





Plasma and Intrapulmonary Pharmacokinetics, and Dosage Regimen Optimization of Linezolid for Treatment of Gram-Positive Cocci Infections in Patients with Pulmonary Infection After Cerebral Hemorrhage

Yongli Wei ^{1,*}, He Zhang ^{1,*}, Maowu Fu², Rui Ma ¹, Ronghui Li², Lingti Kong ³

¹Grade Three Laboratory of Traditional Chinese Medicine Preparation of the National Administration of Traditional Chinese Medicine, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, 250014, People's Republic of China; ²Department of Neurosurgery, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, 250014, People's Republic of China; ³Department of Pharmacy, the First Affiliated Hospital of Bengbu Medical College, Bengbu, 233004, People's Republic of China

*These authors contributed equally to this work

Correspondence: Ronghui Li, Neurosurgery Department, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, 250014, People's Republic of China, Email 13356669936@163.com; Lingti Kong, Department of Pharmacy, the First Affiliated Hospital of Bengbu Medical College, Bengbu, 233004, People's Republic of China, Email konglingti@163.com

Purpose: The objective of this study was to perform pharmacokinetics/pharmacodynamics (PK/PD) analysis of linezolid in patients with intracerebral hemorrhage and to provide suggestions regarding dosing and treatment regimens.

Patients and Methods: Ten patients with cerebral hemorrhage and pulmonary infection were enrolled in this study. Plasma and sputum samples were obtained at specific time points after the seventh infusion. Linezolid concentration was measured using HPLC, and PK parameters were calculated using the non-compartmental model. The probability of target attainment (PTA) and the cumulative fraction of response (CFR) in response to different dosing regimens (1200 mg/900 mg/600 mg/300 mg, q12h) were calculated based on the ratio of area under the curve to minimum inhibitory concentration (AUC/MIC).

Results: The C_{max} and AUC of linezolid were 12.89 $\mu\text{g/mL}$ and 70.42 h $\cdot \mu\text{g/mL}$ for plasma, and 16.48 $\mu\text{g/mL}$ and 92.95 h $\cdot \mu\text{g/mL}$ for sputum. The average penetration rate of linezolid in sputum, as represented by the ratio of AUC, was 131.99%. In response to the conventional dosing regimen (600mg, q12h), the PTA in the plasma or sputum was >90% only when MIC was ≤ 1 mg/L. Linezolid had the highest CFR against *Streptococcus pneumoniae*, followed by *Enterococcus faecalis* and *Enterococcus faecium*, with the lowest value for *MRSA*.

Conclusion: This was the first study to evaluate PK/PD of linezolid in plasma and in the lungs of patients with cerebral hemorrhage and may assist in selecting appropriate dosing regimens for linezolid in these patients.

Keywords: linezolid, pharmacokinetics, dosage regimen, gram-positive cocci, cerebral hemorrhage

Introduction

The incidence of cerebral hemorrhage has increased in recent years, and patients with cerebral hemorrhage are often in critical condition and exhibit varying degrees of disturbance in consciousness.^{1,2} Pulmonary infection is a common and serious complication in patients with cerebral hemorrhage, and it is also a primary cause of multiple organ failure and death.^{1,2} Previous studies have shown that the efficacy and safety of the antibiotic linezolid, a cost-effective option, were superior to those of vancomycin.³⁻⁷ These results suggested that linezolid should be the first-line antibiotic for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA).

Linezolid can be used to treat infections caused by gram-positive bacteria, such as *Staphylococcus aureus* (sensitive and resistant to *methicillin*), *Streptococcus pneumoniae*, and vancomycin-resistant *Enterococcus*.^{8–10} In addition, linezolid also has been shown to exert antibacterial activity against *Mycobacterium tuberculosis*.¹⁰ Linezolid prevents formation of the 70S ribosomal complex by binding to the 23S site of the 50S subunit, thereby blocking the initial stage of protein synthesis. This unique mechanism of action results in limited cross-resistance with other antibacterial drugs that inhibit protein synthesis.¹¹ Furthermore, linezolid distributes well throughout bodily tissues and fluids, which makes it ideal for clinical use.^{12,13} However, linezolid should be used sparingly to prevent induction of bacterial drug resistance.¹⁴

Pharmacokinetics/pharmacodynamics (PK/PD) research combines PK and PD characteristics to elucidate the time of action and effective concentration of a drug dose and can help to characterize the relationships among drugs, human body systems, and pathogens.¹⁵ Pharmacokinetic/pharmacodynamic modeling for antibacterial drugs has become a research hotspot for the treatment of infections and has led to increased drug efficacy, reduced occurrence of adverse reactions, and reduced development of bacterial resistance.^{16–18} In 2016, the guidelines jointly issued by the American Infectious Disease Society and American Thoracic Society (IDSA/ATS) emphasized for the first time that medical professionals should not use drugs based only on the package insert, but should consider the PK/PD properties of antimicrobial agents for selection of antibiotics and doses. This guidance highlights the importance of PK/PD properties in guiding clinical treatment.⁴

Linezolid is a time-dependent antibiotic with a strong post-antibiotic treatment effect. The PK/PD evaluation index is the ratio of the 24 hours area under the concentration–time curve to the minimum inhibitory concentration (AUC_{0-24h}/MIC).^{19,20} Several studies on PK/PD modeling have been performed in patients who are critically ill, obese, burns, and undergoing continuous renal replacement therapy.^{21–24} However, no PK/PD studies have focused on linezolid in the lung tissues of patients with cerebral hemorrhage. The present study evaluated the PK of linezolid in patients with cerebral hemorrhage and pulmonary infection, then simulated treatment of several common gram-positive bacteria with different dosing regimens based on PK/PD modeling to determine the optimal treatment scheme. This study will help to improve the efficacy of linezolid in the treatment of infection in patients with cerebral hemorrhage.

Materials and Methods

Chemicals and Reagents

Linezolid and chloramphenicol standards were obtained from the National Institutes for Food and Drug Control (Beijing, China). Linezolid for injection (Zyvox) was purchased from the Fresenius Kabi Norge drugstore (Oslo, Norway). Acetonitrile of high-performance liquid chromatography (HPLC) grade was purchased from Fisher Scientific (Waltham, MA, USA).

Study Subjects

This study was conducted in the Affiliated Hospital of the Shandong University of Traditional Chinese Medicine. Ten patients with cerebral hemorrhage and pulmonary infection were enrolled in the study from August 2017 to September 2021. The patients who met the following criteria were included in this study: (I) age of >18 years; (II) patients who had a cerebral hemorrhage and pulmonary infection; (III) patients suitable for treatment with linezolid.

Study Design and Sample Collection

Linezolid was infused for 1 h (600 mg) every 12. Before the seventh infusion and 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, and 12.0 after the seventh infusion, blood and sputum samples were collected. The blood samples were centrifuged (3000 rpm, 5 min) to isolate plasma, and 0.2 mL plasma samples were stored at -20°C until analysis. Because the sputum was relatively viscous, it was diluted 2:1 with acetonitrile (w:v) prior to centrifugation, then processed in the same manner as the blood samples to separate the supernatant.

Sample Preparation

Twenty microliters of internal standard (chloramphenicol, 1 mg/mL) and 0.4 mL of acetonitrile were added to the plasma or sputum (0.2 mL) samples in 1.5 mL Eppendorf tubes, and the samples were vortexed and centrifuged at 14,000 rpm for 5 min. Then, 10 μ L of the organic layer was injected onto the HPLC system for analysis.

Linezolid Assay

Linezolid concentrations in the plasma and sputum samples were determined using a validated HPLC-UV method.²⁵ The samples were separated on a Hypersil BDS C₁₈ column (2.1 \times 100 mm, 3.5 μ M) maintained 30°C. The mobile phase was water-acetonitrile (80:20, v:v) delivered at 0.6 mL/min. The detection wavelength was 254 nm. The limit of quantification was 0.20 μ g/mL, and linearity was validated from 0.20 μ g/mL to 20.0 μ g/mL for both plasma and sputum. At high, medium, and low concentrations (10.0 μ g/mL, 2.0 μ g/mL, and 0.20 μ g/mL), the intra-day and inter-day precision of plasma and sputum were lower than 11.4%, 13.5% and 12.1%, 11.6%, respectively. The accuracies in plasma and sputum were 88.2–112.0% and 91.2%–108.5%, respectively. The average recoveries from plasma and sputum were 82.1% and 80.3%, respectively.

Non-Compartmental Pharmacokinetics Analysis

Pharmacokinetic characteristics were calculated using pharmacokinetic software (WinNonlin 6.1) based on each patient's drug concentration versus time parameter, and a non-compartmental model was used for the evaluation.

Dosage Regimen Optimization

The AUC/MIC value is commonly used as the PK/PD index. An AUC_{0-24h}/MIC greater than 80 generally represents satisfactory anti-infection performance.^{19,23,26}

We used Crystal Ball software to perform Monte Carlo simulations on the plasma and sputum samples with different dosing regimens. The probabilities of target attainment (PTAs) of AUC_{0-24h}/MIC corresponding to the typical MIC values were obtained. The MIC distributions of linezolid against the major gram-positive cocci (*MRSA*, *Enterococcus faecium*, *Enterococcus faecalis*, and *Streptococcus pneumonia*) were obtained from the website of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), and the cumulative fraction of response (CFR) was calculated as follows:

$$CFR = \sum_{i=1}^n PTA(MIC_i) \cdot p(MIC_i)$$

For the PTA or CFR, an expected value greater than 90% was considered the optimal dosage regimen.^{27,28}

Results

Patient Demographics

Ten patients were enrolled, including 5 males and 5 females with a mean age of 68.50 \pm 11.97 years (range: 48–87 years). The characteristics of all patients are summarized in Table 1.

Pharmacokinetic Parameters

The observed plasma concentration versus time profiles for linezolid are shown in Figure 1. The plasma pharmacokinetic parameters of linezolid are shown in Table 2. The maximum plasma concentration (C_{max}) was 12.89 \pm 1.48 μ g/mL and the concentration reached at 1 h after the intravenous infusion, and the area under the plasma concentration curve from zero to the last sampling time (AUC_{0-12h}) was 70.42 \pm 14.19 h· μ g/mL.

The observed sputum concentrations versus time for linezolid are shown in Figure 2, and the pharmacokinetic parameters for linezolid in sputum are shown in Table 3. The C_{max} was 16.48 \pm 2.72 μ g/mL at 1.90 \pm 0.32 h after intravenous infusion, and the AUC_{0-12h} was 92.95 \pm 9.61 h· μ g/mL. The average penetration rate of linezolid in the sputum as represented by the ratio of the AUC_{0-12h} was 131.99%.

Table 1 The Baseline Characteristics of the Study Subjects

Patient No.	Sex	Age (Years)	WBC ($\times 10^9/L$)	NEU (%)	CrCl (mL/min)	Albumin (g/L)	APACHE II Score	PSI Risk Class	Pathogen
1	Male	67	13.39	87.5	81.72	27.8	18	IV	MRSA
2	Female	83	13.89	82.5	60.53	26.9	16	IV	/
3	Female	70	15.65	88.1	95.67	31.6	24	III	MDR-SP
4	Female	87	16.12	89.2	49.87	29.4	26	IV	/
5	Male	63	15.34	93.5	84.29	39.3	17	III	MRSA
6	Male	53	14.06	85.1	74.42	26.0	21	III	MRSA
7	Male	48	21.22	92.7	159.60	37.5	18	III	MRSA
8	Female	73	12.52	90.5	99.59	53.0	22	III	MDR-SP
9	Male	73	18.80	90	159.21	27.7	21	IV	/
10	Female	68	11.02	81	78.27	33.5	19	III	MRSA

Notes: “/” Indicates that the pathogen is not clear. In order to control the infection as soon as possible, linezolid was given empirically.

Abbreviations: WBC, white blood cell count; NEU, percentage of neutrophils; CrCl, creatinine clearance rate. PSI, Pneumonia Severity Index; MRSA, methicillin-resistant *Staphylococcus aureus*; MDR-SP, multi-drug resistant *Streptococcus pneumoniae*.

Pharmacokinetics/Pharmacodynamics Target Attainment

The PTAs of different dosing regimens in plasma and sputum at different MIC values are shown in Table 4. When using the conventional dosing regimen (600 mg, q12h), the PTA in plasma was greater than 90% only when the MIC was ≤ 1 mg/L, and the PTA was greater than 90% when the MIC was 2 mg/L in sputum.

Table 5 shows the MIC values and the distribution frequencies of linezolid against *MRSA*, *Enterococcus faecium*, *Enterococcus faecalis*, and *Streptococcus pneumoniae*. The CFR values for different dosing regimens based on the AUC_{0-24h}/MIC (Table 5) against each bacterium are displayed in Table 6. For each bacterium, the CFR values increased with increased doses. Linezolid had the highest CFR against *Streptococcus pneumoniae*, followed by *Enterococcus faecalis* and *Enterococcus faecium*, with the lowest value for MRSA.

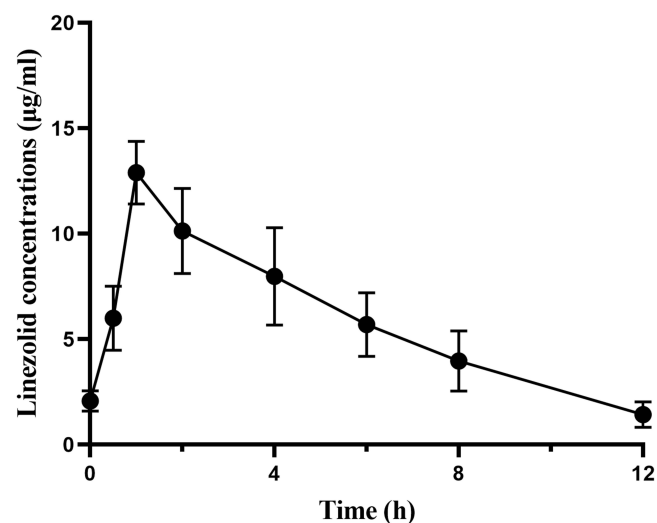
**Figure 1** Plasma concentration–time curves of linezolid in patients (n=10).

Table 2 The Pharmacokinetic Parameters of Linezolid in Plasma

Patient No.	$T_{1/2}$ (h)	T_{max} (h)	C_{max} ($\mu\text{g/mL}$)	AUC_{0-12h} ($\text{h } \mu\text{g/mL}$)	CL (L/h)	Vd (L)
1	5.68	1.00	13.29	61.29	8.41	68.84
2	6.47	1.00	9.86	46.91	10.13	94.63
3	4.62	1.00	11.51	47.78	11.46	76.37
4	12.27	1.00	13.14	83.91	4.46	79.00
5	8.39	1.00	12.71	82.18	5.82	70.36
6	7.29	1.00	15.41	74.73	6.73	70.79
7	6.23	1.00	13.40	68.90	7.52	67.62
8	5.53	1.00	14.05	75.74	7.26	57.96
9	12.47	1.00	12.32	86.54	5.05	90.90
10	6.29	1.00	13.22	76.25	6.94	62.98
Mean \pm SD	7.52 \pm 2.75	1.00 \pm 0.00	12.89 \pm 1.48	70.42 \pm 14.19	7.38 \pm 2.17	73.94 \pm 11.60

Abbreviations: $T_{1/2}$, terminal elimination half-life; C_{max} , maximal plasma concentration; T_{max} , time to C_{max} ; AUC_{0-12h} , area under the concentration versus time curve from 0 to 12 h; CL, total body clearance; Vd, volume of distribution.

Discussion

In previous pharmacokinetic studies, samples containing linezolid were primarily obtained from the venous blood of healthy volunteers. Therefore, changes in drug concentration in the blood did not truly reflect changes in concentrations at the infection site. In addition, the pathophysiological characteristics of critically ill patients can result in changes in the pharmacokinetic parameters of drugs, which can alter the exposure to drugs at the infection site, resulting in altered efficacy. Recent studies have focused on pharmacokinetics in special populations, such as patients who are critically ill, patients who suffered burns, patients with tuberculosis, and children^{21–24} have provided a theoretical basis for clinical use of linezolid. However, the intrapulmonary pharmacokinetics of linezolid in patients with cerebral hemorrhage and pulmonary infection have not been characterized. In this study, we elucidated the pharmacokinetics of linezolid in the plasma and the lung, and used Monte Carlo simulation to optimize dosing.

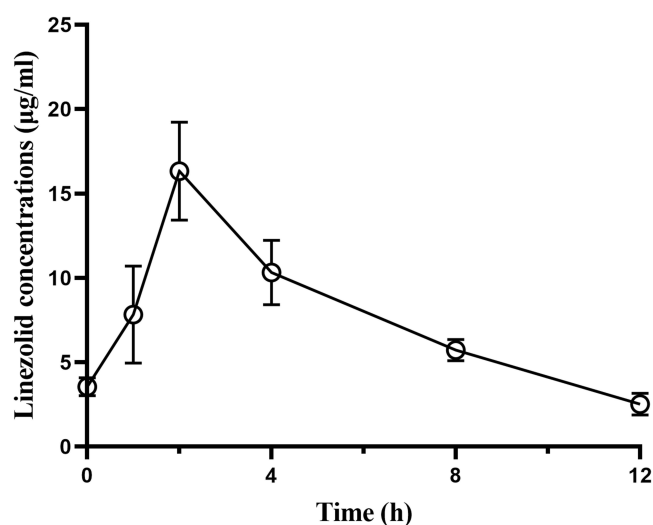


Figure 2 Sputum concentration–time curves of linezolid in patients (n=10).

Table 3 The Pharmacokinetic Parameters of Linezolid in the Sputum

Patient No.	T _{1/2} (h)	T _{max} (h)	C _{max} (µg/mL)	AUC _{0-12h} (h µg/mL)	CL (L/h)	Vd (L)
1	9.53	2.00	14.65	85.23	5.34	73.40
2	7.35	2.00	19.06	103.97	4.83	51.26
3	7.67	2.00	20.44	108.70	4.46	49.31
4	6.71	1.00	14.26	88.32	5.65	54.73
5	10.29	2.00	19.11	86.72	4.60	68.23
6	12.7	2.00	15.38	81.66	4.70	86.05
7	12.98	2.00	17.62	104.33	3.39	63.48
8	8.47	2.00	12.18	89.13	5.20	63.54
9	11.63	2.00	17.98	96.22	4.04	67.78
10	10.89	2.00	14.10	85.18	4.84	76.04
Mean±SD	9.82±2.24	1.90±0.32	16.48±2.72	92.95±9.61	4.71±0.65	65.38±11.53

Abbreviations: T_{1/2}, terminal elimination half-life; C_{max}, maximal plasma concentration; T_{max}, time to C_{max}; AUC_{0-12h}, area under the concentration versus time curve from 0 to 12 h; CL, total body clearance; Vd, volume of distribution.

Table 4 The PTAs of Linezolid in Plasma and Sputum Samples for Different Minimum Inhibitory Concentrations

Dosage Regimens	MIC Values (mg/L)						
	0.25	0.5	1	2	4	8	16
Plasma							
1200 mg/q12h	100.00	100.00	100.00	99.68	22.43	0.00	0.00
900 mg/q12h	100.00	100.00	100.00	90.37	1.45	0.00	0.00
600 mg/q12h	100.00	100.00	99.65	22.97	0.00	0.00	0.00
300 mg/q12h	100.00	99.66	22.70	0.00	0.00	0.00	0.00
Sputum							
1200 mg/q12h	100.00	100.00	100.00	100.00	91.80	0.00	0.00
900 mg/q12h	100.00	100.00	100.00	100.00	7.96	0.00	0.00
600 mg/q12h	100.00	100.00	100.00	91.92	0.00	0.00	0.00
300 mg/q12h	100.00	100.00	92.13	0.00	0.00	0.00	0.00

Note: Green shading indicates a value greater than 90%.

Abbreviations: PTA, probability of target attainment; MIC, minimum inhibitory concentration.

The volume of distribution (73.94 L) was higher in healthy volunteers than that in patients who were critically ill or had liver dysfunction (58.3 L to 36.5 L) (Table 2).^{26,29-31} These differences may be related to disease status in cerebral hemorrhage acute renal failure and the differences of combined drugs,³² which highlighted the need to characterize pharmacokinetics in this population.

The penetration rate of drugs in the lung determines the concentration of drugs in the lung and is the key factor that determines the efficacy of drugs against lung infections. In a previous study, the steady-state epithelial lining fluid (ELF) concentrations in critically ill patients with ventilator-assisted pneumonia showed a mean linezolid penetration percentage of approximately 100%.³³ In critically ill patients with obesity,³⁴ the pulmonary penetration in response to

Table 5 Minimum Inhibitory Concentration Values and Distribution Frequency of Linezolid Against Gram Positive Cocci (Data Obtained from the European Committee on Antimicrobial Susceptibility Testing, EUCAST)

MIC ($\mu\text{g/mL}$)	MRSA		<i>Enterococcus faecalis</i>		<i>Enterococcus faecium</i>		<i>Streptococcus pneumoniae</i>	
	Nos	%	Nos	%	Nos	%	Nos	%
0.06	0	0.00	0	0.00	0	0.00	10	0.02
0.125	0	0.00	15	0.05	9	0.06	35	0.06
0.25	0	0.00	36	0.11	27	0.19	593	0.98
0.5	0	0.00	606	1.93	403	2.80	4665	7.75
1	36	1.45	13,977	44.49	4630	32.14	39,282	65.24
2	1304	52.50	16,245	51.71	8936	62.04	15,577	25.87
4	1142	45.97	490	1.56	377	2.62	18	0.03
8	1	0.04	8	0.03	9	0.06	0	0.00
16	1	0.04	7	0.02	1	0.01	0	0.00
32	0	0.00	5	0.02	0	0.00	0	0.00
64	0	0.00	0	0.00	0	0.00	0	0.00
Total	2484	100	31,415	99.92	14,404	99.92	60,207	99.96

Abbreviations: MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 6 The CFR Values for Different Dosing Regimens Against MRSA, *Enterococcus faecium*, *Enterococcus faecalis*, and *Streptococcus pneumoniae* in Plasma and Sputum

Dosage Regimens	CFR Values Against Different Bacteria			
	MRSA	<i>Enterococcus faecalis</i>	<i>Enterococcus faecium</i>	<i>Streptococcus pneumoniae</i>
Plasma				
1200 mg/q12h	64.09	98.48	97.62	99.85
900 mg/q12h	49.56	93.34	91.29	97.43
600 mg/q12h	13.50	58.31	49.33	79.77
300 mg/q12h	0.33	12.18	10.33	23.59
Sputum				
1200 mg/q12h	96.15	99.73	99.63	99.95
900 mg/q12h	57.60	98.42	97.44	99.93
600 mg/q12h	49.70	94.12	92.22	97.83
300 mg/q12h	1.34	43.08	32.66	68.92

Note: Green shading indicates a value greater than 90%.

Abbreviations: CFR, cumulative fraction of the response; MRSA, methicillin-resistant *Staphylococcus aureus*.

intermittent or continuous administration was 98.8% or 87.1%, respectively. Our study showed that the penetration rate of linezolid in the sputum, as represented by the AUC_{0-12h} , was 131.99% (Tables 2 and 3). These results showed that linezolid had a good penetration rate in the lung, even higher than the concentration in the blood.

The pulmonary drug concentration does not match the blood concentration; therefore, administration schemes should be designed according to the pulmonary concentration. When the MIC value was 4 mg/L as the dose was increased to 1200 mg, q12h, the PTA in the sputum was greater than 90%. In contrast, the PTA in the plasma was not equivalent (Table 4). If clinical conditions limit collection of sputum, the concentration in plasma could be used, but it should be considered that the concentration in the lung may be higher than that in the plasma.

Table 6 shows that linezolid had the highest CFR against *Streptococcus pneumoniae*, which agreed with previous reports.^{33,35} According to the results of this study and other studies,^{36,37} the typical dosing regimen (600mg, q12h) only achieved a PTA greater than 90% for MRSA when the MIC was ≤ 1 mg/L, but the MIC for MRSA in response to linezolid was typically greater than or equal to 2 mg/L. This finding indicates that MRSA may require an increased dose or a combined drug regimen, depending on clinical symptoms. However, current clinical guidelines recommend use of linezolid for the treatment of MRSA, and linezolid has been reported to be effective against MRSA.³⁶⁻³⁸ The differences between our findings and those of other studies may be as follows. First, the patient groups included in different studies may respond differently to treatment, and there may be a lower subconcentration of linezolid in the cerebral hemorrhage group. Second, the target value of $AUC_{0-24h}/MIC > 80$ may be set too high, and the difference between theoretical research and clinical practice should be considered. Future studies should address these differences. In addition, drug toxicity must be considered.³⁹

This study was subject to the following limitations. First, the sample size was small (10 patients), subsequent population pharmacokinetic study with more patients are warranted to identify the key covariates affecting pharmacokinetics. Second, the PK/PD target of $AUC_{0-24h}/MIC > 80$ in previous studies was mostly based on plasma, and the applicability of this value to intrapulmonary studies requires further evaluation.

In conclusion, this study provided an empirical basis for treatment options when the MIC is ≤ 2 mg/L and the routine administration regimen for linezolid (600mg, q12h) may be effective for the treatment of pulmonary infection. In addition, due to individual differences in pharmacokinetics caused by different pathophysiological characteristics and administration of combined medications, a population pharmacokinetics study and evaluation of clinical efficacy needs to be performed to further optimize dosing and administration strategy.

Ethical Approval

This study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine, and the informed consents were obtained from patients' families.

Funding

This work was supported by the special fund for TDM research from the Shandong Provincial Medical Association (No. YXH2020ZX052) and the talent training plan of Bengbu Medical College (No. by51201316).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Gregório T, Pipa S, Cavaleiro P, et al. original intracerebral hemorrhage score for the prediction of short-term mortality in cerebral hemorrhage: systematic review and meta-analysis. *Crit Care Med*. 2019;47(6):857–864. doi:10.1097/ccm.0000000000003744
2. Diener H, Hankey G. Primary and secondary prevention of ischemic stroke and cerebral hemorrhage: JACC focus seminar. *J Am Coll Cardiol*. 2020;75(15):1804–1818. doi:10.1016/j.jacc
3. Kato H, Hagihara M, Asai N, et al. Meta-analysis of vancomycin versus linezolid in pneumonia with proven methicillin-resistant *Staphylococcus aureus*. *J Glob Antimicrob Resist*. 2021;24:98–105. doi:10.1016/j.jgar.2020

4. Kalil A, Metersky M, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the infectious diseases society of America and the American thoracic society. *Clin Infect Dis*. 2016;63(5):e61–e111. doi:10.1093/cid/ciw353
5. Fernández-Barat L, Motos A, Panigada M, et al. Comparative efficacy of linezolid and vancomycin for endotracheal tube MRSA biofilms from ICU patients. *Crit Care*. 2019;23(1):251. doi:10.1186/s13054-019-2523-5
6. Huon J, Boutoille D, Caillon J, et al. Linezolid versus vancomycin cost in the treatment of staphylococcal pneumonia. *Med Mal Infect*. 2020;50(3):252–256. doi:10.1016/j.medmal.2019.07.012
7. Collins C, Schwemm A. Linezolid versus vancomycin in the empiric treatment of nosocomial pneumonia: a cost-utility analysis incorporating results from the ZEPHYR trial. *Value Health*. 2015;18(5):614–621. doi:10.1016/j.jval.2015.04.007
8. Hashemian S, Farhadi T, Ganjparvar M. Linezolid: a review of its properties, function, and use in critical care. *Drug Des Devel Ther*. 2018;12:1759–1767. doi:10.2147/dddt.S164515
9. Zahedi Bialvaei A, Rahbar M, Yousefi M, et al. Linezolid: a promising option in the treatment of gram-positives. *J Antimicrob Chemother*. 2017;72(2):354–364. doi:10.1093/jac/dkw450
10. Chen H, Du Y, Xia Q, et al. Role of linezolid combination therapy for serious infections: review of the current evidence. *Eur J Clin Microbiol Infect Dis*. 2020;39(6):1043–1052. doi:10.1007/s10096-019-03801-x
11. Vardakas K, Kiumis I, Falagas M. Association of pharmacokinetic and pharmacodynamic aspects of linezolid with infection outcome. *Curr Drug Metab*. 2009;10(1):2–12. doi:10.2174/1389200097870
12. Bajjnath S, Shobo A, Bester L, et al. Neuroprotective potential of linezolid: a quantitative and distribution study via mass spectrometry. *J Mol Histol*. 2016;47(4):429–435. doi:10.1007/s10735-016-9685-0
13. Wen S, Zhang T, Yu X, et al. Bone penetration of linezolid in osteoarticular tuberculosis patients of China. *Int J Infect Dis*. 2021;103:364–369. doi:10.1016/j.ijid.2020.11.203
14. Dilworth T, Beck E, Pedersen R, et al. High rate of linezolid intermediate susceptibility and resistance among enteric vancomycin-resistant *Enterococcus* (VRE) recovered from hospitalized patients actively screened for VRE colonization. *Infect Control Hosp Epidemiol*. 2019;40(7):821–822. doi:10.1017/ice.2019.116
15. Trang M, Dudley M, Bhavnani S. Use of Monte Carlo simulation and considerations for PK-PD targets to support antibacterial dose selection. *Curr Opin Pharmacol*. 2017;36:107–113. doi:10.1016/j.coph.2017.09.009
16. Song X, Zeng M, Wu Y, et al. Competence mining of vancomycin (VAN) in the management of infections due to bacterial strains with high VAN minimum inhibitory concentrations (MICs): a novel dosing strategy based on pharmacokinetic/pharmacodynamic modeling. *Front Microbiol*. 2021;12:649757. doi:10.3389/fmicb.2021.649757
17. Beredaki M, Georgiou P, Siopi M, et al. Voriconazole efficacy against *Candida glabrata* and *Candida krusei*: preclinical data using a validated in vitro pharmacokinetic/pharmacodynamic model. *J Antimicrob Chemother*. 2020;75(1):140–148. doi:10.1093/jac/dkz425
18. Leng B, Yan G, Wang C, et al. Dose optimisation based on pharmacokinetic/pharmacodynamic target of tigecycline. *J Glob Antimicrob Resist*. 2021;25:315–322. doi:10.1016/j.jgar.2021.04.006
19. Yang M, Zhao L, Wang X, et al. Population pharmacokinetics and dosage optimization of linezolid in critically ill pediatric patients. *Antimicrob Agents Chemother*. 2021;65(5):e02504–e02520. doi:10.1128/aac.02504-20
20. Zhao W, Kong L, Wu C, et al. Prolonged infusion of linezolid is associated with improved pharmacokinetic/pharmacodynamic (PK/PD) profiles in patients with external ventricular drains. *Eur J Clin Pharmacol*. 2021;77(1):79–86. doi:10.1007/s00228-020-02978-x
21. Mokline A, Gharsallah L, Rahmani I, et al. Pharmacokinetics and pharmacodynamics of Linezolid in burn patients. *Ann Burns Fire Disasters*. 2018;31(2):118–121.
22. Blackman A, Jarugula P, Nicolau D, et al. Evaluation of linezolid pharmacokinetics in critically ill obese patients with severe skin and soft tissue infections. *Antimicrob Agents Chemother*. 2021;65(2):e01619–e01620. doi:10.1128/aac.01619-20
23. Simon P, Busse D, Petroff D, et al. Linezolid concentrations in plasma and subcutaneous tissue are reduced in obese patients, resulting in a higher risk of underdosing in critically ill patients: a controlled clinical pharmacokinetic study. *J Clin Med*. 2020;9(4):1067. doi:10.3390/jcm9041067
24. Barrasa H, Soraluca A, Usón E, et al. Impact of augmented renal clearance on the pharmacokinetics of linezolid: advantages of continuous infusion from a pharmacokinetic/pharmacodynamic perspective. *Int J Infect Dis*. 2020;93:329–338. doi:10.1016/j.ijid
25. Wu X, Tang Y, Zhang X, et al. Pharmacokinetics and pharmacodynamics of linezolid in plasma/cerebrospinal fluid in patients with cerebral hemorrhage after lateral ventricular drainage by Monte Carlo simulation. *Drug Des Devel Ther*. 2018;12:1679–1684. doi:10.2147/DDDT.S168757
26. Barrasa H, Soraluca A, Isla A, et al. Pharmacokinetics of linezolid in critically ill patients on continuous renal replacement therapy: influence of residual renal function on PK/PD target attainment. *J Crit Care*. 2019;50:69–76. doi:10.1016/j.jcrc.2018.11.016
27. Tietjen A, Kroemer N, Cattaneo D, et al. Population pharmacokinetics and target attainment analysis of linezolid in multidrug-resistant tuberculosis patients. *Br J Clin Pharmacol*. 2021;88(4):1835–1844. doi:10.1111/bcp.15102doi:10.1111/bcp.15102
28. Rodríguez-Gascón A, Aguirre-Quñonero A, Aspiazú M, et al. Pharmacokinetic/pharmacodynamic analysis of tedizolid phosphate compared to linezolid for the treatment of infections caused by gram-positive bacteria. *Antibiotics*. 2021;10(7):755. doi:10.3390/antibiotics10070755
29. Wang X, Wang Y, Yao F, et al. Pharmacokinetics of linezolid dose adjustment for creatinine clearance in critically ill patients: a multicenter, prospective, open-label, observational study. *Drug Des Devel Ther*. 2021;15:2129–2141. doi:10.2147/dddt.S303497
30. Dehghanfar P, Bürger C, Zeitlinger M, et al. Penetration of linezolid into soft tissues of healthy volunteers after single and multiple doses. *Antimicrob Agents Chemother*. 2005;49(6):2367–2371. doi:10.1128/aac.49.6.2367-2371
31. Zhang S, Zhu Z, Chen Z, et al. Population pharmacokinetics and dosage optimization of linezolid in patients with liver dysfunction. *Antimicrob Agents Chemother*. 2020;64(6):e00133–e00120. doi:10.1128/aac.00133-20
32. Saeed F, Adil MM, Piracha BH, et al. Acute renal failure worsens in-hospital outcomes in patients with intracerebral hemorrhage. *J Stroke Cerebrovasc Dis*. 2015;24(4):789–794. doi:10.1016/j.jstrokecerebrovasdis.2014.11.012
33. Dryden M, Andradevic A, Bassetti M, et al. A European survey of antibiotic management of methicillin-resistant *Staphylococcus aureus* infection: current clinical opinion and practice. *Clin Microbiol Infect*. 2010;16(Suppl1):3–30. doi:10.1111/j.1469-0691.2010.03135.x
34. De Pascale G, Fortuna S, Tumbarello M, et al. Linezolid plasma and intrapulmonary concentrations in critically ill obese patients with ventilator-associated pneumonia: intermittent vs continuous administration. *Intensive Care Med*. 2015;41(1):103–110. doi:10.1007/s00134-014-3550-y

35. Dryden M. Linezolid pharmacokinetics and pharmacodynamics in clinical treatment. *J Antimicrob Chemother.* 2011;66(Suppl4):iv7–iv15. doi:10.1093/jac/dkr072
36. Brown N, Brown E. Treatment of methicillin-resistant *Staphylococcus aureus* (MRSA): updated guidelines from the UK. *J Antimicrob Chemother.* 2021;76(6):1377–1378. doi:10.1093/jac/dkab
37. Liu C, Bayer A, Cosgrove S, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis.* 2011;52(3):e18–e55. doi:10.1093/cid/ciq146
38. Gilbert DN, Chambers HF, Eliopoulos GM. *The Sanford Guide to Antimicrobial Therapy 2020*. 50th ed. Sperryville: Antimicrobial Therapy; 2020.
39. Rao G, Konicki R, Cattaneo D, et al. Therapeutic drug monitoring can improve linezolid dosing regimens in current clinical practice: a review of linezolid pharmacokinetics and pharmacodynamics. *Ther Drug Monit.* 2020;42(1):83–92. doi:10.1097/ftd.0000000000000000

Infection and Drug Resistance

Dovepress

Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/infection-and-drug-resistance-journal>