Semi-mechanistic pharmacokinetic-pharmacodynamic modeling of rifampicin treatment response in tuberculosis acute mouse model

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Objectives

Rifampicin is one of four drugs taken as part of a standard treatment regimen for tuberculosis. The aim was to build a semi-mechanistic pharmacokinetic-pharmacodynamic (PKPD) model of rifampicin in tuberculosis acute mouse model.

Methods

Rifampicin blood concentrations after different single oral doses (1, 3, 10, 30 or 100 mg/kg), single intravenous (12 mg/kg) and multiple oral administrations (10 mg/kg for 3 days) were used in the population PK analysis. One sample from each healthy mouse (n=30) after single dosing administration and several samples from each healthy mouse (n=3) were available from multiple dosing administrations.

C57BL/6 mice (n=60) were intratracheally infected with Mycobacterium tuberculosis H37Rv at day 0[1]. Rifampicin (1, 3, 26, 30 or 98 mg/kg) was administered daily by oral gavage during day 1 to day 8. Fifteen mice received no treatment (natural-growth). Rifampicin treated and non-treated mice were sacrificed at days 2, 3, 4 and 9 and at days 1, 9 and 18, respectively. The lungs were obtained, homogenized and plated to measure the colony-forming units (CFU). All modeling were done using NONMEM, version 7.2 [2, 3] . In order to account for PD data below limit of quantification, the M3 method was used. Xpose was used for data exploration and visualization, model diagnostics and model comparison[4]. PsN[5] was used for prediction-corrected visual predictive check (pcVPC) of models.

Results and Discussion

A one compartment model with first-order absorption and elimination provided the best fit to the PK data. The volume of distribution was significantly higher for the lowest oral dose (1 mg/kg). Inter-animal variability (IIV) in absorption rate constant (ka) and clearance (CL) was estimated to 43.8% and 18.9%, respectively. The bioavailability was estimated to 67.6% (Table 1). The pred-corrected VPC is shown in (Figure 1).

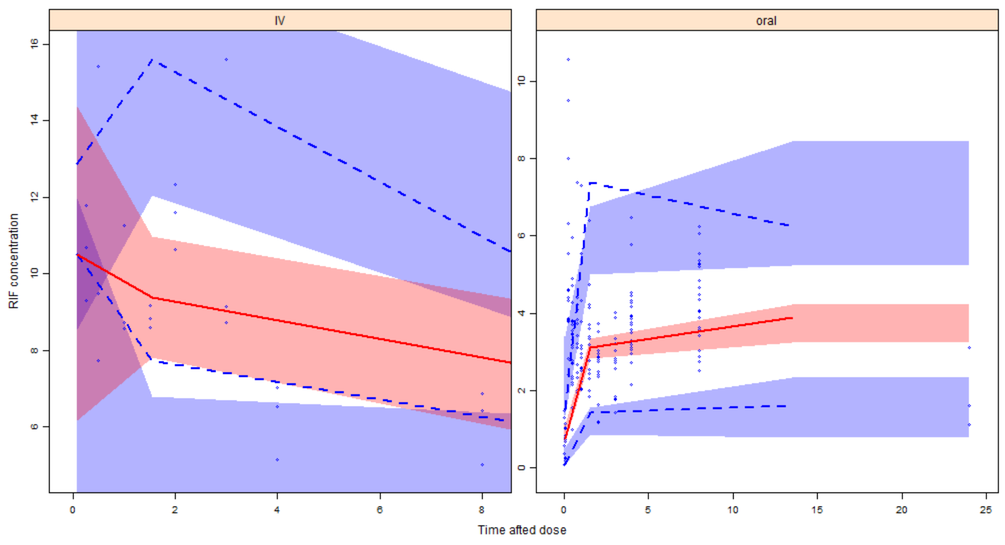

Figure 1. pcVPC of the mouse rifampicin POPPK model. Blue circles – pred-corr observations; red solid line – median of the observations; red dotted lines – 5th and 95th percentile of the observed data; blue shaded areas- 95% confidence intervals for the 5th percentile and 95th percentiles of simulated data; pink shaded area – 95% confidence interval for the median of the simulated data.

The PD model consisted of fast-multiplying bacteria, slow-multiplying bacteria, non-multiplying bacteria and dead bacteria (Figure 2). The drug effect was incorporated as inhibition on growth rate and stimulation of death rate of fast-multiplying and slow-multiplying bacteria (Table 2). The final PKPD described the data well (Figure 3).

PK Parameters	Typical values	RSE (%)
CL (h^{-1})	99.5	8
V (ml)	1180	4
k_a (h^{-1})	0.938	14
V at 1 mg/kg (ml)	2260	9
F (%)	0.67	6
IIV on k_a (%)	43.5	26
IIV on CL (%)	8.8	48
Prop residual error (%)	0.284	9

Table 1. Final PK parameter estimates

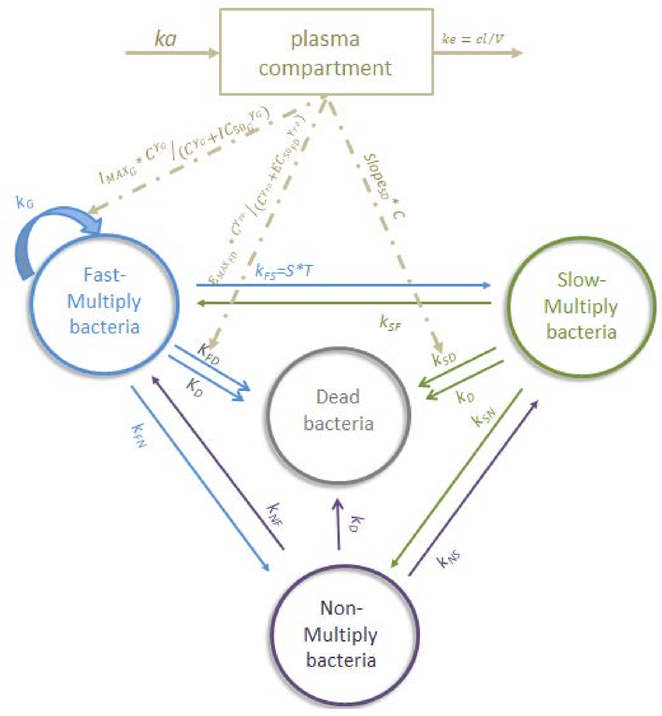

Figure 2. Final PKPD model

PD Parameters	Typical values	2.5% CI	97.5% CI
Inoculum for drug treated mice (CFU/ml)	51648	47236	58373
Inoculum for no drug (CFU/ml)	8525	6961	9813
k_G (h^{-1})	0.034	0.033	0.036
k_D (h^{-1})	0.000001 FIX	-	-
S (h^{-1})	7.8E-05	7.1E-05	8.6E-05
k_{SF} (h^{-1})	0.036	0.032	0.040
k_{SN} (h^{-1})	0.0052	0.0048	0.0057
k_{NS} (h^{-1})	0.19	0.15	0.22
k_{FN} (h^{-1})	9.9E-07	8.8E-07	1.0E-06
k_{NF} (h^{-1})	0 FIX	-	-
γ_G	0.47	0.41	0.57
I_{MAX_G}	0.75	0.73	0.77
IC_{50_G} (ug/ml)	0.56	0.49	0.64
γ_{FD}	2.53	2.32	2.65
$E_{MAX_{FD}}$	0.47	0.43	0.54
$EC_{50_{FD}}$ (ug/ml)	9.97	9.15	11.18
$Slope_{SD}$ (ml/h*ug)	8.4E-04	7.8E-04	9.4E-04
IIV on Inoculum for drug treated mice (%)	42.3	38.9	45.1
Additive residual error on ln scale	0.32	0.28	0.51

Table 2. Final PD parameter estimates

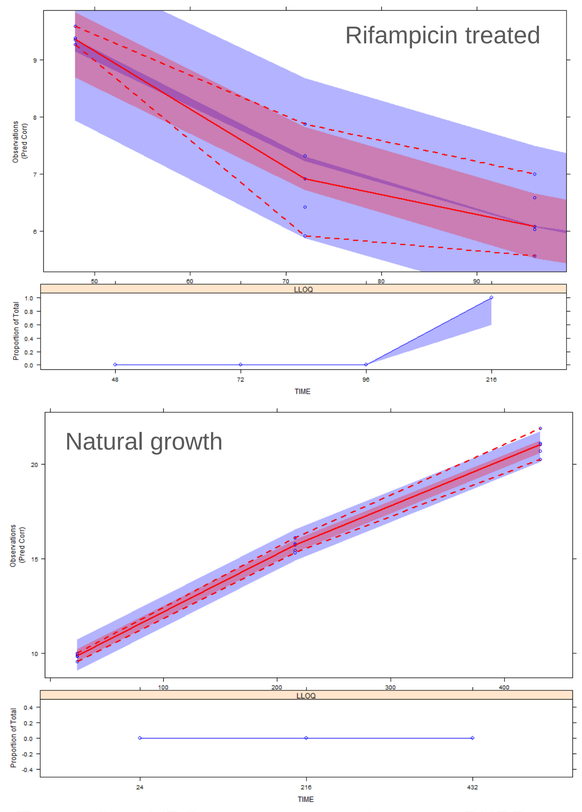

Figure 3. pcVPC of the mouse rifampicin PKPD model. Blue dots–observations; red line– median of the pred-corr observations; Red dotted lines – 5th and 95th percentile of the observed data; blue shaded areas- 95% confidence intervals for the 5th percentile and 95th percentiles of simulated data; pink shaded area – 95% confidence interval for the median of the simulated data. Blue solid line in lower plots-median of LOQ data, blue shaded area in lower plots-95% confidence intervals for median of LOQ data

Conclusions

The semi-mechanistic PKPD model captured well the bi-exponential decline in CFU and was able to link drug effect in a mechanistic way to sub-states of *M. tuberculosis*.

References

[1] Rullas J, García JI, Beltrán M, Cardona PJ, Cáceres N, García-Bustos JF, Angulo-Barturen I. Fast standardized therapeutic-efficacy assay for drug discovery against tuberculosis. Antimicrob Agents Chemother. 2010 May;54(5):2262-4

[2] Beal, S., Sheiner, L.B., Boeckmann, A., & Bauer, R.J., NONMEM User's Guides. (1989-2009)

[3] Icon Development Solutions, Ellicott City, MD, USA, 2009

[4] Jonsson EN, Karlsson MO. Xpose - an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comput Methods Programs Biomed. Jan 1999;58(1):51-64

[5] Lindbom L, Pihlgren P, Jonsson EN. PsN-Toolkit - a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. Sep 2005;79(3):241-257

Ethics

All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EU and the GSK Policy on the Care, Welfare and Treatment of Animals.

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