Saudi Pharmaceutical Journal 27 (2019) 1061–1063

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Determining therapeutic trough ranges for linezolid

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ARTICLE INFO

Article history:
Received 23 February 2019
Accepted 22 September 2019
Available online 25 September 2019

Keywords:
Linezolid
Therapeutic drug monitoring
Pharmacokinetics

ABSTRACT

Linezolid (LZD) is an oxazolidinone approved for the treatment of gram-positive infections. Therapeutic drug monitoring is increasingly used to optimize LZD dosing. The therapeutic target for LZD is to achieve an area under the concentration-time curve over 24 h divided by the MIC (AUC/MIC) > 100. In this study, we determined the trough ranges associated with this therapeutic AUC. Concentration-time profiles for 999 virtual patients were simulated using a previously published pharmacokinetic model for LZD. AUC was estimated for each virtual patient using the trapezoidal method. We determined the trough ranges that achieve the therapeutic target of AUC/MIC > 100 at different MIC values of 1, 2 and 4 μg/mL. Trough samples correlated well with LZD AUC (R^2 = 0.87). For trough concentration of 2–5 μg/mL, 99% had an AUC_{0-24} > 100 μg·h·ml^{-1}, 23% had an AUC_{0-24} > 200 μg·h·ml^{-1} and none had an AUC_{0-24} > 400 μg·h·ml^{-1}. For trough concentrations of 5–8 μg/ml, 87% of the patients had an AUC_{0-24} > 200 μg·h·ml^{-1} and none had an AUC_{0-24} > 400 μg·h·ml^{-1} To achieve the therapeutic target of an AUC/MIC > 100, it is suggested that trough ranges be set at 2–5 μg/ml if the MIC < 2 and 5–8 μg/ml if the MIC = 2; however, at an MIC of 4 μg/ml, it is difficult to achieve an AUC/MIC > 100 without increasing the risk of LZD toxicity.

1. Introduction

Linezolid (LZD) is commonly used for the treatment of infections by gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and streptococci. LZD pharmacokinetics exhibit high inter-subject variability (Pea et al., 2012; Swoboda et al., 2010); up to 20-fold inter-patient variability in LZD trough concentrations has been reported (Pea et al., 2012; Cattaneo et al., 2016; Galar et al., 2017). Causes for this high variability include: age, weight, renal function, co-medications like rifampicin and critical illness (Morata et al., 2016, 2013). Elevated LZD trough concentrations increase the risk of hematological side effects (Pea et al., 2012; Cattaneo et al., 2016; Hiraki et al., 2012; Song et al., 2015; Matsumoto et al., 2014; Cattaneo et al., 2013). In the study by Cattaneo et al., patients who developed hematological toxic effects had with higher trough concentrations (9 μg/mL vs. 4.9 μg/mL) (Cattaneo et al., 2013). Similarly, in the study by Matsumoto et al., Cmin values > 8.2 μg/mL were associated with increased risk of thrombocytopenia (Matsumoto et al., 2014). Therefore, it is recommended to maintain trough concentrations < 8 μg/mL (Cattaneo et al., 2016).

On the other hand, LZD efficacy is mainly linked to the area under the concentration-time curve over 24 h divided by the minimum inhibitory concentration (AUC/MIC) ratio (Rayner et al., 2003; Craig, 2003; Boak et al., 2007). The pharmacokinetics/pharmacodynamics target for linezolid is to achieve an AUC/MIC > 80–100. Therefore, achieving therapeutic concentrations and avoiding toxic trough concentrations are critical for LZD dosing. Therapeutic drug monitoring (TDM) has been recommended as a tool to optimize LZD dosing (Pea et al., 2012; Cattaneo et al., 2016; Morata et al., 2016). TDM can decrease the variability associated with LZD and improve treatment outcome (Pea et al., 2012; Cattaneo et al., 2016). TDM would be particularly useful in cases where LZD will be used chronically (>3 weeks) such as in treatment of bone/skin infections and drug resistant tuberculosis, as prolonged treatment increase the risk of side effects (De Vriese et al., 2006; Soriano et al., 2005). In clinical practice, TDM is performed using LZD trough concentrations with or without peak concentrations (Alsultan and Peloquin, 2014; Pea et al., 2010). That is because LZD trough concentrations are strongly correlated with the AUC. In addition, toxicity is linked to trough

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2019.09.002
1319-0164/

concentrations (Alffenaar et al., 2010). The goal is to maintain trough concentrations < 8 μg/mL. A limitation for this approach is that it does not take the MIC values into account. Therefore, in this paper we assessed the correlation between LZD trough and AUC to determine the trough ranges that maximize the probability of achieving an AUC/MIC > 100 at different MIC values.

2. Materials and methods

2.1. Population pharmacokinetics model and simulation data set

We used the previously published paper by Boak et al., to simulate the time concentration profile for 999 virtual patients (Boak et al., 2014). A one-compartment pharmacokinetic model with linear elimination was used; clearance (*Cl*) and the volume of distribution (V) were defined according to the following equations:

$$Cl = \left(\frac{weight}{65}\right)^{0.75} \times (RF_i \times Cl_R + Cl_{NR})$$

$$RF_i = GFR_i/120$$

$$\mathrm{V} = 44.3 \times \left(\frac{weight}{65}\right)$$

where RF_i is the renal function; *GFR* is the glomerular filtration rate estimated using the Cockcroft and Gault formula; Cl_R is the renal clearance and equals 2.17 l/h; and Cl_{NR} is the nonrenal clearance and equals 4.55 l/h for a 65-kg patient with a GFR of 120 ml/min.

Based on the model, we simulated the concentration-time profiles for 999 virtual individuals. These virtual individuals were equally divided into groups 1, 2, and 3 based on creatinine clearances of 40, 80, and 120 ml/min, respectively. Assuming a log normal distribution for body weight (74 ± 0.2 kg, mean ± SD), simulations were performed using the Simulx (Lixoft, 2018R1) function of the R statistical software. Concentrations were simulated at 30-min increments from time zero to 12 h under steady-state conditions. Simulations were performed with residual variability to replicate the clinical scenario. Each virtual patient received LZD at 600 mg as a 60-min IV infusion every 12 h. To ensure the validity of the simulations, we modeled the simulated data set with Monolix (Lixoft, 2018R1) (Lavielle and Mentre, 2007). The objective of this was to compare pharmacokinetic parameters estimated from the simulated dataset to the estimates from the original model.

2.2. AUC estimation & reduced data set

AUC_{0-24} was estimated for each virtual patient using the trapezoidal method and was considered as the reference AUC. Simulated datasets were reduced to contain the trough sample only. The trough concentration was considered as the sample obtained 30 min before the start of the next dose.

2.3. Correlation between troughs and AUC using simple linear regression

To assess the strength of correlation between troughs and AUCs, we estimated the coefficient of determination, bias and precision. Bias and precision were calculated as follows (Sheiner and Beal, 1981):

$$Bias\% = \frac{\sum(AUC\ \ predicted - AUC\ \ \text{reference})}{N} * \left(\frac{100}{ymean}\right)$$

$$Precision\% = \sqrt{\frac{\sum(AUC\ \ predicted - AUC\ \ \text{reference})^2}{N}} * \left(\frac{100}{ymean}\right)$$

We used simple linear regression to calculate the predicted AUC for each trough.

2.4. Trough ranges associates with AUC/MIC > 400

We determined the trough ranges that achieve the therapeutic target of AUC/MIC > 100 at different MIC values of 1, 2 and 4 μg/mL.

3. Results

Pharmacokinetic parameters estimated from the simulated dataset matched those reported in the original publication (Table 1). Trough (n = 48) concentrations < 0.5 μg/ml were considered below the limit of quantification (BLQ) and were excluded from the analysis (Stein et al., 2005).

As expected, trough concentrations exhibited good correlation with the AUC_{0-24} (R^2 = 0.87, bias = 0.45%, precision = 17%). The target AUC/MIC ratio for LZD was set at 100. Assuming MIC concentrations of 1, 2 and 4 μg/ml, target AUC_{0-24} s were calculated to be 100, 200 and 400 $\mu g \cdot h \cdot ml^{-1}$, respectively. Trough concentrations associated with AUC_{0-24} of 100, 200 and 400 $\mu g \cdot h \cdot ml^{-1}$ were estimated to be 0.22, 4.8 and 13.8 μg/ml, respectively. For trough concentration of 2–5 μg/mL 99% had an $AUC_{0-24} > 100\ \mu g \cdot h \cdot ml^{-1}$, 23% had an $AUC_{0-24} > 200\ \mu g \cdot h \cdot ml^{-1}$ and none had an $AUC_{0-24} > 400\ \mu g \cdot h \cdot ml^{-1}$. For trough concentrations of 5–8 μg/ml, 87% of the patients had an $AUC_{0-24} > 200\ \mu g \cdot h \cdot ml^{-1}$ and none had an $AUC_{0-24} > 400\ \mu g \cdot h \cdot ml^{-1}$ (Table 2).

4. Discussion

In this study, we determined the optimal trough ranges to achieve the therapeutic target for LZD of an AUC/MIC > 100. At an MIC of 2, an AUC/MIC > 100 can be achieved with trough concentrations of 5–8 μg/ml; at an MIC of 1 μg/ml, the target AUC/MIC can be achieved with trough concentrations of 2–5 μg/ml. At an MIC of 4 μg/ml, it is difficult to achieve therapeutic concentrations without exposing patients to toxic concentrations. These target trough concentrations may facilitate TDM for LZD. Previous studies have recommended that target trough concentra-

Table 1
Pharmacokinetic parameters estimated from modeling the simulated datasets compared to those reported in the original model.

	Original model		Simulated dataset	
V	44.3		44.5	
CV% for V	3.6		5.4	
Slope effect of weight on V	1		1.05	
Cl	6.72		6.82	
CV% for *Cl*	48.9		48.8	
Slope effect of weight on *Cl*	0.75		0.51	
Residual variability	a	0.3	a	0.287
	b	0.225	b	0.20

All pharmacokinetic parameter estimates are scaled to 65 kg and 120 ml/min for Clcr.

Table 2
Probabilities of achieving target $AUC_{0-24} > 100$, 200 and 400 $\mu g \cdot h \cdot ml^{-1}$ based on trough levels.

	$AUC_{0-24} > 100$	$AUC_{0-24} > 200$	$AUC_{0-24} > 400$
2–5 μg/ml	99%	23%	0%
5–8 μg/ml	100%	87%	0%
8–11 μg/ml	100%	100%	26%

tions be <8 μg/ml to avoid toxicity (Cattaneo et al., 2016; Matsumoto et al., 2014; Cattaneo et al., 2013). In the study by Matsumoto et al., LZD trough concentrations > 8.4 increased risk of hematologic toxicity (Matsumoto et al., 2014). In the study by Pea et al., the risk of hematologic toxicity increased at trough concentrations above 6.5 μg/mL (Pea et al., 2012). The recommended target trough concentrations for both an MIC of 1 and particularly at 2 μg/ml are close to and might overlap with the toxicity threshold, indicating LZD has a narrow therapeutic index. This combined with LZD high variability further necessitates TDM during LZD therapy. In addition to monitoring linezolid concentrations, it is important to monitor patients complete blood count especially in predisposed patients (Gerson et al., 2002).

The best approach to do TDM for LZD would be to use a Bayesian approache to estimate the AUC for the patient (Sprague and Ensom, 2009). The goal would be to achieve an AUC/MIC > 100. However, Bayesian approaches are still not very common in practice. An alternative approach is to target trough concentrations that maximize the probability of achieving an AUC/MIC > 100. For most instances in infectious disease, we treat patients empirically without knowing the MIC. In this case it would be reasonable to assume an MIC of 2 μg/ml, which is the breakpoint for LZD against most gram-positive bacteria. Therefore, the target trough range for LZD in general would be 5–8 μg/ml. Once, the MIC has been determined, the trough concentration can be targeted for the specific MIC.

It is difficult to compare the target trough ranges from this analysis with prior studies. Previous studies that used linear regression to assess the correlation between trough concentrations and AUC only provided predicted AUC at a certain trough concentration. They did not provide the predicted AUC at a range of trough concentrations. In the study by Pea et al., trough concentrations associated with AUCs of 200 and 400 $\mu g \cdot h \cdot ml^{-1}$ were 3.9 and 12.25 μg/ml, respectively (21). Trough concentrations estimated in this study (4.8 and 13.8 μg/ml) were comparable to these reported values.

Our study has several limitations. It is based solely on simulations. We did not have an external data set to validate if these trough ranges correlate well with an AUC/MIC > 100 across different populations. Also, the target trough concentrations recommended in this study need to be validated to ensure their safety and efficacy.

5. Conclusions

In conclusion, that target trough concentrations of 5–8 μg/ml are required for achieving an AUC/MIC > 100 if the MIC is = 2 μg/ml. If the MIC is ≥ 4, it will be difficult to achieve therapeutic concentrations without increasing the risk of hematologic toxicities.

Acknowledgments

The author acknowledges financial support from the Researchers Supporting Project number (RSP-2019/39), King Saud University, Riyadh, Saudi Arabia.

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