The value of Model-based Therapeutic Drug Monitoring in Tuberculosis Treatment – Optimized Target for Rifampicin

UPPSALA UNIVERSITET

Robin Svensson[1], Katarina Niward[2,3], Lina Davies Forsman[4,5], Judith Bruchfeld[4,5], Jakob Paues[2,3], Thomas Schön[2,6] and Ulrika Simonsson[1]

[1]Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, [2]Department of Clinical and Experimental Medicine, Linköping University, Sweden [3]Department of Infectious Diseases, Linköping University, Sweden [4]Department of Medicine Solna, Unit of Infectious Diseases, Karolinska Institutet, Sweden [5]Department of Infectious Diseases, Karolinska University Hospital Solna, Stockholm, Sweden [6]Department of Clinical Microbiology and Infectious Diseases, Kalmar County Hospital, Sweden

Correspondance: robin.svensson@farmbio.uu.se, +46730 – 655 638

Introduction

Rifampicin acts as a cornerstone of tuberculosis (TB) treatment. Therapeutic drug monitoring (TDM) is becoming increasingly used for TB treatment. Bayesian model-based TDM is of benefit for rifampicin due to auto-induction and non-linear pharmacokinetics (PK) [1] where non-model-based TDM is sub-optimal.

A new optimized target for rifampicin is desperately needed since the common target of achieving C_{max} of ~8 mg/L is too low given recent data indicating that at doses up to 40 mg/kg of rifampicin were well tolerated [2].

Objective

This work evaluated a Bayesian model-based TDM approach for rifampicin accounting for the known auto-induction and dose non-linearity in bioavailability.

Methods

33 TB patients in Sweden were given rifampicin at 10 mg/kg as part of standard treatment. Rifampicin plasma concentrations were measured at pre-dose and following 2, 4 and 6 hours post-dose after 14 days of treatment and at pre-dose and at 2 hours at weeks 4 and 12. A new optimized TDM target for rifampicin of day 14 C_{max} of 35 mg/L was established using the observed geometric mean of day 14 C_{max} following 35 mg/kg rifampicin [2]. C_{max} was preferred over AUC as the target due to the post-antibiotic effect of rifampicin where C_{max} and not AUC will drive the antibiotic effect.

A Bayesian model-based TDM dose was derived for each patient by first using a previous rifampicin PK model accounting for non-linear PK of high dose rifampicin [1]. The model was used to obtain individual PK parameters for each patient through a Bayesian step using fixed and random parameters (Table 1) and observed data.

Secondly, the calculated individual PK parameters were used to predict the Bayesian model-based C_{max} at day 14 following higher doses of 15-50 mg/kg.rifampicin.

The highest dose not exceeding the TDM target of day 14 C_{max} of 35 mg/L were predicted for each patient.

Simulated C_{max} and $AUC_{0\text{-}24h}$ were summarized for each dose level and compared with literature values [2].

The analysis was carried out in NONMEM 7.3 [3] with the M3 method for samples below the limit of quantification (BLOQ).

Results

- 224 rifampicin concentrations from 33 patients were analysed (34.4% BLOQ).
- The model described the observed data well (Figure 1) suggesting that the appropriate model was used.
- The Bayesian model-derived TDM dose in this patient population ranged from 20-45 mg/kg (mode: 25 mg/kg, Table 2 and Figure 2) to meet the TDM target of 35 mg/L. 25 mg/kg is lower than the observed 35 mg/kg dose which is due to a higher CL in our patient population.
- The predicted C_{max} and $AUC_{0\text{-}24h}$ (Figures 3 and 4) agreed well with literature values [1, 2] which validated the PK model on an individual level.
- The predicted relative increase in $AUC_{0\text{-}24h}$ for 35 mg/kg compared with 10 mg/kg was 5.3 times higher (Figure 2) which is higher than to be expected under the assumption of linear PK which shows the need for model-based TDM compared to non-model-based TDM.

VPC of the PK model [1]

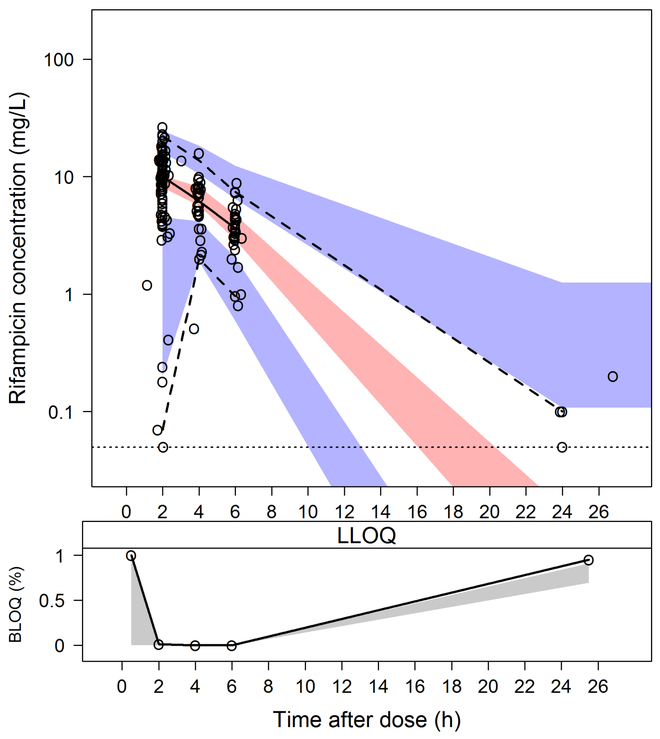

Figure 1 Visual predictive check of applied rifampicin PK model

Distribution of doses

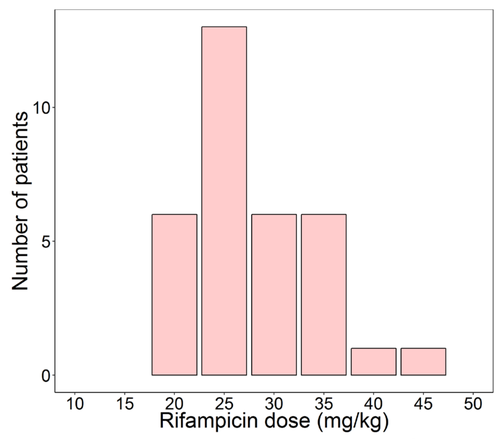

Figure 2 Distribution of maximal dose.

Predicted C_{max} for increasing rifampicin doses and potential new target

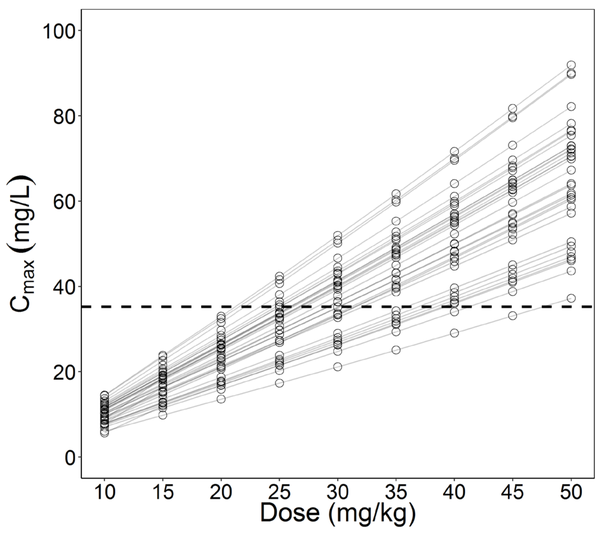

Figure 3 Individual predictions of C_{max}. Dashed line indicates 35 mg/L.

Predicted $AUC_{0\text{-}24h}$ for increasing rifampicin doses

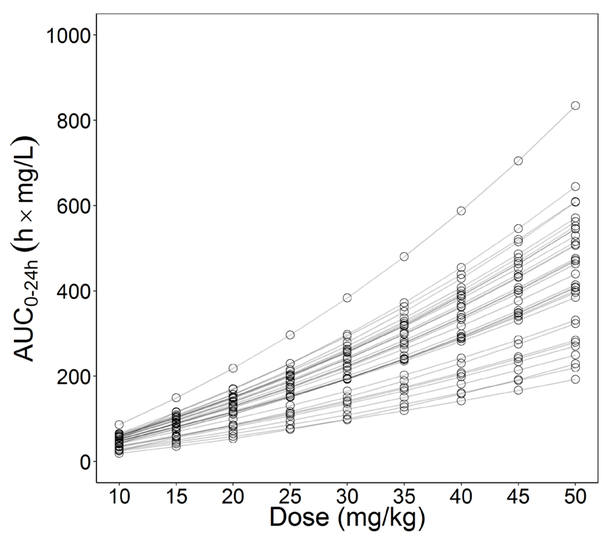

Figure 3 Individual predictions of $AUC_{0\text{-}24h}$.

Table 1 Model parameters from [1]

Parameter	Typical value	IIV (%CV)	IOV (%CV)
V_{max} (mg/h)	525	30.0	-
k_m (mg/L)	35.3	35.8	18.9
Corr V_{max}-k_m (%)	-	38.9	-
V (L/70 kg)	87.2	7.86	-
k_a (h^{-1})	1.77	33.8	31.4
E_{max}	1.16	-	-
EC_{50} (mg/L)	0.0699	-	-
k_{ENZ} (h^{-1})	0.00603	-	-
MTT (h)	0.513	38.2	56.4
NN	23.8	77.9	-
F	-	-	15.7
F_{max}	0.504	-	-
ED_{50} (mg)	67.0		
Prop error (%CV)	23.6	-	-

Table 2 Highest rifampicin dose to achieve C_{max} below 35 mg/L

Rifampicin dose	% of patients
10 mg/kg	0
15 mg/kg	0
20 mg/kg	18.2
25 mg/kg	39.4
30 mg/kg	18.2
35 mg/kg	18.2
40 mg/kg	3.03
45 mg/kg	3.03
50 mg/kg	0

Conclusion

Model-based TDM is warranted for dose optimization and personalised medicine for rifampicin due to its complex PK which makes predictions of individualized dosing impossible unless a model-based approach is used. This study shows that the applied PK model is optimal for TDM of rifampicin. Using a new optimized TDM target of day 14 C_{max} of 35 mg/L would lead to a dose with the potential of being safe and with optimized effect on an individual patient level.

References

[1] Svensson RJ, Aarnoutse RE, Diacon AH, Dawson R, Gillespie SH, Boeree MJ & Simonsson USH. A population pharmacokinetic model incorporating saturable pharmacokinetics and autoinduction for high rifampicin doses. Clin Pharmacol Ther 2017. doi: 10.1002/cpt.778

[2] Boeree MJ, Diacon AH, Dawson R, Narunsky K, du Bois J, Venter A, Phillips PPJ, Gillespie SH, McHugh TD, Hoelscher M, Heinrich N, Rehal S, van Soolingen D, van Ingen J, Magis-Escurra C, Bruger D, Plemper van Balen G & Aarnoutse RE. A dose ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. Am J Respir Crit Care Med 2015. 191(9): 1058-1065.

[3] Beal S, Sheiner LB, Boeckmann A & Bauer RJ. NONMEM Users Guides. 1989-2013. Icon Development Solutions, Ellicott City, Maryland, USA.