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Simple strategy to assess linezolid exposure in patients with multi-drug-resistant and extensively-drug-resistant tuberculosis

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ABSTRACT

Linezolid is used increasingly for the treatment of multi-drug-resistant (MDR) and extensively-drug-resistant (XDR) tuberculosis (TB). However, linezolid can cause severe adverse events, such as peripheral and optical neuropathy or thrombocytopenia related to higher drug exposure. This study aimed to develop a population pharmacokinetic model to predict the area under the concentration curve (AUC) for linezolid using a limited number of blood samples.

Data from patients with MDR-/XDR-TB who received linezolid and therapeutic drug monitoring as part of their TB treatment were used. Mw\Pharm 3.82 (Mediware, Zuidhorn, The Netherlands) was used to develop a population pharmacokinetic model and limited sampling strategy (LSS) for linezolid. LSS was evaluated over a time span of 6 h. Blood sampling directly before linezolid administration and 2 h after linezolid administration were considered to be the most clinically relevant sampling points.

The model and LSS were evaluated by analysing the correlation between $AUC_{12h,observed}$ and $AUC_{12h,estimated}$. In addition, LSS was validated with an external group of patients with MDR-/XDR-TB from Sondalo, Italy.

Fifty-two pharmacokinetic profiles were used to develop the model. Thirty-three profiles with a 300 mg dosing regimen and 19 profiles with a 600 mg dosing regimen were obtained. Model validation showed prediction bias of 0.1% and r^2 of 0.99. Evaluation of the most clinically relevant LSS showed prediction bias of 4.8% and r^2 of 0.97. The root mean square error corresponding to the most relevant LSS was 6.07%.

The developed LSS could be used to enable concentration-guided dosing of linezolid.

1. Introduction

Although tuberculosis (TB) is entering the elimination phase in most developed countries [1], it remains a major problem in many developing countries. Although the number of TB-related deaths has decreased by 22% since 2000, TB remains one of the leading causes of death worldwide [2]. In 2015, it is estimated that 10.4 million new TB infections occurred, and TB accounted for approximately 1.4 million deaths [2]. However, according to the World Health Organization (WHO), an estimated 49 million lives were saved between 2000 and 2015 due to accurate diagnosis and treatment [2].

Despite improvements in diagnostics and treatment, some major challenges have to be overcome. One of these challenges is the treatment of multi-drug-resistant TB (MDR-TB) and extensively-drug-resistant TB (XDR-TB). According to WHO, 580 000 new TB cases were eligible for MDR-TB treatment in 2015, yet only 125 000 cases were enrolled [2]. Furthermore, 7579 cases of XDR-TB were detected in 2015. MDR-TB strains are resistant to (at least) rifampicin and isoniazid, both of which belong to the most potent first-line group of anti-TB drugs. XDR-TB strains are resistant to (at least) isoniazid, rifampicin, a fluoroquinolone and a second-line injectable drug (e.g. kanamycin, amikacin or capreomycin) [3].

Unfortunately, treatment outcomes for these cases are still largely suboptimal [4–6]. Whereas the treatment of human

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immunodeficiency virus (HIV) has improved drastically over the past years, there is still dire need for more efficacious and less toxic treatment regimens for MDR-/XDR-TB. To improve treatment outcome of MDR-/XDR-TB infections, new regimens are being investigated, including bedaquiline (BDQ) and pretomanid (PMD) in combination with linezolid (LZD) [7]. LZD showed an additional bactericidal and sterilizing effect to treatment regimens containing BDQ+PMD [3]. In addition, Guglielmetti et al [8] showed the importance of LZD+BDQ for the treatment of MDR-TB. Furthermore, in vitro, the addition of LZD to regimens containing clarithromycin, ethambutol, moxifloxacin, amikacin or clofazimine is shown to have a synergistic effect against MDR- and non-MDR-TB bacilli [9].

LZD has been shown to have similar minimal inhibitory concentrations (MICs) for MDR-TB strains as for non-MDR strains [10]. In addition, LZD has been reported to have a similar in vitro bactericidal effect on latent *Mycobacterium tuberculosis* bacilli as rifampicin [11]. This activity may cause LZD to play an increasingly important role in the treatment of MDR-/XDR-TB [12].

A recent study [13] showed that 71% of patients with chronic XDR-TB using LZD monotherapy were cured. In this prospective clinical trial, 38 patients with XDR-TB received LZD monotherapy 300 mg or 600 mg per day. Patients received LZD for a median duration of 781 days. All 27 patients who finished the trial were cured from the XDR-TB infection. This study thereby provides evidence that long-term use of LZD can be beneficial for the treatment of MDR-/XDR-TB.

Unfortunately, prolonged use of LZD is often associated with the occurrence of severe adverse events, such as peripheral and optical neuropathy [12], which may be a limiting factor for the widespread use of LZD. LZD toxicity is shown to be more frequent at higher dosages (i.e. 600 mg twice daily [14,15]), resulting in several initiatives exploring lower dosages ranging from 300 to 600 mg once daily [12,13,16].

Therapeutic drug monitoring (TDM) can be used to determine the optimal drug dose by measuring the blood concentration of the particular drug [17]. Drug-exposure-related toxicity and efficacy, in combination with large interpatient variability [18], are the most important reasons to individualize the dose to optimize treatment for the individual patient. In the case of LZD, the area under the concentration curve (AUC) to MIC ratio was found to be the optimal pharmacokinetic parameter for TDM [19–21] with a target AUC_{24h}/MIC ratio >100 [21–23]. Rayner et al [22] showed a breaking point in the probability of bacterial eradication at an AUC/MIC ratio of ca. 100 for patients who suffered from a lower respiratory tract infection caused by MDR Gram-positive organisms. In addition, the correlation between LZD concentrations and activity is almost linear for AUC/MIC ratios <120. However, when LZD concentrations are above the MIC for 100% of the dosage time, this linear correlation is no longer applicable [23]. Therefore, targeting LZD AUC/MIC ratios well above 100 will not lead to higher antimicrobial activity.

TDM based on a full LZD concentration curve can be challenging due to limited resources. A suitable alternative is the use of a limited sampling strategy (LSS) to estimate AUC based on a few blood samples [19]. Therefore, the aim of this study was to develop a robust population pharmacokinetic (PPK) model in combination with an improved practical LSS to enable individualized dosing of LZD in patients with MDR-/XDR-TB.

2. Methods

2.1. Patients and study design

Cohort 1 included data of MDR-/XDR-TB patients who were hospitalized between 2007 and 2014 at the TB centre in Haren, University Medical Centre Groningen, The Netherlands, and was used to develop the PPK model. Cohort 2 included data from 35 MDR-/XDR-TB patients who were hospitalized between 2007 and 2014 at the TB centre in Sondalo, Italy. Cohort 2 was used as an external evaluation set for the developed model. All patients received LZD and underwent TDM as part of their daily TB treatment. TDM and MIC determination were both performed as part of the routine MDR-/XDR-TB treatment protocol in the TB centre. TDM was performed at least 1 week after LZD commencement to ensure steady state kinetics. Blood samples were taken directly before administration of LZD and 1 h, 2 h, 3 h, 4 h, 8 h and, in some cases, 12 h after administration. For patients lacking a $t = 12$ h sample, the LZD concentration at $t = 12$ h was assumed to be equal to the concentration at $t = 0$ h, since samples were taken in a steady state. Patients had no dietary restrictions. LZD was administered under directly observed treatment. Due to the retrospective nature of this study and because TDM was already part of the routine treatment protocol in the TB centre, the need for the subjects to provide informed consent was waived by the local ethics committee (IRB 2013.492).

Data on demographics, patient characteristics, LZD plasma concentrations [24] and LZD dosing regimen (including 300 mg twice daily and 600 mg twice daily) were collected from the medical charts. Patients aged <18 years and pregnant women were excluded as these groups included too few patients to perform a covariate analysis. Patient data were excluded if blood samples were collected before the steady state was reached. In addition, patients were excluded when data on sampling time or time of administration of the drug or drug dose were missing or erratic. Pharmacokinetic data were processed using Mw\Pharm 3.82 (Mediware, Zuidhorn, The Netherlands).

The concentration–time curves were used to develop a one-compartment PPK model using an iterative two-stage Bayesian procedure (KinPop module, MwPharm 3.82, Mediware).

An analytical concentration-dependent error of 8% with an intercept of 0 (standard deviation = 0 + 0.08 * C) was applied. The analytical error was obtained from the analytical laboratory at University Medical Centre Groningen [24]. A log-normal distribution was assumed to be appropriate for the pharmacokinetic parameters. Model evaluation was performed by generating submodels through data splitting. Submodels were obtained by alternately removing four curves from the original model (n-4). Concentration curves were randomized to determine the curves that had to be removed for each submodel.

AUC_{12h} of each removed curve was estimated by using the corresponding submodel ($AUC_{12h,estimated}$). Furthermore, $AUC_{12h,\ observed}$ of each curve was calculated by using the KinFit module (non-compartmental kinetics). The KinFit module uses numerical integration to estimate AUC. Agreement between $AUC_{12h,estimated}$ and $AUC_{12h,observed}$ was assessed by performing Bland–Altman analysis.

2.2. Limited sampling strategy

Monte Carlo (MC) simulation for 1000 patients was generated for two representative curves. MC simulation is used to simulate patients based on PK parameters calculated by the PK model. To be convenient for daily practice, only LSSs within a 6-h timespan were evaluated.

A maximum of four samples was allowed for the LSS evaluation. AUC(SS) was chosen as the parameter to be optimized. Timepoint combinations with a root mean square error (RMSE) <15%, bias <5% and r^2 >95% were considered acceptable [19].

The most clinically relevant and most precise LSS was evaluated by comparing $AUC_{12h,estimated}$ with $AUC_{12h,observed}$. $AUC_{12h,observed}$ was calculated with the actual LZD concentrations using the KinFit module. $AUC_{12h,estimated}$ and $AUC_{12h,observed}$ were compared by assessing the agreement between the two methods with Bland–Altman analysis.

To evaluate the relevance of outliers, AUC_{24h}/MIC ratios of the outliers were calculated. Three MIC values, based on wild-type MIC values [25], were used (0.5–0.25–0.125 mg/L) for this evaluation.