Long-Term Intake of Linezolid Elevates Drug Exposure and Reduces Drug Clearance and Elimination in Adults With Drug-Resistant Pulmonary Tuberculosis

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Purpose: Pharmacokinetic (PK) studies are critical for dose optimization, and there is a paucity of linezolid (LZD) PK data for prolonged use in drug-resistant tuberculosis (DR-TB). Therefore, the authors evaluated the pharmacokinetics of LZD at two-time intervals in DR-TB during long-term use.

Methods: PK evaluation of LZD was performed at the end of the 8th and 16th weeks of treatment in a randomly selected subset of adult pre-extensively drug-resistant pulmonary tuberculosis patients (n = 18) from a multicentric interventional study (Building Evidence to Advance Treatment of TB/BEAT study; CTRI/2019/01/017310), wherein a daily dose of 600 mg LZD was used for 24 weeks. Plasma LZD levels were measured using a validated high-pressure liquid chromatography (HPLC) method.

Results: The LZD median plasma C_{max} was comparable between the 8th and 16th weeks [18.3 mg/L, interquartile range (IQR: 15.5–20.8 and 18.8 mg/L, IQR: 16.0–22.7, respectively)]. However, the trough concentration increased significantly in the 16th week (3.16 mg/L, IQR: 2.30–4.76), compared with the 8th week (1.98 mg/L, IQR: 0.93–2.75). Furthermore, compared with the 8th week, in the 16th week, there was a significant increase in drug exposure ($AUC_{0\text{-}24}$ = 184.2 mg*h/L, IQR: 156.4–215.8 versus 233.2 mg*h/L, IQR: 187.9–277.2), which corroborated with a longer elimination half-life (6.94 hours, IQR: 5.55–7.99 versus 8.47 hours, IQR:7.36–11.35) and decreased clearance (2.91 L/h, IQR: 2.45–3.33 versus 2.19 L/h, IQR: 1.49–2.78).

Conclusions: Long-term daily intake of 600 mg LZD resulted in a significant elevation in trough concentration (>2.0 mg/L) in 83% of the study participants. Furthermore, increased LZD drug exposure may be partly because of decreased clearance and elimination. Overall, the PK data underscore the need for dose adjustment when LZDs are intended for long-term treatment.

Key Words: drug metabolism, multidrug resistance, second-line drug, tuberculosis

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INTRODUCTION

Tuberculosis (TB) is a major public health problem and, as per the estimates of the World Health Organization (WHO), in 2021, 5.3 million people were diagnosed with pulmonary tuberculosis worldwide. India solely accounted for roughly 36% of TB deaths of 82% of global mortality among HIV negatives. Importantly, drug-resistant tuberculosis (DR-TB) constitutes nearly 3.6% of newly diagnosed TB cases and 18% of previous TB cases worldwide in 2021.[1] Unlike drug-sensitive TB, the treatment success rate of drug-resistant TB is very low, ranging between 47% and 57%, and a large proportion of people fail to be cured and succumb to this disease.[1,2] India constitutes a considerable proportion of the global burden of DR-TB cases (more than 150,000 cases in 2020). According to a report, in India, 49,679 cases were diagnosed with DR-TB, whereas more than 42,000 patients were on treatment for the year 2020.[2] The emergence of drug-resistant forms of TB is one of the greatest challenges in disease management for various reasons, including the lack of availability of novel antibiotics. Hence, this has propelled various stakeholders to opt for the use of repurposed drugs and/or develop newer regimens to obtain better efficacy and reduce treatment duration and toxicity, so that the TB elimination goal of 2030, as set by WHO, is achieved.[3]

In this context, linezolid (LZD), a synthetic novel class of oxazolidinone is recognized as a potent antimicrobial agent and used in the treatment regimen of DR-TB along with other

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second-line anti-TB drugs.[4] The recent meta-analysis has evidenced a promising efficacy with the use of linezolid for treating multidrug-resistant and extensively drug-resistant TB (MDR-TB & XDR-TB, respectively).[5] However, several adverse events (hematologic, neurologic, and gastrointestinal) associated with LZD often limit its widespread use. Although some of the toxicities are reversible upon dose reduction and/or discontinuation, a higher toxicity frequency was reported with a 600-mg daily linezolid dose, because of the lack of an optimal dose defined for LZD in the treatment regimen.[5,6] The normal plasma peak concentration (C_{max})/therapeutic range of LZD ranges between 10 and 20 mg/L,[7] whereas the trough concentration (C_{min}) of >2.0 mg/L is considered as the toxic threshold level.[8] Therefore, therapeutic drug monitoring (TDM) and the assessment of the drug exposure/pharmacokinetic (PK) evaluation of LZD are critical for TB treatment, especially DR-TB. However, intensive PK assessments of LZD in drug-resistant TB are limited. To date, studies have reported the intensive PK of LZD at only a one-time point of treatment (i.e., after attaining the steady-state level). In addition, these studies vary widely in several aspects, including drug dosage, the time at which the PK was performed, and the number of time points/intervals.[9–13] Furthermore, meta-analysis studies have highlighted these limitations and knowledge gaps in understanding the pharmacokinetics of LZD.[5,6,14] Notably, Wasserman et al[11] have underscored that a single time-point PK evaluation of LZD was one of the limitations of their study. Thus, it is apparent that the pharmacokinetic properties of LZD are not fully understood, and there is specifically a need to understand its pharmacokinetics beyond a one-time point or after attaining steady-state levels. With this background, we assessed the intensive PK of LZD at the end of the 8th and 16th weeks of treatment in a subset of patients with pre-extensively drug-resistant pulmonary tuberculosis (pre-XDR-TB) from a cohort.

MATERIALS AND METHODS

Materials

All chemicals and reagents used were of ultrapure and/or high-pressure liquid chromatography (HPLC) grade. Pure LZD was purchased from Sigma–Aldrich (Merck KGaA, Darmstadt, Germany).

Ethics

The institutional ethics committee approval was obtained from the respective participating institutions and sites (National Institute for Research in Tuberculosis (NIRT), 2018017; Groups of TB Hospitals (GTBH), FMR/IREC/EXT/02/2019; National Institute for Tuberculosis and Respiratory Diseases (NITRD), 10786; Rajan Babu Institute of Pulmonary Medicine and Tuberculosis (RBIPMT), 3046/RBIPMT/18; B. J. Medical College and Hospital (BJMCH), 09/2019), before initiating the study. Written informed consent was obtained from all participants before they were included in the study. This study was registered in the Clinical Trials Registry of India (CTRI/2019/01/017310).

Study Design and Population

This was an observational PK study performed in a subset of adult patients (n = 18) from a multicentric interventional study that evaluated the safety and efficacy of a new treatment regimen consisting of BDQ, DLM, LZD, and CFZ in pre-XDR TB (n = 165) for 6–9 months (Building Evidence to Advance Treatment of TB/BEAT – study).[15] The LZD dose of 600 mg daily was used in the regimen for 24 weeks.

Pharmacokinetic Evaluation of Linezolid

For intensive PK evaluation, blood samples were collected according to the original/parent study protocol (for BDQ and DLM), that is, before administration of the drug (pre-dose) and after administration at time intervals of 2, 4, 5, 6, 8, 12, and 24 hours (post-dose) in lithium heparin vacutainer tubes at the end of the 8th and 16th weeks of treatment. Plasma was separated from the whole blood, aliquoted, and stored at −80°C. However, for the LZD PK, one of the aliquots of the stored plasma was randomly chosen from the samples collected in the 8th week by a person blinded to the sample details, except for the patient ID number of the total cohort. However, in the 16th week, plasma samples from the same patient were selected and used for the LZD assay.

Plasma LZD Measurement by Reverse-Phase High-Pressure Liquid Chromatography (HPLC)

Plasma linezolid was measured by a reverse-phase HPLC method as described earlier.[16] In brief, 100 μL of plasma sample was added to 200 μL of acetonitrile, mixed vigorously, and centrifuged at 6720 g for 10 minutes to precipitate proteins. The resulting supernatant (200 μL) was transferred to another tube, evaporated under dry nitrogen, and then reconstituted with 100 μL of the mobile phase. From this, 20 μL was injected into the HPLC system for analysis. An appropriate dilution was made for samples whose concentration exceeded the range (i.e. 0.2–20.0 mcg/mL) of the method reported.

Statistical Analysis

For LZD PK analysis, the sample size was arbitrarily fixed at approximately 10% of the total sample size of the original protocol/parent study (n = 165), although a formal sample size calculation was not performed. Pharmacokinetic data distribution was examined using the Shapiro–Wilk test. The Mann–Whitney *U* test was used to compare groups at two time intervals. The Wilcoxon signed-rank test was performed to determine significant differences in various PK parameters between the two time points. Values are expressed as medians with interquartile range (IQR) or frequencies (%). A noncompartmental model was applied for LZD PK evaluation using STATA 15.0 (StataCorp, TX). The geometric mean was calculated using the log-transformed PK parameter values. SPSS software (version 25.0) was used for the statistical analysis (IBM Armonk, NY).

RESULTS

Demographic Characteristics

Among the chosen samples (n = 18), 13 were men (72%) and 5 were women (28%) with a median age of 28.5 years (IQR: 19.8–35.3) with 53.6 kg body weight (IQR: 44.8–62.6) and BMI of 19.5 kg/m^2 (IQR: 16.8–21.7). Nearly 67% of the study participants had a cavity, and this was predominantly observed in men. In addition, the chest X-ray examination showed the involvement of ≤3 zones among 67% of the study participants, whereas the remaining were of >3 zones (33%). All participants were fluoroquinolone-resistant according to drug susceptibility testing. A sputum smear grade >2+ was found in 47% of the study population, and the mycobacterial growth indicator tube culture test at baseline showed that all 18 study participants were positive (Table 1).

Pharmacokinetics of Linezolid

The median plasma C_{max} of linezolid in the 8th and 16th weeks were 18.3 mg/L (IQR: 15.5–20.8) and 18.8 mg/L (IQR: 16.0–22.7), respectively, and reached 2.0 hours (T_{max}) of postdrug administration. However, compared with the 8th week, the median plasma C_{min} (1.98 versus 3.16 mg/L; *P = 0.001*), $AUC_{0\text{-}24}$ (184.2 versus 233.2 mg*h/L; *P* = 0.003), and elimination half-life ($T_{1/2}$ = 6.94 versus 8.47 hours; *P* = 0.001) were significantly higher in the 16th week. Conversely, the elimination rate constant (k_e = 0.10 versus 0.09 h^{-1}; *P* = 0.001) and apparent total clearance (CL/F = 2.91 versus 2.19 L/h; *P = 0.005*) were significantly lower at the end of the 16th week when compared with the 8th week. However, the volume of distribution (Vd/F = 28.51 versus 27.40 L) remained unaltered (Table 2). Furthermore, to assess the central tendency of LZD PK parameters, the geometric means for the 8th and 16th weeks and the ratios were calculated and are presented in Table 3. The time-course plasma concentration of LZD for up to 24 hours at the 8th and 16th weeks was graphically represented in Figure 1.

Table 4 summarizes the trough concentrations relative to the toxic threshold level (2.0 mg/L) and the normal plasma peak concentration/therapeutic range of LZD (10–20 mg/L) of this study population. It may be noted that 83% of the participants had a median trough concentration higher than 2.0 mg/L in the 16th week, which was almost double when compared with the 8th week (50.0%). Importantly, a daily dose of 600 mg LZD yielded normal plasma peak concentration (C_{max}) among 61% of the study population, whereas 39% showed a supratherapeutic level and none showed levels below the range in the 16th week. Although a similar pattern was observed in the 8th week, one of the participants had a level below 10 mg/L. Furthermore, drug exposure levels ($AUC_{0\text{-}24}$) exceeding 200 mg*h/L were observed in 28% of the participants in the 8th week, whereas in the 16th week, 67% of the study population showed higher levels of LZD exposure (Table 4).

DISCUSSION

This is the first study to provide the pharmacokinetic characteristics of LZD in patients with pre-XDR-TB at

TABLE 1. Demographic Details of the Study Participants

	Total Median (IQR) or Frequency (%) (n = 18)	Male Median (IQR) or Frequency (%) (n = 13)	Female Median (IQR) or Frequency (%) (n = 5)
Age (y)	28.5 (19.8–35.3)	29.0 (21.0–32.0)	28.0 (18.5–43.0)
Weight (kg)	53.6 (44.8–62.6)	54.0 (46.0–60.4)	50.1 (39.5–65.9)
BMI (kg/m^2)	19.5 (16.8–21.7)	19.5 (16.8–21.1)	20.9 (17.1–29.7)
Sputum smear at baseline			
Scanty	1 (5.6%)	1 (7.7%)	0
1+	8 (44.4%)	6 (46.2%)	2 (40%)
2+	6 (30.3%)	5 (38.5%)	1 (20%)
3+	3 (16.7%)	1 (7.7%)	2 (40%)
MGIT culture at baseline			
Positive	18 (100%)	13 (100%)	5 (100%)
Chest X ray—Presence of cavity	12 (66.7%)	10 (77%)	2 (40%)
Chest X ray—Zones involvement			
≤3 zones	12 (66.7%)	8 (61%)	4 (80%)
>3 zones	6 (33.3%)	5 (39%)	1 (20%)
Radiological lesions			
Unilateral	8 (44.4%)	5 (39%)	3 (60%)
Bilateral	10 (55.6%)	8 (61%)	2 (40%)
Drug-susceptibility testing (DST)			
Fluoroquinolone-resistant	18 (100%)	13 (92.3%)	5 (80%)

Data were presented as descriptive statistics using frequencies and percentages, whereas certain parameters were given as medians with IQR (as the data did not follow a normal distribution as tested by the Shapiro–Wilks test). MGIT, mycobacterial growth indicator tube; DST, drug susceptibility testing.

TABLE 2. Steady-State Pharmacokinetics of Linezolid

Pharmacokinetic Parameters	8th week Median (IQR) (n = 18)	16th week Median (IQR) (n = 18)	*P*
C_{min} (mg/L)	1.98 (0.93–2.75)	3.16 (2.30–4.76)	0.001
C_{max} (mg/L)	18.3 (15.5–20.8)	18.8 (16.0–22.7)	0.372
T_{max} (h)	2.0 (2.0–4.0)	2.0 (2.0–4.0)	0.380
AUC_{0-24} (mg*h/L)	184.2 (156.4–215.8)	233.2 (187.9–277.2)	0.003
$T_{1/2}$ (h)	6.94 (5.55–7.99)	8.47 (7.36–11.35)	0.001
k_e (h^{-1})	0.10 (0.09–0.13)	0.09 (0.06–0.10)	0.001
CL/F (L/h)	2.91 (2.45–3.33)	2.19 (1.49–2.78)	0.005
V_d/F (L)	28.51 (23.88–33.44)	27.40 (20.60–34.93)	0.157

Noncompartmental pharmacokinetic analysis of LZD: Values were expressed as the median with IQR. The Mann–Whitney *U* test was used to compare the groups between 2 time intervals, and the Wilcoxon signed-rank test was performed to determine significant differences in the PK parameters between the 2 time points. $P < 0.05$ considered significant. Plasma maximum (C_{max}) and minimum (C_{min}) concentrations were calculated from the time course of drug concentrations. The area under the concentration–time curve over 24 h (AUC_{0-24}) was calculated using the linear trapezoidal method. During the elimination phase, the elimination rate constant (ke) was derived from the slope of log-transformed concentrations. The apparent clearance (CL/F) was calculated by dividing the dose by the AUC. The elimination half-life ($T_{1/2}$) and volume of distribution (V_d/F) were calculated by dividing the natural log of 2 and clearance by the elimination rate constant.

different time intervals during the course of treatment (i.e. the 8th and 16th weeks). The median plasma maximum concentrations (C_{max}) at weeks 8 and 16 were comparable, suggesting that a steady-state level was maintained until week 16 of daily LZD administration. In addition, the median trough concentration (C_{min}) in 50% of the study participants was below the toxicity threshold levels of 2.0 mg/L in the 8th week. However, most (83%) had exceeded this level by the end of the 16th week. The median exposure level (AUC_{0-24} = 184.2 mg*h/L) in the 8th week was comparable to the levels reported (200.2 mg*h/L) in South African DR-TB patients by Wasserman et al[11] and by Lee et al[17] in XDR TB patients (180.4 mg/L/h). Surprisingly, at the end of the 16th week, there was a significant increase in drug exposure with a median level of 233.2 mg*h/L for 24 hours, which corroborated the decreased elimination and clearance of LZD. In addition, the central tendency of the geometric mean ratios of the 16th week to the 8th week for C_{min}, AUC_{0-24} (exposure), elimination half-life, and clearance rate is in line with the finding that long-term intake impedes LZD clearance at the end of the 16th week compared with the 8th week.

Several factors (host and physiochemical properties of a drug molecule) are known to influence the metabolism of a drug and thus affect its pharmacokinetic property.[18–20] Among host factors, impaired renal function has been shown to be associated with LZD clearance, leading to elevated trough concentration and drug exposure, particularly in sepsis and critically ill patients.[21–23] However, studies associated with some of the key indicators of renal function, including creatinine clearance, glomerular filtration rate, and the pharmacokinetic characteristics of LZD in DR-TB are scarce. Nevertheless, in the present study, we speculate that the reduction in clearance (C_L/F) and elimination (as shown by the increased elimination half-life) may partly explain the higher drug exposure, possibly because of changes in renal function at the end of the 16th week compared with the 8th week in this study population with pre-XDR-TB. Nevertheless, these data warrant further investigation to understand LZD metabolism (including renal function) and its pharmacokinetic properties comprehensively during prolonged use. Recently, Rao et al[24] have highlighted some of the limitations in understanding LZD metabolism and the interindividual variability in the pharmacokinetics and pharmacodynamics of LZD and emphasized the need for the TDM of LZD for dose adjustment to improve treatment success. In this context, this study adds evidence to our understanding of the long-term effects of LZD metabolism.

For the first time, we report the pharmacokinetics of LZD at 2 intervals in pre-XDR-TB patients during the treatment period (in the 8th and 16th weeks of treatment).

TABLE 3. LZD Pharmacokinetic Parameters—Geometric Means and Ratios

Pharmacokinetic Parameters	Geometric Mean (90% CI) (n = 18)		Geometric Mean Ratio	
	8th week	16th week	Ratio	90% CI
C_{min}(mg/L)	1.4 (0.95–1.9)	2.9 (2.1–3.9)	2.12	0.56–3.67
C_{max} (mg/L)	17.7 (16.1–19.5)	18.8 (17.3–20.7)	1.06	0.27–2.71
AUC_{0-24}(mg*h/L)	165.1 (142.2–191.7)	222.1 (196.6–250.9)	1.35	0.55–2.95
$T_{1/2}$(h)	6.6 (5.99–7.35)	8.92 (7.78–10.23)	1.35	0.43–3.05
CL/F (L/h)	3.1 (1.6–2.5)	2.0 (2.7–3.5)	0.66	0.08–2.43

90% confidence intervals of the geometric means and ratios (16th to 8th week) of LZD pharmacokinetic parameters. C_{min} and C_{max} are the plasma minimum and maximum concentrations, respectively; AUC_{0-24} is the area under the concentration–time curve over 24 h, $T_{1/2}$ is the elimination half-life, and CL/F is the apparent clearance.

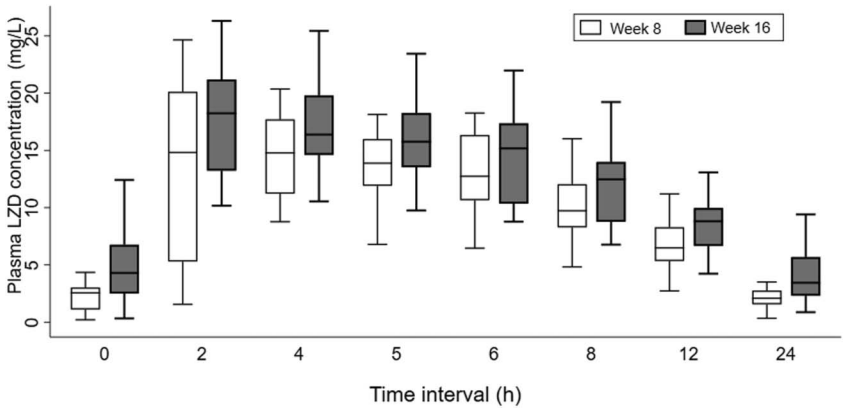

FIGURE 1. Time-course plasma LZD concentration. The box plot represents the data in median with the IQR of plasma LZD concentration over 24 hours (n = 18). Open box—8th week; closed box—16th week.

The sample size is likely one of the limitations of this study, apart from not addressing interactions with other drugs used in the treatment regimen (BDQ, DLM, and CFZ). Nevertheless, the study has its merits because it performed intensive PK evaluation in the same individuals at 2 different times during the treatment period, thus providing new insight into LZD metabolism, as evident from the PK data. Hence, this study has great clinical relevance in the current context of LZD use in the treatment regimen for DR-TB.

CONCLUSION

Although the 600-mg daily linezolid dose maintained a steady-state plasma concentration within the normal range until the 16th week, the trough concentration was higher than the toxic threshold level of 2.0 mg/L in most study subjects, at the end of the 8th and 16th weeks. Furthermore, long-term linezolid intake led to higher drug exposure, possibly resulting from decreased drug clearance and elimination, particularly at the end of the 16th week. Overall, linezolid metabolism and its pharmacokinetic properties seem to be altered during prolonged use. Thus, this study underscores the importance of therapeutic drug monitoring during long-term treatment and the need for dose adjustment or optimization of linezolid during the treatment period of DR-TB.

TABLE 4. Summary of the Linezolid Pharmacokinetic Characteristics of the Study Population

Pharmacokinetic Parameters	8th week Frequency (%) (n = 18)	16th week Frequency (%) (n = 18)
C_{min} (mg/L)		
<2.0	9 (50.0)	3 (16.7)
>2.0	9 (50.0)	15 (83.3)
C_{max} (mg/L)		
<10.0	1 (5.6)	—
10.0–20.0	11 (61.1)	11 (61.1)
>20.0	6 (33.3)	7 (38.9)
AUC_{0-24} (mg*h/L)		
<200.0	13 (72.2)	6 (33.3)
>200.0	5 (27.8)	12 (66.7)

Data were presented as descriptive statistics using frequencies and percentages. C_{min}: plasma minimum/trough concentration; C_{max}: plasma maximum concentration; and AUC_{0-24} – area under the concentration–time curve over 24 h.

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