A Population Pharmacokinetic Model of Linezolid enabling Model-Informed Precision Dosing in Patients with Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis

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INTRODUCTION

Linezolid is one of the core drugs (group A) used for treatment of MDR- and XDR-TB[1]. Treatment of TB using linezolid can result in severe adverse events (i.e. myelosuppression (anemia), peripheral and optic neuropathy, lactic acidosis, hepatotoxicity, and hypoglycemia)[2,3]. Dose-individualization based on pharmacokinetic information can be done to maximize the number of patients within the therapeutic range.

Aims: The aim of this work was to develop a population pharmacokinetic (popPK) model, which in combination with efficacy and safety targets, can be used for model-informed precision dosing (MIPD) of linezolid in the clinic from the first day of administration. Furthermore, clinical trial simulations were performed to evaluate the most optimal dose on an average level following different dosing regimens.

METHODS

The popPK model was built using routine hospital therapeutic drug monitoring data from 70 patients from University Medical Center Groningen, The Netherlands.

Pharmacokinetic parameters were described using the nonlinear mixed-effects modelling software NONMEM (v.7.4.3; Icon Development Solutions).

The project workflow

Structural & stochastic model:

- Number of compartments
- Absorption delay:
  - Absorption lag-time
  - Transit absorption model
- Elimination:
  - Linear elimination (without and with drug-induced auto-inhibition of elimination[4])
  - Michaelis-Menten elimination kinetics
- Inter-individual variability (IIV)
- Inter-occasion variability (IOV)
- Residual unexplained variability (RUV)

Covariate model:

- Allometric scaling
- Covariate model building using stepwise covariate modelling (SCM) approach:
  - Statistical significance ($p<0.05$ for forward inclusion and $p<0.01$ for backwards deletion steps)
  - Clinical significance of covariates (> 20%)

Evaluation of most optimal dose based on pre-specified targets[2,5]:

- Efficacy target: $fAUC_{0\text{-}24h}$/MIC of 119[2]
- Safety target: fC_{min} < 1.38 mg/L[5]

Evaluated for the:

- Typical individual
- 1000 simulated subjects including IIV and IOV

CONCLUSION

A one-compartment model with transit absorption taking into account concentration- and time-dependent auto-inhibition of linezolid elimination was successfully developed, describing linezolid population PK in MDR- and XDR-TB patients. This work proposes a MIPD approach for linezolid applicable from the first day of treatment, and suggests that a 600 mg QD regimen results in adequate efficacy and less safety concerns compared to the other studied regimens in most of the patients.

REFERENCES

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RESULTS

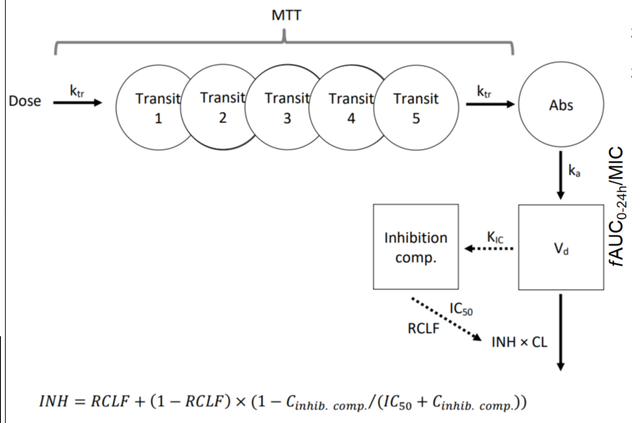

Figure 1. Schematic representation of the final linezolid population pharmacokinetic model

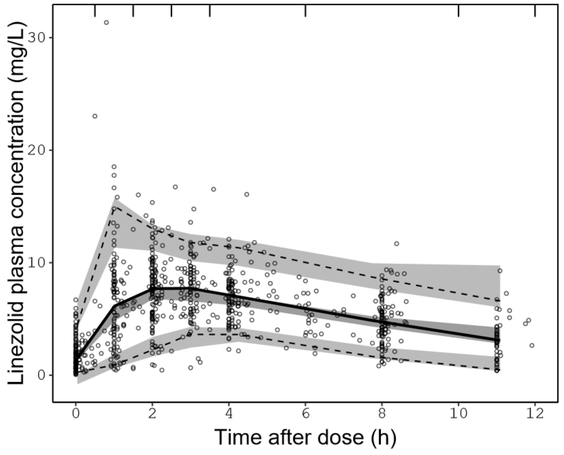

Figure 2. Prediction corrected visual predictive check (pcVPC) of the final linezolid population pharmacokinetic model

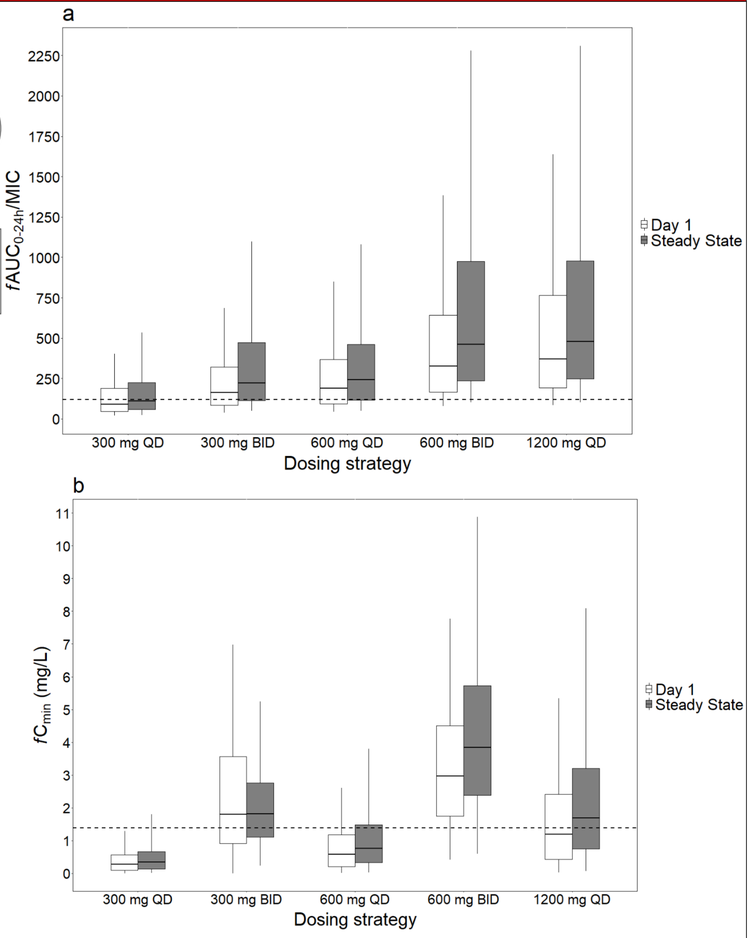

Figure 3. Predictions of distributions (n= 1000) of a) $fAUC_{0\text{-}24h}$/MIC b) fC_{min} based on the final linezolid population pharmacokinetic model for different dosing regimens

The black horizontal dashed lines represents the efficacy target of $fAUC_{0\text{-}24h}$/MIC of 119[2] (panel a) and the safety target of fC_{min} < 1.38 mg/L[5] (panel b)