by the ring-opening of the morpholine ring from linezolid through an oxidation reaction,¹⁶ it was thought that there would be no significant change in their molecular weights and that their chemical properties would not differ significantly. For these reasons, the distribution volumes of linezolid and its metabolites were assumed to be comparable in the present study. No significant covariates were extracted for the volume of distribution of linezolid and its metabolites. And the volume of distribution value was 47.1 L, which was consistent with previous reports.^{10, 23, 24} As in the present study, assuming that the volume of distribution of metabolites is the same as that of linezolid, it is possible that the maximum plasma concentration (C_{max}) of metabolites may be potentially affected as compared to the simulation using the original volume of distribution of metabolites. However, since the excretion process is

expected to be significantly unaffected, the impact on the estimation of C_{min} and AUCs under steady-state may exert limited effects. Considering the above pharmacokinetic and physiological aspects and validation results, the population PK parameters obtained in this study were judged to be clinically appropriate.

An obstacle to the continuation of linezolid treatment is the occurrence of adverse events such as myelosuppression.²⁷ As myelosuppression during linezolid treatment is associated with an increased plasma concentration or AUC for linezolid^{10, 29} or increased concentration ratios of metabolites to linezolid,¹⁹ it may be necessary to evaluate the concentrations of both linezolid and metabolites in the future. Therefore, for its application in toxicity studies in the future, we simulated the plasma concentration, C_{min} and AUC 0-24 h of linezolid and its metabolites for each renal function using the final model. Furthermore, we calculated the metabolite-to-parent ratios for C_{min} and AUCs. However, the comparison of plasma concentrations of linezolid and its metabolites could not be evaluated accurately, because the pharmacokinetics of each compound varied, and the time scale of concentration transition was different. The C_{min} and AUCs of linezolid and its metabolites were predicted to increase with declining renal function. In previous studies relating linezolid C_{min} and/or AUCs to adverse events, Pea et al. reported that maintaining C_{min}: 2-7 mg/L and AUC: 160-300 mg·h/L to improve safety while maintaining efficacy in adult patients on linezolid therapy.⁹ Matsumoto et al. also reported that the threshold to minimize linezolid-induced thrombocytopenia was 8.2 µg/mL.¹⁰ Our simulation suggested that the threshold for patients with moderate to severe renal dysfunction with CL_{cr} < 60 mL/min may exceed the previously reported safety thresholds for C_{min} and AUC, suggesting the need for TDM in future linezolid therapy. However, the number of patients who experienced adverse events such as thrombocytopenia was small in this study, and we were not able to evaluate the relationship between adverse effects and trough C_{min} or AUC. The predicted C_{min} ratios of PNU-142300/linezolid and PNU-142586/linezolid increased approximately by 2.8-fold (0.047–0.133) and 2.1-fold (0.127–0.268), respectively, with declining renal function, and similarly, the AUC ratios increased approximately by 2.7-fold (0.039–0.106) and 2.0-fold (0.113–0.222), respectively. In other words, the C_{min} and AUC ratios were not consistent with renal function, indicating that the rate of metabolite accumulation was higher in patients with renal dysfunction than in those with normal renal function. Hence, this study showed that clearances of linezolid and its metabolites were decreased, and plasma concentrations were increased in patients with

renal dysfunction. However, metabolites were more sensitive to renal function and plasma concentrations were more likely to increase compared to linezolid. Souza et al. demonstrated that the metabolite-to-parent ratios of PNU-142300 and PNU-142586 were significantly higher in the renal impairment group than in the patient group without renal impairment.¹⁸ Wang et al. showed that the metabolite-to-parent concentration ratio of PNU-142300 may be associated with toxicity of myelosuppression.¹⁹ In this study, the metabolite-to-parent ratios of PNU-142586 also increased in patients with renal dysfunction as well as PNU-142300. In order to investigate the indicators and association of adverse events in linezolid toxicity studies, it may be necessary to consider the plasma concentration and the metabolite-to-parent ratios. The population PK model constructed in this study can be used to predict the pharmacokinetics of linezolid and its metabolites, and it may become a useful tool for PK/PD studies in the future.

Our study had several limitations. First, the final model was internally validated; external validation was not executed as this was a single-center study with limited sample size. Second, we were not able to evaluate the relationship between C_{min} , AUC, and their ratios of linezolid and its metabolites calculated using Monte Carlo simulation, and the occurrence of adverse events such as myelosuppression. Third, the extrapolation to patients with the moderate to severe impaired renal function needs to be done with caution, as there were a few these patients in this study. As a future direction, we need to increase the number of subjects and evaluate the accuracy of the model by external validation, and investigate the impact of the concentration or ratios of linezolid and its metabolites on the occurrence of adverse drug reactions. Furthermore, it is necessary to consider setting a cut-off value for the estimation of the level of adverse events.

Conclusions

We developed the first population PK model in which CL_{Cr} was incorporated as a covariate in the CL of linezolid and its metabolites. Using the final model constructed, it was possible to predict the plasma concentration, C_{min} , and AUC of linezolid and its metabolites appropriately. In addition, the C_{min} and AUC ratios of metabolites per linezolid increased with decreasing renal function, suggesting that the metabolites are more affected by renal function than linezolid. The model could be a useful tool for future studies on optimal dosing and toxicity analyses.

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Table. 1 Patient characteristics.

Characteristic	
Gender (male / female)	23 (15 / 8)
Age (year)	64 (26–87)
Body weight (kg)	61.1 (39.0–109.5)
Body mass index (kg/m ²)	23.4 (16.1–36.2)
Linezolid dose (mg/dose)	600
Linezolid dose (mg/kg/dose)	9.8 (5.5–15.4)
Blood sampling point	82
Laboratory data	
Serum creatinine (mg/dL)	0.73 (0.30–5.21)
Creatinine clearance (mL/min)	78.9 (16.4–207.4)
eGFR (mL/min/1.73m ²)	77.1 (9.4–152.7)
Blood urea nitrogen (mg/dL)	15 (5–65)
Aspartate aminotransferase (U/L)	32 (14–133)
Alanine aminotransferase (U/L)	39 (9–311)
Total bilirubin (mg/dL)	0.5 (0.2–1.5)
Albumin (g/dL)	2.5 (1.3–3.7)
White blood cell count ($\times 10^3/\mu\text{L}$)	5.9 (2.4–18.9)
Hemoglobin (g/dL)	10.2 (7.4–15.0)
Platelet count ($\times 10^3/\mu\text{L}$)	236 (19–566)
qSOFA score (0/1/2/3), n	15/8/0/0
Type of infection	
bacteremia	10
respiratory tract infection	4
central nervous system infection	4
skin and soft tissue infection	3
osteoarticular infection	1
unknown	1
Isolated Gram-positive organisms	
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	7
Methicillin-resistant coagulase-negative staphylococci (MRCNS)	4
Corynebacterium	4
Methicillin-susceptible <i>Staphylococcus aureus</i> (MSSA)	2
<i>Enterococcus faecium</i>	2
empiric	5

Data are presented as the median (range).

eGFR: estimated glomerular filtration rate, qSOFA: quick sequential organ failure assessment

Table. 2 Stepwise search for covariate analysis and the final model development process.

Model No.	Equation	OFV	Δ OFV	AIC	Compared with	P-Value
1	Basic model	670.69		696.69		
2	$V_{\text{linezolid}}$ on weight	670.05	-0.64	698.05	No.1	NS
3	$CL_{\text{linezolid}}$ on CLcr	657.96	-12.73	685.96	No.1	<0.01
4	$CL_{\text{linezolid}}$ on CLcr, $CL_{\text{PNU142300}}$ on CLcr	642.57	-15.39	672.57	No.3	<0.01
5*	$CL_{\text{linezolid}}$ on CLcr, $CL_{\text{PNU142300}}$ on CLcr, $CL_{\text{PNU142586}}$ on CLcr	619.62	-22.95	651.62	No.4	<0.01
6	$CL_{\text{linezolid}}$ on eGFR, $CL_{\text{PNU142300}}$ on eGFR, $CL_{\text{PNU142586}}$ on eGFR	623.51	3.89	655.51	No.5	NS

OFV: objective function value, AIC: Akaike information criteria, V: volume of distribution, CL: clearance, CLcr: creatinine clearance,

eGFR: estimated glomerular filtration rate

Table. 3 Population pharmacokinetic parameters of the final pharmacokinetic model for linezolid and its metabolites.

Parameter	Final model			Bootstrap analysis (n = 1,000)		
	Estimate	CV (%)	95% CI	Median	CV (%)	95% CI
$CL_{\text{linezolid}} \text{ (L/h)} = \theta_1 \times (CL_{cr}/4.73)^{\theta_2} \times \exp(\eta CL_{\text{linezolid}})$						
$\theta_1 \text{ (L/h)}$	3.86	8.8	3.19–4.53	3.84	9.5	3.24–4.68
θ_2	0.41	18.0	0.26–0.56	0.41	21.2	0.24–0.58
$CL_{\text{PNU142300}} \text{ (L/h)} = \theta_3 \times (CL_{cr}/4.73)^{\theta_4} \times \exp(\eta CL_{\text{PNU142300}})$						
$\theta_3 \text{ (L/h)}$	7.27	13.6	5.32–9.22	7.38	14.1	5.39–9.43
θ_4	0.98	11.3	0.76–1.19	0.98	14.1	0.69–1.23
$CL_{\text{PNU142586}} \text{ (L/h)} = \theta_5 \times (CL_{cr}/4.73)^{\theta_6} \times \exp(\eta CL_{\text{PNU142586}})$						
$\theta_5 \text{ (L/h)}$	13.54	11.8	10.39–16.70	13.69	12.5	10.66–17.59
θ_6	0.79	18.6	0.50–1.09	0.78	22.4	0.46–1.12
$V_{\text{linezolid}} (= V_{\text{PNU142300}} = V_{\text{PNU142586}}) = \theta_7 \times \exp(\eta V)$						
$\theta_7 \text{ (L)}$	47.1	9.6	38.1–56.0	47.1	11.3	39.1–60.0
Interindividual variability [ω^2]						
$CL_{\text{linezolid}}$	0.150			0.150		
$CL_{\text{PNU142300}}$	0.418			0.416		
$CL_{\text{PNU142586}}$	0.298			0.299		
$V_{\text{linezolid}}$	0.0310			0.0319		
Residual variability [σ]						
Linezolid	0.244	14.2	0.175–0.312	0.240	14.6	0.171–0.307
PNU142300	0.594	39.3	0.134–1.054	0.585	65.5	0.00447–1.887
PNU142586	0.120	17.2	0.0795–0.161	0.116	20.4	0.0733–0.162

CV: coefficient of variation, CI: confidence interval

Figure legends

Figure. 1 Overview of the population pharmacokinetic model of linezolid and its metabolites. V indicates the volume of distribution and CL indicates the clearance for the linezolid and its metabolites. Formation clearance of metabolites and elimination clearance to unchanged linezolid were calculated as fixed fraction of the elimination clearance of linezolid.

Linezolid intravenous administration

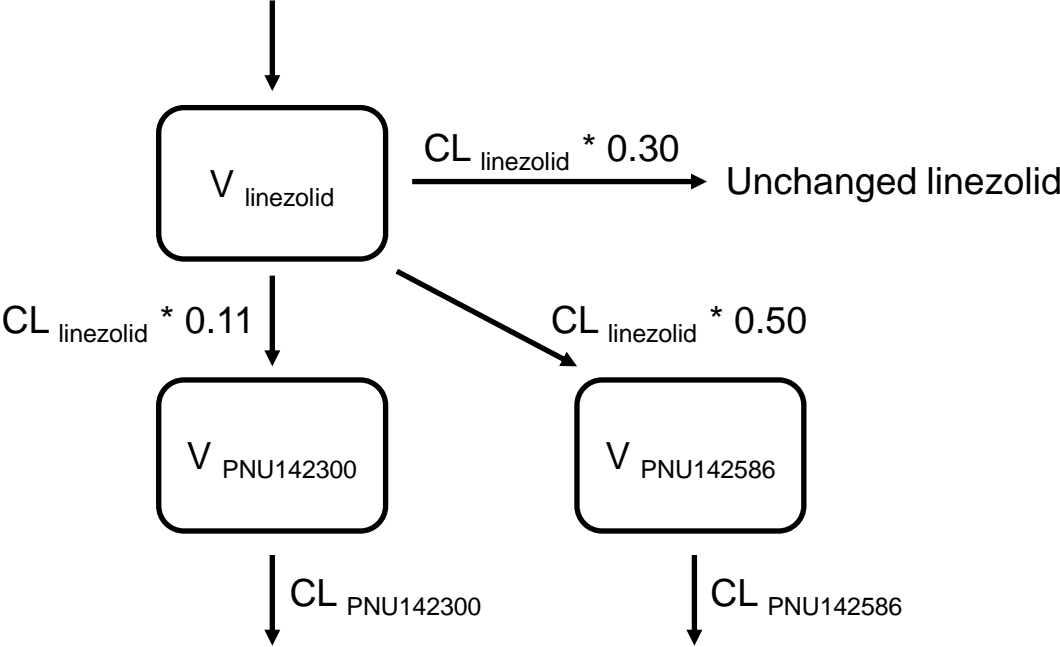


Figure. 2 Goodness-of-fit plot for the final model. (a, b, and c) The observed concentrations (DV) versus population-predicted concentrations (PRED); (d, e, and f) the DV versus individual-predicted concentrations (IPRED); (g, h, and i) the conditional weighted residuals (CWRES) versus time after dose.

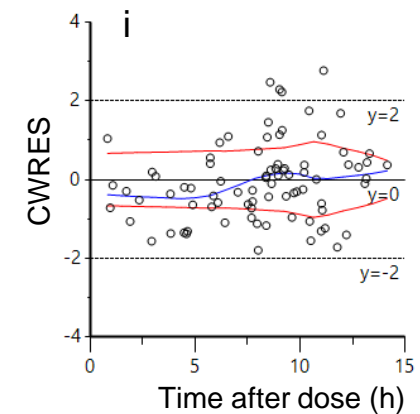
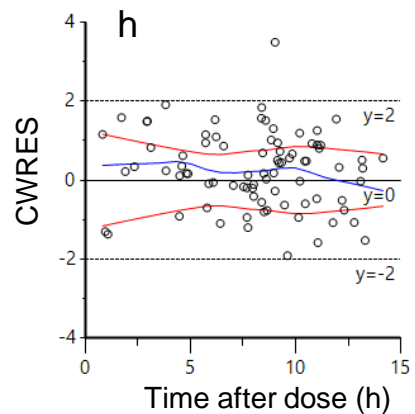
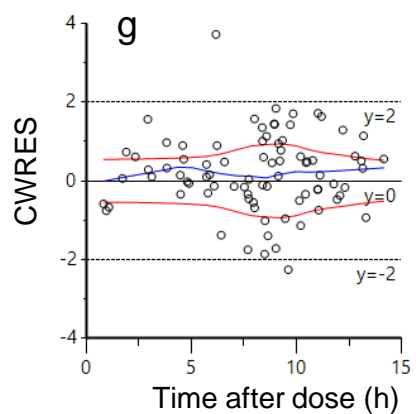
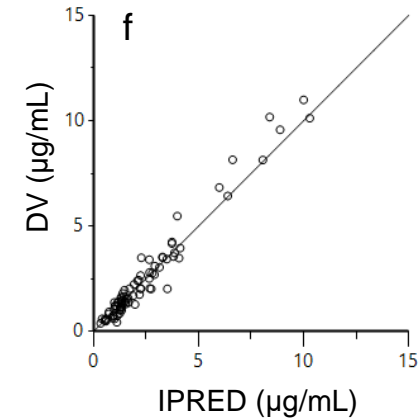
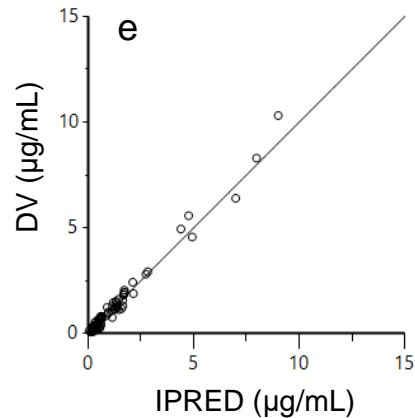
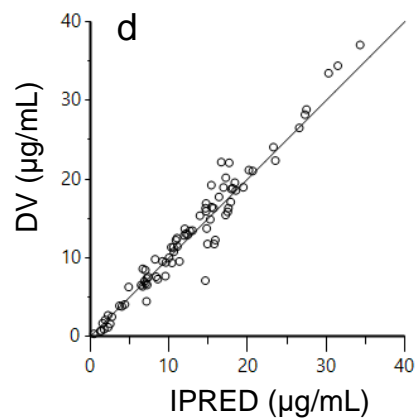
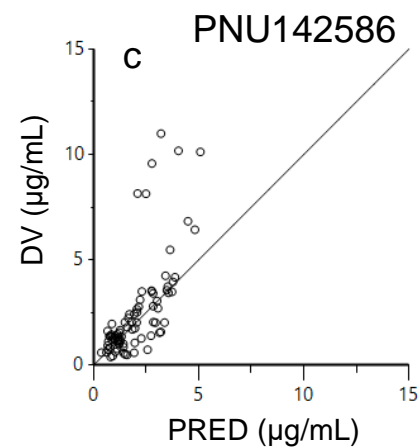
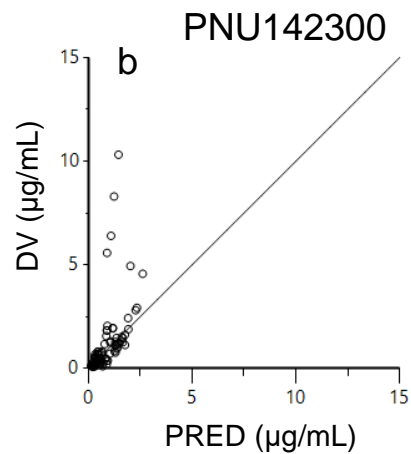
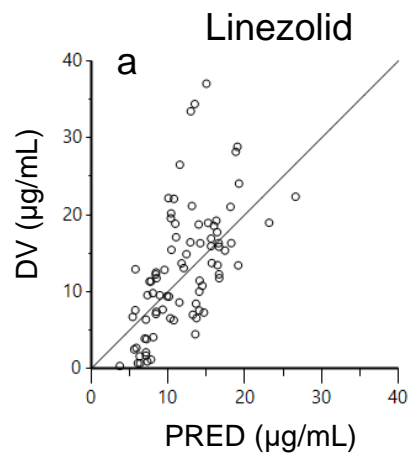


Figure. 3 A total of 10,000 Monte Carlo simulations for plasma concentrations (a-c), trough concentrations (d, e) and area under the curve (AUC) (g, h) for linezolid (LZD) and its metabolites and those of ratio (metabolites/LZD) (f, i) in a typical patient classified for creatinine clearance according to the final model when LZD was administered at a dose of 600 mg twice daily. The top edge of the box plots is the 75th percentile with 1.5 IQR (interquartile range). The upper quartile is the 75th percentile and the median line is the 50th percentile. The lower quartile is the 25th percentile and the lower edge is 25th percentile plus IQR.

