Pharmaceutical Sciences Asia

Pharm Sci Asia 2021; 48(4), 375-380

DOI:10.29090/psa.2021.04.20.069

Research Article

# Pharmacokinetics and pharmacodynamics of low dose 300 mg once daily oral linezolid for treatment of tuberculosis

Sutep Jaruratanasirikul[1*], Jetsada Piwluang[2], Somchai Sriwiriyajan[2,3], Monchana Nawakitrangsan[1], Maseetoh Samaeng[1], Nuntiya Theerapakanunt[1]

[1] Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkla, Thailand
[2] Department of Pharmacology, Faculty of Science, Prince of Songkla University, Hat Yai, Songkla, Thailand
[3] Division of Health and Applied Sciences, Faculty of Science, Prince of Songkla University, Hat Yai, Songkla, Thailand

***Corresponding author:**
Sutep Jaruratanasirikul
jasutep@medicine.psu.ac.th

**Keywords:**
Pharmacokinetics, Pharmacodynamics, Linezolid, Tuberculosis, Multidrug- resistance



## ABSTRACT

Tuberculosis (TB), an infectious disease caused by the *Mycobacterium tuberculosis* bacteria, continues to be an immense global public health problem and still remains a leading cause of death among infectious diseases, especially in developing countries. In the last few decades, the incidences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB have been increasing and have become a significant public health threat in many countries. Linezolid, an oxazolidinone antimicrobial agent, has been shown to be effective against *M. tuberculosis*, including MDR- and XDR-TB. However, a daily regimen of 1200 mg or even 600 mg of linezolid for treatment of MDR- and XDR-TB has potential toxicities. A daily 300 mg dose of linezolid would be an effective treatment against MDR- and XDR-TB with fewer adverse effects. The objective of this study was to determine the pharmacokinetics (PK) of a 300 mg daily dose of oral linezolid for achieving the pharmacodynamic (PD) targets. Thirty healthy subjects received 300 mg oral linezolid once daily and PK studies were carried out on day 5 after the beginning of drug administration. The mean value of $AUC_{0\text{-}24}$ of this agent was calculated for the achievement of PD targets. The mean values of $V_d$, CL and $AUC_{0\text{-}24}$ were 29.08 ± 10.75 L, 3.69 ± 1.58 L/h and 94.38 ± 35.12 mg.h/L, respectively. The $AUC_{0\text{-}24}$/MIC ratio for a MIC of 0.9 and 0.75 mg/L were approximately 100 and 119, respectively. In conclusion, 300 mg of linezolid daily is an alternative antibiotic option in patients with intolerance to the side effects of the standard dosage regimens.

## 1. INTRODUCTION

Tuberculosis (TB), an infectious disease caused by the *Mycobacterium tuberculosis* bacteria, continues to be an immense global public health problem and remains a leading cause of infectious disease deaths, especially in developing countries. Approximately one-quarter of the population in the world are infected with this microorganism and some 10 million people develop new active disease annually, resulting in approximately 3 million deaths, particularly in immunocompromised hosts such as patients living with human immunodeficiency virus infections, malnutrition or diabetes[1-3]. Both rapid and accurate diagnosis and adequate treatment of TB are necessary to eliminate the disease and prevent transmission of *M. tuberculosis*. In the last few decades, the

incidence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB have been increasing at somewhat alarming rates and TB has become a significant public health threat in several countries[2]. Poor adherence by patients to their TB drugs, interpatient pharmacokinetic (PK) variability and poor penetration of antituberculosis drugs into the lesions, leading to inadequate tissue concentrations, have been shown to be highly associated with drug resistance[4,5]. Therefore, it is difficult for physicians to take care of these patients with only a limited choice of effective antituberculosis drugs for treatment of MDR- and XDR-TB.

Linezolid, an oxazolidinone antimicrobial agent, has been shown to be effective against *M. tuberculosis*, including MDR- and XDR-TB[6,7]. However, the standard dosage regimens of daily 1200 mg or 600 mg of linezolid have potential toxicities, notably myelosuppression and neurotoxicity[6-8]. In patients who received long-term treatment with linezolid, higher drug concentrations were significantly associated with inducing thrombocytopenia. The average minimum plasma concentrations in patients with and without thrombocytopenia were 19.9 mg/L and 6.97 mg/L, respectively[9]. In addition, a study of mitochondrial toxicity-associated adverse events (AE) in patients with XDR-TB, all patients with a mean linezolid trough concentration ≥2 mg/L developed an AE, whereas at trough concentration < 2 mg/L, less than half developed an AE[10]. Therefore, the level of plasma concentration of linezolid is associated with inducing toxicities and dose adjustments might be required. Previous studies in drug resistant TB found that a daily 300 mg dose of linezolid was effective against MDR- and XDR-TB with fewer adverse effects[11,12]. Therefore, the aim of the current study was to determine the PK of linezolid 300 mg once daily for achieving the pharmacodynamic (PD) targets for the treatment of TB.

## 2. MATERIALS AND METHODS

### 2.1. Subjects

The protocol for this study was approved by the Ethics Committee of Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University (Ref Number: REC 61-087-14-1). Written informed consent was obtained from each subject prior to the study. Prior to recruitment, all potential subjects underwent a pre-study evaluation to ensure that they had no underlying illnesses and were not currently taking or had not recently taken any medications. The study was conducted in 30 nonsmoking, nonalcoholic, non-allergic to linezolid, not pregnant or on lactation, not having a concurrent gastrointestinal disease, not obese healthy volunteers. All subjects had a creatinine clearance rate greater than 90 mL/mins as evaluated by the Cockcroft and Gault equation. All subjects had normal biochemical and hematological laboratory profiles.

### 2.2. Drugs and chemicals

Linezolid 600 mg tablets were donated from Siam Pharmaceutical (Thailand) Co.,Ltd. Standard linezolid powder, product No. MM 3300.00, lot No. 87246 was purchased from LGC Science, Germany. Internal standard, 2-ethoxybenzamide, lot No. STBF5307V was purchased from Sigma-Aldrich, St. Louis, Missouri, USA. All solvents were of high-performance liquid chromatography (HPLC) grade.

### 2.3. Study design and blood sampling

Each subject received 300 mg (one-half 600 mg tablet) once daily of oral linezolid with 100 mL distilled water for 5 days. Linezolid PK studies were carried out on day 5 after beginning the administration of linezolid. Blood samples (5 mL) were obtained through a peripheral venous catheter at the following times: shortly before (time 0) and then at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 6, 8, 10 and 24 hours after the administration of linezolid on day 5.

### 2.4. Linezolid assay

Plasma concentrations of linezolid were determined by UPLC using an analytic method modified from Cios A. et al[13]. Briefly, 2-ethoxybenzamide was used as the internal standard. 50 μL of the internal standard and 0.5 mL of methanol (for protein precipitation) were added into 0.3 mL of the plasma sample. The mixture was vortexed for 30 sec and then centrifuged at 15,000 rpm for 15 min. The supernatant was filtrated with a VertiClean™ NYLON Syringe Filter, 13 mm, 0.20 μm. A 20 μL of the sample solution was injected, using an Agilent UPLC 1290 Infinity II (Agilent Technology, Santa Clara, USA), onto an XSelected® CSH™ C18, 2.5 μm 3.0 × 100 mm Column XP. The mobile phase was composed of a mixture of 50 mM potassium

dihydrogen orthophosphate buffer, pH 3.5, and acetonitrile in a ratio of 74:26% v/v at a flow rate of 0.6 mL/min. The sample was analyzed by a UV-VIS diode array detector (Agilent Technology, Santa Clara, USA) at a wavelength of 258 nm. The lower limit of detection of linezolid was 0.2 mg/L. The method was found to be linear in the concentration range of 0.2-20 mg/L by following the regression equation Y = 1.0983x - 0.088 with correlation coefficient ($r^2$) of 0.9998. The intra-assay reproducibility values characterized by coefficients of variation (CVs) were 9.56%, 8.99% and 2.55% for samples containing 0.6, 8 and 16 mg/L, respectively. For intra-assay reproducibility, the relative biases were 8.27%, -5.41%, and -9.92% for samples containing 0.6, 8 and 16 mg/L, respectively. The inter-assay reproducibility values characterized by coefficients of variation (CVs) were 8.36%, 5.21% and 7.89% for samples containing 0.6, 8 and 16 mg/L, respectively. For inter-assay reproducibility, the relative biases were 3.19%, 3.82%, and 3.21% for samples containing 0.6, 8 and 16 mg/L, respectively. A short-term stability study showed that at room temperature for samples containing 0.6 and 16 mg/L, the concentrations of linezolid losses were < 4% for at least 6 h. A long-term stability study found that at -20 °C for samples containing 0.6 and 16 mg/L, the concentrations of linezolid losses were < 10% for at least 30 days. The percentages of recovery were 93.09 ± 0.04%, 108.73 ± 1.72% and 96.01 ± 2.02% for samples containing 0.6, 8, and 16 mg/L, respectively.

### 2.5. Pharmacokinetic analysis

PK analyses were conducted using one-compartment pharmacokinetic analysis. The maximum plasma concentrations ($C_{max}$), minimum plasma concentrations ($C_{min}$), areas under the concentration–time curves between 0 and 24 h ($AUC_{0-24}$), elimination half-lives ($t_{1/2}$), apparent volume of distribution ($V_d$), total clearance (CL), and elimination rate constants ($k_e$) were determined using the WinNonlin Version 1.1 (Scientific Consulting Inc., NC, USA). The results were expressed as mean values ± standard deviations.

## 3. RESULTS

Thirty healthy subjects were enrolled in the study (14 males and 16 females) with mean age of 22.87 ± 1.63 years (range 21 to 27 years), mean weight of 58.27 ± 7.76 kg (range 45 to 71 kg) and mean body mass index of 21.45 ± 1.51 kg/m$^2$ (range 19.13 to 23.98 kg/m$^2$). The mean PK parameters are shown in Table 1. The mean plasma linezolid concentration-time data are shown in Figure 1. The $V_d$, CL and $AUC_{0-24}$ were 29.08 ± 10.75 L, 3.69 ± 1.58 L/h and 94.38 ± 35.12, respectively. The $AUC_{0-24}$/MIC ratio for a MIC of 0.94 mg/L achieved the PK/PD target of 100. The $AUC_{0-24}$/MIC ratio for a MIC of 0.79 mg/L achieved the PK/PD target of 119.

**Table 1.** The mean pharmacokinetic parameters of linezolid in the thirty healthy study subjects who received 300 mg once daily oral linezolid for 5 days.

| PK parameter | |
|---|---|
| $C_{max}$ (mg/L) | 9.03 ± 2.42 |
| $C_{min}$ (mg/L) | 1.25 ± 0.68 |
| $AUC_{0-24}$ (mg.h/L) | 94.38 ± 35.12 |
| $V_d$ (L) | 29.08 ± 10.75 |
| CL (L/h) | 3.69 ± 1.58 |
| $t_{1/2}$ (h) | 6.38 ± 3.30 |
| $k_e$ (h$^{-1}$) | 0.15 ± 0.10 |

$C_{max}$, maximum plasma concentration; $C_{min}$, minimum plasma concentration; $AUC_{0-24}$, the area under the concentration–time curve between 0 and 24 h; $V_d$, the volume of distribution; CL, the total clearances, $t_{1/2}$, elimination half-life; $k_e$, the elimination rate constant

## 4. DISCUSSION

Drug-resistant TB, including MDR- and XDR-TB, has become one of the important public health challenges in several countries. The WHO estimated that approximately half a million new cases of MDR-TB had been reported recently and only 50% of these drug- resistant cases had been successfully treated with antituberculous drugs[3]. The key issue of widespread drug-resistant pathogens is that only a limited number of effective antituberculous agents are available for use in treatment, and most of these are associated with

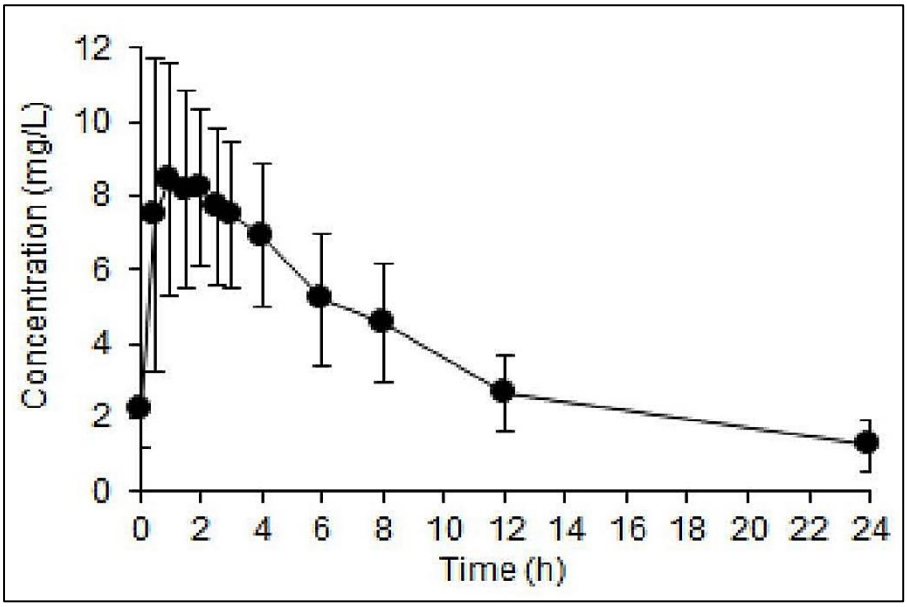


**Figure 1.** Mean plasma linezolid concentration-time data of the thirty healthy study subjects.

poor outcomes and/or intolerability of the treatment. Linezolid has been found to exhibit a broad range of antimicrobial activity against Gram-positive microorganisms as well as MDR-and XDR-TB[7,14]. This agent has excellent PK with an absolute bioavailability of almost 100%. Following the WHO guidelines on drug-resistant TB treatments, linezolid 600 mg orally every 12 h is currently proposed as one component of the recommended regimen for treatment of MDR- and XDR-TB[15]. The Infectious Diseases Society of America (IDSA) also recommends linezolid 600 mg orally once daily for the treatment of drug-resistant TB[16]. Previous PK studies in healthy volunteers showed that the mean value of AUC of a single dose of 600 mg orally of linezolid was 91.40-109.5 mg.h/L[17,18], and the study patients with XDR-TB showed that the mean value of $AUC_{0-\infty}$ of multiple doses of 600 mg orally of this drug was 180.40 mg.h/L[19]. However, long-term treatment with this agent usually results in several serious toxicities, including bone marrow suppression and peripheral neuropathy[6-8]. In order to attempt to determine a more tolerable dosage regimen of this useful drug, we conducted the current study to determine the PK of multiple doses of 300 mg once daily of oral linezolid. In the study we found that the mean values of $V_d$, CL and $AUC_{0-24}$ of 300 mg once daily of linezolid were 29.08 ± 10.75 L, 3.69 ± 1.58 L/h and 94.38 ± 35.12 mg.h/L, respectively. The mean value of $AUC_{0-24}$ of this agent in the current study was approximately 94 mg.h/L which is comparable to the values obtained from multiple doses of 300 mg once daily in patients with XDR-TB[19] and a 600 mg single dose regimen in healthy volunteers[17,18]. Therefore, the two doses of multiple doses of 600 and 300 mg once daily were dose proportional exposures.

For linezolid, the $AUC_{0-24}$/MIC ratio is the PK/PD index that best correlates with anti-microbial efficacy[6,20]. The WHO technical report on PK/PD of linezolid used in the treatment of drug-resistant TB recommended that the optimal activity was achieved at the PD targets of an $AUC_{0-24}$/MIC ratio of 100[6]. In addition, based on the hollow fiber system model of tuberculosis, the optimal activity was achieved in one study at the PK/PD target of 119[20]. However, to date no clinical trials confirming the correlation between PK/PD targets to maximize efficacy and clinical outcomes of this agent for the treatment of drug-resistant TB are available. A previous study of the susceptibilities of linezolid against MDR-TB from the Taiwan Centers for Disease Control and Prevention (CDC) which were part of a United States CDC study found that the $MIC_{90}$ of linezolid was 0.25 mg/L (range <0.06-0.5 mg/L)[21]. Another study from China of *in vitro* activity and MIC distributions of linezolid against MDR- and XDR-TB found that the $MIC_{90}$ was 0.25 mg/L[22]. In the current study, the $AUC_{0-24}$/MIC ratio for the MIC of 0.9 and 0.75 mg/L achieved the PK/PD targets of 100 and 119, respectively. Moreover, according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC distributions, the dosage regimen of 300 mg daily can cover the $MIC_{90}$ of *M. tuberculosis*[23]. Therefore, the results from the current study indicate that a low dose 300 mg once daily of oral

linezolid can provide good coverage for patients with MDR- and XDR-TB. As further confirmation, previous studies in patients with drug-resistant TB found that linezolid 300 mg orally once daily was effective for the treatment of MDR- and XDR-TB with lower neuropathic side effects than a daily dosage of either 600 mg or 1200 mg[11,12].

This study had a few limitations that must be considered. First, the study was conducted to determine the PK of a low dose of 300 mg once daily of linezolid, but not for proving the efficacy of this low dosage regimen for the treatment of TB. Second, PD assessment using a Monte Carlo simulation for achieving the PK/PD target was not performed.

## 5. CONCLUSIONS

The current study on the PK of linezolid found that the mean values of $AUC_{0\text{-}24}$ of low dose 300 mg once daily achieved the PD targets of $AUC_{0\text{-}24}$/MIC ratio of 100 and 119 for a MIC of 0.9 and 0.75 mg/L of TB, respectively. Therefore, this low dosage regimen of linezolid could be an alternative antibiotic option for treatment of MDR- and XDR-TB in patients with intolerance to the side effects of the standard dosage regimens of linezolid. However, further large well-defined clinical trials are needed to confirm the efficacy and safety of low dose 300 mg once daily oral linezolid.

## 6. ACKNOWLEDGEMENTS

We thank Mr David Patterson for help with editing the English of the manuscript.

### Conflicts of interest

The authors declare that they have no competing interests related to this work.

### Funding

This work was supported by a faculty grant from the Faculty of Medicine, Prince of Songkla University.

### Ethics approval

The protocol for this study was approved by the Ethics Committee of Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University (Ref Number: REC 61-087-14-1).

### Article info:

Received April 29, 2020
Received in revised form September 2, 2020
Accepted November 13, 2020

## REFERENCES

1. Glaziou P, Floyd K, Raviglione MC. Global epidemiology of tuberculosis. Semin Respir Crit Care Med. 2018;39(3):271-85.
2. Global Tuberculosis report 2018. Geneva: World Health Organization: 2018. License: CC BY-NC-SA 3.0 IGO.
3. Global Tuberculosis report 2019. Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO.
4. Srivastava S, Pasipanodya JG, Meek C, Leff R, Gumbo T. Multidrug-resistant tuberculosis not due to noncompliance but to between-patient pharmacokinetic variability. J Infect Dis. 2011;204(12):1951-9.
5. Dartois V. The path of anti-tuberculosis drugs: from blood to lesions to mycobacterial cells. Nat Rev Microbiol. 2014;12(3):159-67.
6. World Health Organization. (2018). Technical report on the pharmacokinetics and pharmacodynamics (PK/PD) of medicines used in the treatment of drug-resistant tuberculosis. World Health Organization. Geneva. License: CC BY-NC-SA 3.0 IGO.
7. Park IN, Hong SB, Oh YM, Kim MN, Lim CM, Lee SD, et al. Efficacy and tolerability of daily-half dose linezolid in patients with intractable multidrug-resistant tuberculosis. J Antimicrob Chemother. 2006;58(3):701-4.
8. Schecter GF, Scott C, True L, Raftery A, Flood J, Mase S. Linezolid in the treatment of multidrug-resistant tuberculosis. Clin Infect Dis. 2010;50(1):49-55.
9. Ogami C, Tsuji Y, To H, Yamamoto Y. Pharmacokinetics, toxicity and clinical efficacy of linezolid in Japanese pediatric patients. J Infect Chemother. 2019;25(12):979-86.
10. Song T, Lee M, Jeon HS, Park Y, Dodd LE, Dartois V, et al. Linezolid trough concentrations correlate with mitochondrial toxicity-related adverse events in the treatment of chronic extensively drug-resistant tuberculosis. EBioMedicine. 2015;2(11):1627–33.
11. Koh WJ, Kwon OJ, Gwak H, Chung JW, Cho SN, Kim WS, et al. Daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis. J Antimicrob Chemother. 2009;64(2):388-91.
12. Koh WJ, Kang YR, Jeon K, Kwon OJ, Lyu J, Kim WS, et al. Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. J Antimicrob Chemother. 2012;67(6):1503-7.
13. Cios A, Kuś K, Szymura-Oleksiak J. Determination of linezolid in human serum by reversed-phase high-performance liquid chromatography with ultraviolet and diode array detection. Acta Pol Pharm. 2013;70(4) :631-41.
14. Perry CM, Jarvis B. Linezolid: a review of its use in the management of serious gram-positive infections. Drugs. 2001;61(4):525-51.
15. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO.
16. Nahid P, Mase SR, Migliori GB, Sotgiu G, Bothamley GH, Brozek JL, et al. Treatment of drug-resistant tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. Am J Respir Crit Care Med. 2019;200(10):e93-e142.
17. Wagenlehner FME, Wydra S, Onda H, Kinzig-Schippers M, Sörgel F, Naber KG. Concentrations in plasma,

urinary excretion, and bactericidal activity of linezolid (600 milligrams) versus those of ciprofloxacin (500 milligrams) in healthy volunteers receiving a single oral dose. Antimicrob Agents Chemother. 2003;47(12): 3789-94.
18. Pharmacia & Upjohn Company. ZYVOX® (linezolid) injections, tablets and oral suspension. NewYork, NY: Pharmacia & Upjohn Company Division of Pfizer Inc; 2018
19. Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med. 2012;367(16) :1508-18.
20. Srivastava S, Magombedze G, Koeuth T, Sherman C, Pasipanodya JG, Raj P, et al. Linezolid dose that maximizes sterilizing effect while minimizing toxicity and resistance emergence for tuberculosis. Antimicrob Agents Chemother. 2017;61(8):e00751-17.
21. Cavanaugh JS, Jou R, Wu MH, Dalton T, Kurbatova E, Ershova J, et al. Susceptibilities of MDR Mycobacterium tuberculosis isolates to unconventional drugs compared with their reported pharmacokinetic/pharmacodynamic parameters. J Antimicrob Chemother. 2017;72(6):1678-87.
22. Zong Z, Jing W, Shi J, Wen S, Zhang T, Huo F, et al. Comparison of in vitro activity and MIC distributions between the novel oxazolidinone delpazolid and linezolid against multidrug-resistant and extensively drug-resistant Mycobacterium tuberculosis in China. Antimicrob Agents Chemother. 2018;62(8):e00165-18.
23. European Committee on Antimicrobial Susceptibility Testing. MIC- and inhibition zone diameter distributions of microorganisms without and with resistance mechanisms; 2020 [cited 2020 Sep 11]. Available from: https://mic.eucast.org/Eucast2/.