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Population Pharmacokinetic/Pharmacodynamic Study of Linezolid in Hospital-Acquired Pneumonia Patients with Renal Insufficiency

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Purpose: The optimal treatment strategy in patients with hospital-acquired pneumonia (HAP) due to Gram-positive bacteria and renal insufficiency remains challenging. The objective of this study was to compare the outcomes of linezolid versus teicoplanin in HAP patients with renal insufficiency and to explore optimal dosage strategy for linezolid.

Methods: The retrospective study enrolled adult patients treated with intravenous linezolid or teicoplanin at Suzhou Municipal Hospital between July 2018 and August 2023. For the comparative pharmacodynamic study, effectiveness, safety and target attainment of trough concentration (C_{min}) for teicoplanin versus linezolid treatment in HAP patients with document Gram-positive bacteria and renal insufficiency were compared. For the population pharmacokinetics (PPK) analyses, linezolid concentrations collected exclusively from HAP patients with renal insufficiency were used and the optimal dosage strategy was investigated using Monte Carlo simulations.

Results: Linezolid-treated patients had a higher bacterial eradication rate than teicoplanin-treated patients (88.5% vs 63.4%, $P < 0.001$). A higher proportion of patients in the linezolid group experienced at least one adverse reaction (42.0% vs 25.0%, $P = 0.025$). Significantly more supratherapeutic C_{min}, less therapeutic C_{min} were achieved in the linezolid group (adjusted $P < 0.05$). A total of 207 linezolid concentrations from 166 patients with renal insufficiency were available for the PPK analysis. Age and creatinine clearance (CrCL) were identified as significant covariates that influenced clearance. Simulations show that 300 mg q12h provide the optimal exposure in patients with a CrCL of 60 or 45 mL/min, and 200 mg q12h was recommended for patients with a CrCL of 30 or 15 mL/min.

Conclusion: Linezolid-treated patients with HAP and renal insufficiency had higher bacterial eradication rates, supratherapeutic exposure and adverse reactions than teicoplanin-treated patients. Linezolid dose reduction in patients with renal insufficiency improved the probability of achieving optimal exposure.

Keywords: linezolid, population pharmacokinetic, pharmacodynamic, renal insufficiency, hospital-acquired pneumonia

Introduction

Hospital-acquired pneumonia (HAP) is one of the most common healthcare-associated infections, which is associated with increased hospital length of stay, healthcare costs and high mortality.[1,2] Gram-positive bacteria are responsible for a substantial proportion of HAP infections.[3] The isolation of multidrug-resistant Gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), has increased steadily in the past decade.[4] Vancomycin, linezolid and teicoplanin are usually the preferred antibiotics for treating HAP caused by multidrug-resistant Gram-positive

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bacteria.[5–7] The dose-dependent nephrotoxicity of vancomycin has been well recognized, which occurred in up to 40% of patients.[8] Given the risk of nephrotoxicity associated with vancomycin, linezolid and teicoplanin may be considered as preferred alternative choices in patients with renal insufficiency.[9,10]

Two randomized clinical trials have already been performed to compare the efficacy and safety outcomes between linezolid and teicoplanin for the treatment of suspected or proven Gram-positive bacteria.[11,12] Nevertheless, both studies included patients with various sites of infection, without focusing specifically on HAP, which may cause bias toward finding significant results. Furthermore, patients with diverse renal function status were enrolled in these studies, and it is possible that the findings may not generalize to patients with renal insufficiency. Recently, therapeutic drug monitoring is recommended to be employed in patients administrated with linezolid or teicoplanin, in order to maximize the efficacy, while minimizing the likelihood of toxicity.[13,14] To date, the comparative study examining effectiveness, safety and target attainment of trough concentration (C_{min}) for linezolid versus teicoplanin in patients with proven Gram-positive HAP and renal insufficiency is lacking.

Teicoplanin is primarily eliminated by the kidney, with approximately 80% of the dose excreted unchanged via the urine route.[15] Therefore, it is recommended that the maintenance dose should be adjusted according to the renal function.[16] By contrast, linezolid is renally eliminated approximately 30% as the parent compound.[17] No dose adjustment of linezolid is necessary in patients with renal insufficiency, which is recommended in the manufacturer's instruction on the basis of the finding in a single-dose linezolid pharmacokinetic study.[18] However, recent studies have shown that linezolid C_{min} was increased in patients with renal insufficiency than those in normal renal function after multiple-dose administration.[19,20] Moreover, several studies indicated that renal insufficiency, high C_{min} were associated with an increased risk of linezolid-induced thrombocytopenia, which is one of the most frequent adverse reactions in patients receiving linezolid.[21,22] Therefore, dose optimization may be necessary in patients receiving linezolid with renal insufficiency.

Population pharmacokinetics (PPK) modeling is a widely used approach for describing the pharmacokinetic characteristics of drugs in specific population and further proposing optimal dosage regimen. Several studies have developed the PPK models of linezolid in patients with different renal functions,[21,23] however, the concentration data were not exclusively collected from patients with renal insufficiency. Tsuji et al[24] performed a PPK analysis of linezolid among Japanese patients, which involving 68 serum concentrations exclusively from 14 patients with renal insufficiency, and the limited sample number may affect final results of the analysis. In addition, no linezolid dose adjustments were recommended for patients with renal insufficiency in the study.

The purposes of the present study were (i) to compare efficacy, safety and target attainment of linezolid versus teicoplanin in HAP patients with renal insufficiency; (ii) to characterize pharmacokinetics parameters of linezolid in patients with renal insufficiency, and to explore the optimal dosage strategy for this special population using Monte Carlo simulation.

Material and Methods

Study Design and Patients

The retrospective study enrolled adult patients who treated with intravenous linezolid or teicoplanin at Suzhou Municipal Hospital between July 2018 and August 2023. Eligible patients were included if (i) age ≥ 18 years; (ii) diagnosed with HAP; (iii) with renal insufficiency (creatinine clearance [CrCL] <90 mL/min); (iv) had at least one steady-state C_{min}. The exclusion criteria were as follows: (i) missing demographic, clinical or laboratory information at baseline or after therapy, such as platelet count and serum creatinine; (ii) treated with linezolid or teicoplanin for less than one week; (iii) underwent renal replacement therapy; (iv) had a baseline platelet count less than 75000/μL; (v) with baseline hemoglobin of <6.8 g/dl for males or 6 g/dl for females; (vi) accompanied by known bleeding disorders or other bleeding disorders; (vii) with severe hepatic impairment. The definition of renal insufficiency was based on the US Food and Drug Administration updated guidance in 2010.[25] The CrCL value was estimated using the Cockroft–Gault formula. The diagnosis of HAP was based on the guidelines of the American Thoracic Society and the Infectious Diseases Society of America (2016).[5] The steady-state C_{min} of teicoplanin is defined as the concentration determined 30 min before the next dose of teicoplanin on day 3 to day 5 after completion of the loading dose regimen. The steady-state C_{min} of linezolid is

defined as the concentration measured at least 48 h post-initiation of therapy, 30 min or immediately prior to the next dose of linezolid. Patients who met the criteria and with document Gram-positive bacteria from the respiratory tract sample were evaluated in the comparative pharmacodynamic study, regardless of whether they were concomitant with Gram-positive bacteria from non-respiratory tract-derived samples. Gram-positive cocci were detected using a VITEK2 system, whereas Gram-positive bacillus were detected using the Kirby-Bauer method. For the PPK analyses, the patients receiving linezolid who met the criteria were enrolled. Ethical approval was obtained from the Ethics Committee of Suzhou Municipal Hospital (Approval No. K-2021-012). Written informed consent was obtained from participants or legally authorized representatives prior to the initiation of any study procedure. The study was performed according to the Declaration of Helsinki.

Dosing Regimen

Based on the manufacturer's instructions, teicoplanin was administered at three loading doses of 6–12 mg/kg every 12 h, followed by a maintenance dose which was half or one-third of the usual dose (6–12 mg/kg/d). Linezolid was administered at a standard dose of 600 mg q12h according to the package label. Clinicians were free to independently decide whether and how to adjust the dosage regimen based on steady-state C_{min}.

Concentration Determination

Serum concentrations of linezolid and teicoplanin were determined using high-performance liquid chromatography-tandem mass spectrometry methods. The linear concentration range was from 0.5 to 50.0 mg/L for linezolid. The accuracy ranged from −0.6% to 5.1%, with the intra-day and inter-day precisions of the linezolid analysis were within 3.5% and 7.0%, respectively. The quantification of teicoplanin was validated over a concentration range of 1–100 mg/L. The accuracy ranged from −0.6% to 6.7%, with the intra-day and inter-day precisions were within 5.5% and 8.0%, respectively. Further details on the determination of linezolid and teicoplanin are described in the Supplementary methods.

Data Collection

The following demographic and clinical data were collected for each patient from the hospital information system by two trained staff for input and check, such as sex, age, weight, diagnosis of infection, comorbidities, complications. Microbiological information including specimens collected for culture, the type of microbiological isolates; treatment regimen (such as dosage, interval, duration of administration and concomitant antibiotics, etc)., concentrations and laboratory values (such as platelet count, serum creatinine, alanine aminotransferase, etc.) were also collected.

Comparative Pharmacodynamic Study

The primary endpoints of the comparative pharmacodynamic study were clinical efficacy and microbiological efficacy, and the secondary endpoints included adverse reactions, all-cause 28-day mortality, and target attainment of C_{min}. The clinical efficacy is classified as treatment success (the resolution or improvement of signs and symptoms) or failure (persistence or deterioration of signs and symptoms) at the end of treatment, which was evaluated by two physicians. The microbiological efficacy is categorized as microbiological success and failure. Microbiological success is defined as documented eradication of the baseline pathogen or presumed eradication when clinical success is achieved, accompanied by the absence of follow-up cultures. Microbiological failure is defined as the absence of either documented or presumed pathogen eradication. The all-cause 28-day mortality rate is defined as any death that occurred within 28 days after HAP diagnosis. Concentration exposure of linezolid and teicoplanin were classified into three categories: therapeutic exposure, supratherapeutic exposure and subtherapeutic exposure. Therapeutic exposure is defined as C_{min} of 10–30 mg/L[26] for teicoplanin and 2–8 mg/L[13] for linezolid, respectively. Supratherapeutic exposure is defined as C_{min} above the target range, whereas subtherapeutic exposure is defined as C_{min} below the target range.

Safety outcomes measures include thrombocytopenia, anemia, hepatotoxicity, nephrotoxicity and any other adverse events related to therapy, such as gastrointestinal disorders. Thrombocytopenia was defined as a ≥25% reduction of platelet count from baseline for patients with platelet count below the lower limit of normal at baseline or a platelet count of less than 112500/μL for patients with baseline platelet maintained at a normal range.[21,27] Anemia was defined as

a hemoglobin concentration <10 g/dL or a 2 g/dL decrease if the baseline value was less than the lower limit of normal.[28] Hepatotoxicity was defined as alanine aminotransferase or aspartate transaminase exceeded three times the upper limit of normal, or total bilirubin more than twice the upper limit of normal.[29] Acute kidney injury was identified as an increase in serum creatinine by ≥26.5 μmol/L within 48 h or an increase in serum creatinine by ≥1.5 times baseline value within the prior 7 days or a urine volume less than 0.5 mL/kg/h for 6 h.[30]

PPK Study

One and two compartments with linear elimination were evaluated as the potential structural base model for linezolid. Additive, proportional, and combined additive and proportional error models were assessed to account for residual variability. Potential covariates affecting the pharmacokinetic parameters were incorporated into the final model by a stepwise forward inclusion with an objective function value (OFV) decrease of at least 3.84 points ($P < 0.05$) followed by backward elimination approach with an OFV increase of at least 6.64 points ($P < 0.01$).

The final model was assessed based on goodness-of-fit (GOF) plots, prediction-corrected visual predictive check (pc-VPC) plots, and a nonparametric bootstrap approach. The following GOF plots were employed, including observed concentrations vs individual predictions (IPRED) or population predictions (PRED), conditional weighted residuals (CWRES) vs time or PRED. The nonparametric bootstrap with 1000 resamples was conducted to generate the median and 95% confidence intervals of the estimated parameters. For the pc-VPC, the simulated concentrations of linezolid were compared with the observed values by superimposing the median, 5th and 95th values for the observed concentrations with 90% prediction bands of each of these percentiles from the simulations.

Monte Carlo simulations were performed for 1000 virtual individuals to predict patient-specific linezolid exposures on the basis of final PPK model. The following dosing regimens were simulated: 600, 400, 300 or 200 mg every 12 h. The infusion time was set to 1 h. For convenience in clinical practice, C_{min} has been frequently selected as the pharmacokinetic/pharmacodynamic index in previous studies.[22,31] To maximize linezolid efficacy and minimize the risk of toxicity, the recommended target C_{min} range is 2–8 mg/L. The probability of target attainment (PTA) was calculated for each dosage regimen among simulated individuals with CrCL values ranging from 15 to 90 mL/min, with age of 30, 50, 70, 90 or 100 years old. The dosage regimens with the highest PTA were recommended.

Statistical Analysis

The normality of the distribution is checked using the Shapiro–Wilk test for continuous variables. When these data are not normally distributed, the variables are expressed as medians and IQRs. When these data are in accordance with normal distribution, the variables are expressed as mean ± SD. Differences in patient characteristics between groups are assessed using the Mann–Whitney *U*-test when the continuous variables are not normally distributed, otherwise an independent *t*-test is used. Categorical variables are expressed as frequencies and percentages and differences in patient characteristics between groups were assessed using the Pearson's chi-squared test or Fisher's exact test. All statistical tests of hypothesis are two-sided and performed at the significance level of 0.05. Bonferroni correction was applied for multiple comparison among concentration exposure categories of linezolid and teicoplanin, type of Gram-positive bacteria and source of Gram-positive bacteria. All statistical analyses were performed using the SPSS, version 23 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 9).

Results

Comparative Pharmacodynamic Study

It was the first comparison of the efficacy, safety and target attainment of linezolid and teicoplanin in patients with renal insufficiency for the treatment of HAP. A total of 157 patients who met the criteria were enrolled in pharmacodynamic study, of whom 81 were treated with linezolid and 76 with teicoplanin. No significant differences in demographic and baseline characteristics were found between the two groups, as displayed in Table 1. More than half of the patients had other concomitant sites of infection. MRSA was the most common Gram-positive bacteria isolated from the respiratory

Table 1 Baseline Characteristics of Patient Enrolled in Comparative Pharmacodynamic Study

Characteristics	Linezolid (n=81)	Teicoplanin (n=76)	*P* value
Demographics			
Gender (male), n (%)	60 (74.1%)	49 (64.5%)	0.192
Age (y), median (IQR)	83 (74,91)	84 (75,89)	0.57
Weight (kg), median (IQR)	60.0 (55.0,65.0)	60.0 (55.0,61.9)	0.142
Mixed infection, n (%)			
Bloodstream infection	21 (25.9%)	15 (19.7%)	0.357
Abdominal infection	13 (16.0%)	18 (23.7%)	0.23
Skin and soft tissue infection	14 (17.3%)	11 (14.5%)	0.631
Urinary tract infection	25 (30.9%)	16 (21.1%)	0.162
Multiple infection	51 (63.0%)	51 (67.1%)	0.587
Complications, n (%)			
MODS	11 (13.6%)	12 (15.8%)	0.696
Respiratory failure	32 (39.5%)	31 (40.8%)	0.87
Septic shock	21 (25.9%)	25 (32.9%)	0.338
Type of respiratory pathogen, n (%)[a]			0.678
Gram-positive only	63 (72.4%)	57 (69.5%)	
Mixed (Gram-positive and Gram-negative)	24 (27.6%)	25 (30.5%)	
Type of Gram-positive bacteria from respiratory tract samples, n (%)[a]			0.99
MRSA	69 (79.3%)	65 (79.3%)	
MRCNS	2 (2.3%)	2 (2.4%)	
Enterococcus	4 (4.6%)	3 (3.7%)	
Gram-positive bacillus	12 (13.8%)	12 (14.6%)	
Source of Gram-positive bacteria from non-respiratory tract-derived samples, n (%)[b]			0.217
Urine	13 (32.5%)	6 (18.8%)	
Blood	20 (50.0%)	15 (46.9%)	
Wound swab	5 (12.5%)	5 (15.6%)	
Drainage liquid	2 (5.0%)	6 (18.8%)	
Type of Gram-positive bacteria from non-respiratory tract-derived samples, n (%)[b]			0.490
MRSA	12 (30.0%)	13 (40.6%)	
MRCNS	5 (12.5%)	5 (15.6%)	
Enterococcus	16 (40.0%)	12 (37.5%)	
Gram-positive bacillus	7 (17.5%)	2 (6.3%)	
Treatment			
Duration (days), median (IQR)	9.0 (8.0,12.0)	9.0 (7.0,13.0)	0.976
Concomitant antibiotics, n (%)	62 (76.5%)	64 (84.2%)	0.228
Laboratory values, median (IQR)			
White blood cell ($\times 10^9$/L)	11.7 (7.4,16.1)	12.5 (8.2,19.3)	0.402
Hemoglobin ($\times 10^9$/L)	89.0 (73.5,104.5)	87.5 (73.0,103.0)	0.561
Platelet ($\times 10^9$/L)	181.0 (134.5,247.5)	152.0 (120.0,233.2)	0.117
C-reactive protein (mg/L)	79.1 (45.0,118.8)	93.7 (37.2,163.1)	0.257
Procalcitonin (μg/L)	1.1 (0.2,5.7)	0.6 (0.2,6.8)	0.717
Total bilirubin (μmol/L)	7.4 (4.8,11.0)	7.8 (4.2,15.1)	0.463
Albumin (g/L)	31.7 (28.5,35.1)	29.6 (25.8,34.4)	0.124
Alanine aminotransferase(U/L)	21.0 (15.5,35.5)	25.0 (17.0,53.8)	0.11
Aspartate transaminase(U/L)	29.0 (21.0,45.5)	33.0 (21.0,72.0)	0.181
Creatinine (μmol/L)	111.0 (88.0,145.9)	125.0 (86.8,156.8)	0.230
CrCL (mL/min)	37.8 (30.2,48.2)	33.8 (25.5,43.4)	0.073

Notes: [a]Respiratory tract samples included oropharyngeal swab, expectorated sputum, and bronchoalveolar lavage results. Gram-positive bacteria were found in 87 respiratory tract samples from the linezolid-treated patients and 82 respiratory tract samples from the teicoplanin-treated patients. [b]Gram-positive bacteria were found in 40 non-respiratory tract-derived samples from the linezolid-treated patients and 32 non-respiratory tract-derived samples from the teicoplanin-treated patients.

Abbreviations: MODS, multiple organ dysfunction syndrome; MRSA, methicillin-resistant *Staphylococcus aureus*; MRCNS, methicillin resistant coagulase negative staphylococci; CrCL, creatinine clearance.

tract. Concomitant Gram-negative and Gram-positive respiratory bacterial infections were present in approximately 30% of the patients. The median CrCL values of patients in the two groups were 37.8 mL/min and 33.8 mL/min, respectively.

As shown in Table 2, although a higher rate of clinical success was observed in the linezolid group when compared to the teicoplanin group, the difference was not statistically significant (74.1% vs 65.8%, $P = 0.257$). Linezolid-treated patients had a significantly higher bacterial eradication rate than teicoplanin-treated patients (88.5% vs 63.4%, $P < 0.001$). There was no statistically significant difference between the two groups in all-cause 28-day mortality (22.2% vs 28.9%, $P = 0.334$). A higher proportion of patients with at least one adverse reaction was observed in the linezolid group than the teicoplanin group (42.0% vs 25.0%, $P = 0.025$). The incidence rates of thrombocytopenia (34.6% vs 17.1%, $P = 0.013$) and anemia (23.5% vs 10.5%, $P = 0.032$) were significantly higher in patients treated with linezolid than those treated with teicoplanin.

A total of 83 linezolid C_{min} and 80 teicoplanin C_{min} were available for analysis. As shown in Figure 1, the proportions of linezolid C_{min} fell into subtherapeutic, therapeutic, and supratherapeutic range were 1.2% (1/83), 36.1% (30/83) and 62.7% (52/83), respectively. Among C_{min} measured in the teicoplanin group, the corresponding ratio was 25.0% (20/80), 66.2% (53/80) and 8.8% (7/80), respectively. The proportion of C_{min} fell in to the three different ranges between the two groups were significantly different ($P < 0.001$). Multiple comparison showed that significantly more supratherapeutic C_{min}, less therapeutic concentration and subtherapeutic exposure were achieved in the linezolid group compared with the teicoplanin group (all adjusted $P < 0.05$).

PPK Study

A total of 207 linezolid concentrations obtained from 166 patients with renal insufficiency were available for the PPK analysis, which were approximately 3-fold more than those collected in Tsuji et al's study.[24] The comparison between baseline characteristics of patients treated with linezolid in the comparative pharmacodynamic study and in the PPK study was illustrated in Table S1. No significant differences in baseline characteristics were found between patients treated with linezolid in the comparative pharmacodynamic study and those in the PPK study. Linezolid pharmacokinetics was adequately described by one compartment disposition model with linear elimination. The additive error model was found to best fit the data. Age and CrCL were identified as significant covariates that affect linezolid clearance. The relationship of covariates in developing the full model was shown in Table S2. The final population PK model was as follows:

$$CL\ (L/h) = 2.7 \times (age/82)^{-0.56} \times (CrCL/42.0)^{0.50} \times \exp(\eta CL)$$

$$V\ (L) = 57.1$$

where CL is the individual clearance, V is the individual volume of distribution, age and CrCL represents the individual age and creatinine clearance, ηCL is the normally distributed random effect with a mean of 0 and a variance of ω^2.

Table 2 The Therapeutic Efficacy and Safety Evaluation of Linezolid versus Teicoplanin in HAP Patients with Renal Impairment

Outcomes	Linezolid (n=81)	Teicoplanin (n=76)	*P* value
Clinical success, n (%)	60 (74.1%)	50 (65.8%)	0.257
Bacterial eradication, n (%)[a]	77 (88.5%)	52 (63.4%)	<0.001
Presumed eradication	39 (44.8%)	28 (34.1%)	
Documented eradication	38 (43.7%)	24 (29.3%)	
Any adverse reaction, n(%)	34 (42.0%)	19 (25.0%)	0.025
Thrombocytopenia	28 (34.6%)	13 (17.1%)	0.013
Anemia	19 (23.5%)	8 (10.5%)	0.032
Hepatotoxicity	5 (6.2%)	7 (9.2%)	0.474
Nephrotoxicity	8 (9.9%)	9 (11.8%)	0.692
Other adverse reactions	2 (2.5%)	3 (3.9%)	0.942
28-day mortality, n (%)	18 (22.2%)	22 (28.9%)	0.334

Notes: [a]Gram-positive bacteria were found in 87 respiratory tract samples from the linezolid-treated patients and 82 respiratory tract samples from the teicoplanin-treated patients.

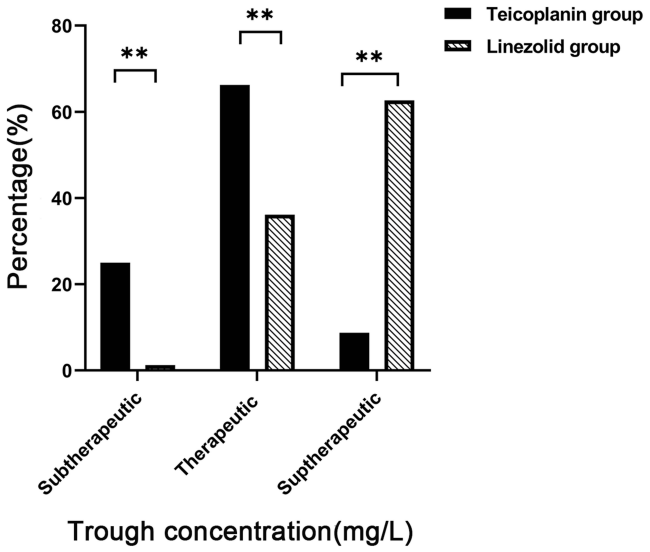

Figure 1 Target attainment of trough concentration (C_{min}) in patients with renal insufficiency receiving linezolid and teicoplanin therapy.
Notes: Therapeutic exposure is defined as C_{min} of 10–30 mg/L for teicoplanin and 2–8 mg/L for linezolid, respectively. Supratherapeutic exposure is defined as C_{min} above the desired range, whereas subtherapeutic exposure is defined as C_{min} below the desired range. **Bonferroni-adjusted $P < 0.05$.

The population parameter estimates derived from the final model are presented in Table 3. Linezolid population mean clearance and volume of distribution were estimated to be 2.7 L/h and 57.1 L, respectively. The GOF plots of the basic and final model are displayed in Figures 2 and 3, which suggested that there was no obvious bias in the model fit. The median values of the parameters estimated by the bootstrap analysis were in agreement with the original parameter estimates, as shown in Table 3. The pc-VPC plot (Figure 4) indicated that the model has a good predictive performance, with acceptable consistency between the observed and simulated concentrations of linezolid.

The optimal regimen was proposed using the Monte Carlo simulations based on a PPK model using the concentration data exclusively from the patients with renal insufficiency. The probability of achieving a C_{min} of less than 2 mg/L, 2–8 mg/L, and more than 8 mg/L are presented in Table 4 for various dosage regimens across different subject groups based on CrCL and age. For patients with median age (approximately 80 y), the simulated probabilities of achieving a therapeutic linezolid C_{min} ranged from 2.4% to 73.6% when receiving a standard dose of 600 mg q12 h. Simulations show that 400mg every q12h most likely achieves appropriate exposure for patients with CrCL value of 90 mL/min. For patients with a CrCL of 60 or 45 mL/min, 300mg q12h may provide the optimal target exposure. Whereas for patients with CrCL of 30 or 15 mL/min, a dose of 200mg q12h is optimal to balance safety and efficacy. For subjects with median CrCL (approximately 40 mL/min) and aged 30 years old, 400mg q12h best achieves the target exposure. Whereas for patients with age of 50 or 70 years old, 300mg q12h may provide the optimal target attainment. The simulation also showed that 200mg q12h was the optimal dosing regimen for patients aged ≥90 years old to achieve the therapeutic range.

Discussion

To the best of our knowledge, this is the first study to compare the efficacy, safety and target attainment of linezolid and teicoplanin in patients with renal insufficiency for the management of HAP. Furthermore, this is so far the largest PPK analysis performed based on 207 linezolid concentrations obtained exclusively from patients with renal insufficiency. In addition, Monte Carlo simulations based on the PPK model were performed to propose the optimal dosage regimens for linezolid in this special population, using concentration data exclusively from the patients with renal insufficiency.

Previous studies enrolled patients with diverse renal function and infection sites, which may cause potential biases affecting the results. Focusing on HAP patients with renal insufficiency, linezolid was found to be associated with superior microbiological success rate compared to teicoplanin. It might be explained by the high pulmonary penetration of linezolid, as reported by Conte et al, who observed that the concentrations of linezolid in epithelial lining fluid were

Table 3 Population PK Parameter Estimates in the Final Model and Bootstrap

Parameter (unit)	Final Model Results		Bootstrap Results	
	Estimate (shrinkage %)	CV (%)	Median	95% CI
Structural model				
TVv(L)	57.1	13.9	57.1	39.1–72.5
TV_{CL} (L/h)	2.7	3.7	2.7	2.5–2.9
θ_{Age}	−0.6	−31.5	−0.6	(−0.9)-(−0.2)
θ_{CrCL}	0.5	14.8	0.5	0.4–0.7
Inter-individual variability				
ω^2_{CL} (%)	0.1 (23.3)	27.3	0.1	
Residual variability				
σ(%)	3.4	13.2	3.3	2.4–4.2

Abbreviations: TVv, typical value of volume of distribution; TV_{CL}, typical value of clearance; θ_{age}, the effect size of age on clearance; θ_{CrCL}, the effect size of creatinine clearance on clearance; ω^2_{CL}, variance of inter-individual variability of clearance; σ, square root of residual variability; SE, standard error; CV, coefficient for variation; CI, confidence interval.

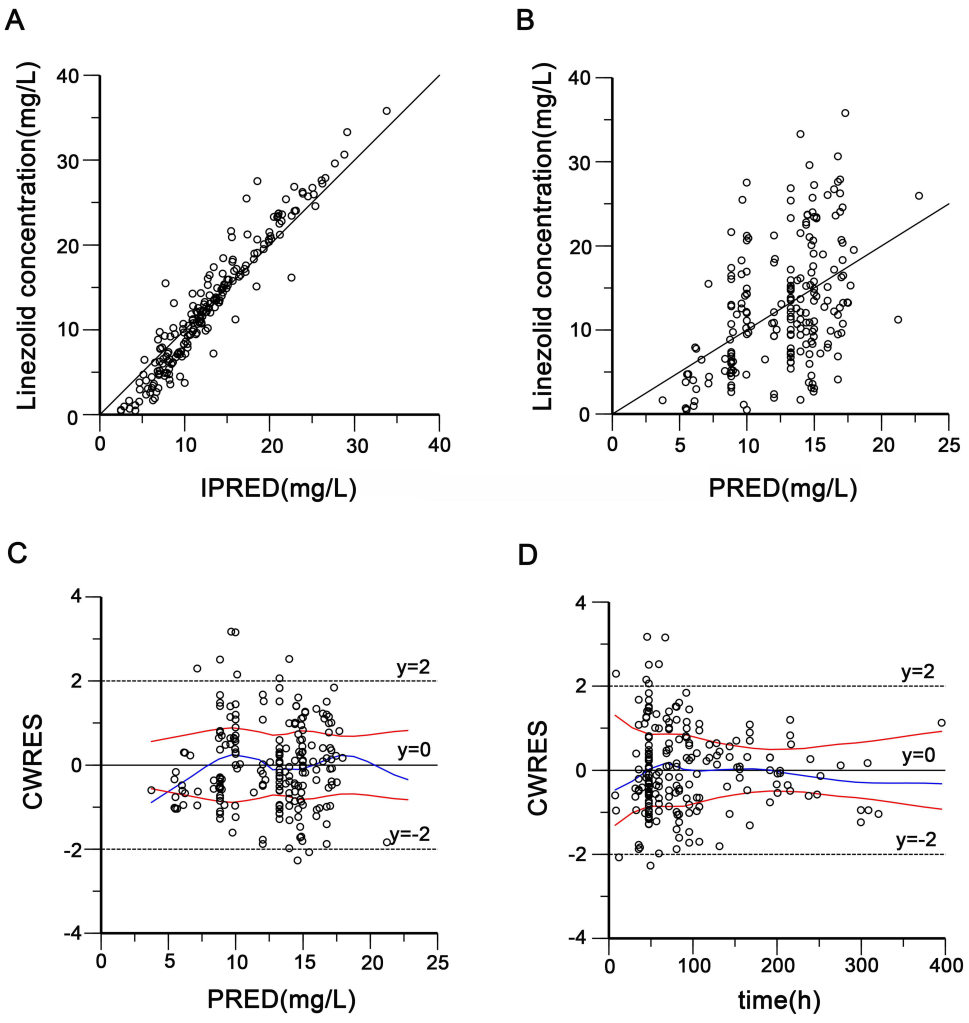

Figure 2 Goodness-of-fit plots for the basic model.

Notes: (**A**) The observed concentrations versus individual predictions (IPRED); (**B**) the observed concentrations versus population predictions (PRED); (**C**) The conditional weighted residuals (CWRES) versus population predictions (PRED); (**D**) the conditional weighted residuals (CWRES) versus time.

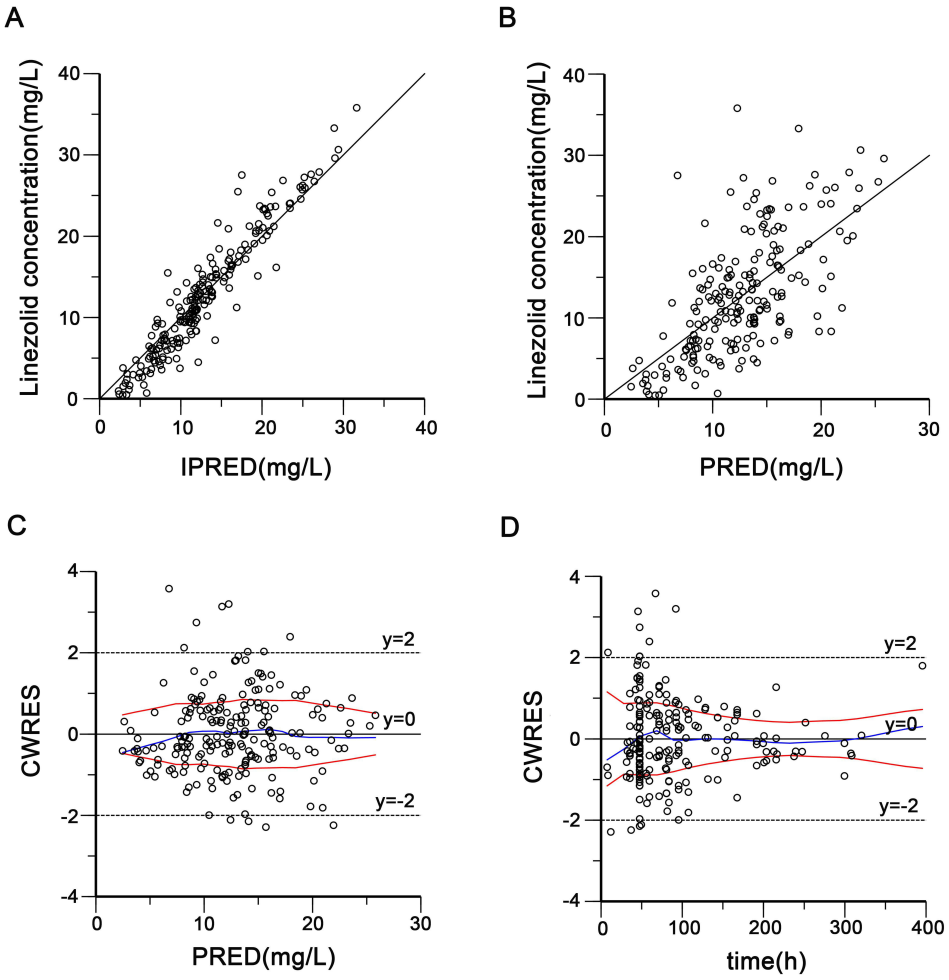

Figure 3 Goodness-of-fit plots for the final model.
Notes: (**A**) The observed concentrations versus individual predictions (IPRED); (**B**) the observed concentrations versus population predictions (PRED); (**C**) The conditional weighted residuals (CWRES) versus population predictions (PRED); (**D**) the conditional weighted residuals (CWRES) versus time.

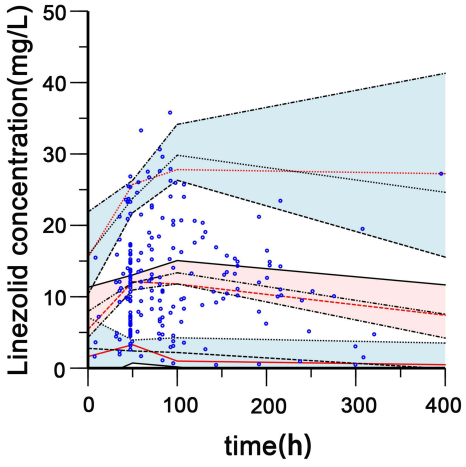

Figure 4 Prediction corrected-visual predictive check of the final model.
Notes: Blue circles represent the observed linezolid concentrations. Red solid and dashed lines represent the 5th, 50th, and 95th percentiles of the observed concentrations and shaded areas represent the 90% CIs of the simulated 5th, 50th and 95th percentiles.

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Table 4 Simulated Probability of Attaining Linezolid C_{min} Stratified by Renal Function and Age in PPK Study

Dosage regimen	Age (y)	CrCL (mL/min)	Probability of attaining linezolid C_{min}		
			2–8	<2	>8
600mg q12h	80[a]	90	73.6%	0.9%	25.5%
	80[a]	60	50.5%	0.3%	49.2%
	80[a]	45	32.7%	0.0%	67.3%
	80[a]	30	14.3%	0.0%	85.7%
	80[a]	15	2.4%	0.0%	97.6%
	100	40[b]	15.4%	0.0%	84.6%
	90	40[b]	20.9%	0.0%	79.1%
	70	40[b]	35.2%	0.1%	64.7%
	50	40[b]	57.4%	0.3%	42.3%
	30	40[b]	83.8%	3.2%	13.0%
400mg q12h	80	90	92.3%	4.9%	2.8%
	80	60	88.8%	0.9%	10.3%
	80	45	79.0%	0.3%	20.7%
	80	30	54.9%	0.0%	45.1%
	80	15	17.0%	0.0%	83.0%
	100	40	57.7%	0.0%	42.3%
	90	40	64.5%	0.2%	35.3%
	70	40	80.7%	0.3%	19.0%
	50	40	90.4%	1.8%	7.8%
	30	40	90.2%	8.9%	0.9%
300mg q12h	80	90	90.3%	9.6%	0.1%
	80	60	95.6%	3.7%	0.7%
	80	45	96.2%	1.2%	2.6%
	80	30	90.3%	0.3%	9.4%
	80	15	57.5%	0.0%	42.5%
	100	40	91.4%	0.3%	8.3%
	90	40	93.7%	0.3%	6.0%
	70	40	96.7%	1.2%	2.1%
	50	40	94.3%	5.3%	0.4%
	30	40	80.5%	19.4%	0.1%
200mg q12h	80	90	70.1%	29.9%	0.0%
	80	60	88.7%	11.3%	0.0%
	80	45	93.6%	6.3%	0.1%
	80	30	98.1%	1.8%	0.1%
	80	15	99.4%	0.2%	0.4%
	100	40	97.5%	2.4%	0.1%
	90	40	97.1%	2.8%	0.1%
	70	40	93.6%	6.3%	0.1%
	50	40	84.0%	16.0%	0.0%
	30	40	53.5%	46.5%	0.0%

Notes: [a]an approximately median value of age; [b]an approximately median value of creatinine clearance.

several-fold higher than those in serum concentrations.[32] However, the clinical response was similar between the two groups in our research, and a possible explanation for this could be that other factors influenced the therapeutic efficacy, such as concomitant Gram-negative bacteria.[31] Linezolid-treated patients with HAP in our study experienced more frequent adverse events such as hematologic abnormalities, which may be partially explained by the higher proportion of supratherapeutic linezolid C_{min}. Boak et al found that the formation of platelet precursor cells was suppressed by 50%

when linezolid C_{min} exceeded the target threshold.[33] Tsuji et al reported that 97% of patients developed linezolid-induced thrombocytopenia via an inhibitory mechanism, rather than platelet destruction in the simulation.[34] Hence, it is more likely that increased linezolid exposure may lead to linezolid-induced thrombocytopenia by inhibiting platelet formation. It indicated that dose optimization of linezolid may be necessary to maximize its efficacy, while minimizing the likelihood of toxicity.

The pharmacokinetics profile of linezolid in patients with renal insufficiency was best described by a one compartment model, which was in agreement with previous studies.[23,35] The mean volume of distribution estimated in our study is 57.1 L, whereas the estimated value varied between 27.6 L and 101.3 L across the studies,[24,36–38] which may be explained by the changes in physiological and pathological characteristics of the patients, such as altered capillary permeability, fluid balance, and organ dysfunction, etc. The estimated linezolid clearance was 2.7 L, which was similar to that reported by Ide et. al,[39] who found that patients with renal insufficiency had significantly lower mean linezolid clearance than those with normal renal function. CrCL was found to be a significant covariate influencing linezolid clearance,[23,24,35,40] whereas other studies showed no influence of CrCL on clearance.[41,42] The inconsistency may be explained in part by the characteristics of patients, for instance, as Xie et al described,[41] the majority of patients had mild and moderate renal insufficiency in their studies, whereas in the present work, patients with mild to severe renal insufficiency were included for analysis. As shown by other investigators,[41,43] age was a significant covariate influencing linezolid clearance. Body weight was not identified as a significant covariate affecting linezolid clearance in our study, which may be attributed to the narrow range of body weights evaluated here.

Tsuji et al[24] developed a PPK model based on the concentration data exclusively from the patients with renal insufficiency; however, the optimal regimen was not proposed using the Monte Carlo simulation. Simulations showed that the use of the standard dosage of 600 mg q12h leads to a low PTA in patients with renal insufficiency, which was in line with those described in earlier studies.[21,23] The failure to achieve the optimal therapeutic range raises significant concerns regarding an increased risk of developing adverse reactions, such as hematologic toxicity. Crass et al[21] suggested that dose reduction of linezolid improved the probability of achieving target therapeutic range in simulated patients with renal insufficiency. However, the simulations were performed based on a PPK model using concentration data from patients with various renal function status. Notably, the recommended dosage regimen provides optimal exposure only in approximately 64%–65% of patients with renal insufficiency. In the present work, dose reduction was proposed in patients with CrCL of 60 mL/min and 90 mL/min, which was similar to that identified in a previous study.[21] However, Wu et al[23] identified that 600 mg q12h was the optimal dosage regimen proposed for patients with CrCL of 60 mL/min or 90 mL/min. The discrepancy between the current study and the study by Wu et al may be attributed to the differences in the baseline characteristics of the included population. The median age of patients enrolled in our study was higher than that in Wu's study (80 vs 60), which might result in a corresponding lower muscle mass in the enrolled patients. Since serum creatinine may be affected by the muscle mass, older individuals with low muscle mass may have an overestimation of CrCL.[44] Therefore, the actual kidney function status of patients enrolled in our study may be worse, and dose reduction may be required in such patients.

Our study has several limitations. First, the investigation was retrospective, and intrinsic limitations, such as selection bias, might influence the outcomes. Second, despite the fact that this study included more linezolid concentrations exclusively from the patients with renal insufficiency than previous studies, the sample size of our study is still limited. Third, this was a single center study, and the findings may not be generalizable to patients admitted to other hospitals. Fourth, the linezolid concentrations collected in the study were mainly C_{min}, which made it difficult to accurately estimate pharmacokinetic characteristics in the distribution phase. Fifth, patients enrolled in the PPK study had CrCL values of less than 90 mL/min, and therefore, the simulation results may not be accurate for patients with CrCL values of 90 mL/min. Sixth, there is a limited possibility to generalize our results to patients with renal insufficiency who receive renal replacement therapy, since patients receiving renal replacement therapy were excluded from the present study.

Conclusion

Patients treated with linezolid had higher rates of bacterial eradication and increased incidences of adverse reactions, including thrombocytopenia and anemia. Significantly more supratherapeutic C_{min} and less therapeutic C_{min} were

achieved in the linezolid group, suggesting that dose optimization of linezolid may be necessary to balance the efficacy and toxicity. A one compartment PPK model of linezolid was developed based on 207 linezolid concentrations obtained exclusively from patients with renal insufficiency. Linezolid clearance was affected by age and CrCL in our analysis. Monte Carlo simulations suggest that 300 mg q12h provides optimal exposure in patients with a CrCL of 60 or 45 mL/min, and 200 mg q12h was recommended for patients with a CrCL of 30 or 15 mL/min.

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Disclosure

We declare that there are no conflicts of interest related to the research.

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