Design optimization for characterization of rifampicin pharmacokinetics in mouse

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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 develop a population pharmacokinetic (POPPK) model for rifampicin in an acute mouse model and to optimize pharmacokinetic sampling schedule for rifampicin oral administration with 5 different dosing levels.

Methods

Rifampicin blood concentrations after different single oral doses, single intravenous and multiple oral administrations[1] were used in the POPPK analysis. One sample from each mouse after single dosing administration and several samples from each mouse after multiple dosing administrations were available. All modeling were done using NONMEM 7.2. Model development was based on goodness of fit plots, objective function value, scientific plausibility, parameters precision and predictive performance, assessed using prediction-corrected Visual Predictive Check (pcVPC).

In order to search for an informative design using potentially less animals, a Stochastic Simulation and Estimation (SSE) approach was utilized using the final POPPK model with 1000 replicates for each scenario. The different scenarios for a naïve pooling approach using single sample data included extending the sampling to 24 hours post-dose and varying the total number of animals (obs/time point). For a nlme approach, number of samples per animal (1-3 samples) were also evaluated. A zipper design were utilized 1-3 samples/animal, but at the same time always collecting samples from at least one animal at 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 8 and 24 hrs post-dose. The imprecision and bias of the simulation results were thereafter judged.

Results and Discussion

A one compartment model with first-order absorption and elimination provided the best fit to the data (Figure 1). The volume of distribution was significantly lower for the lowest oral dose (10.2 mg/kg). Inter-individual variability (IIV) in absorption rate constant (ka) and clearance (CL) were estimated to 41% and 20.5%, respectively.

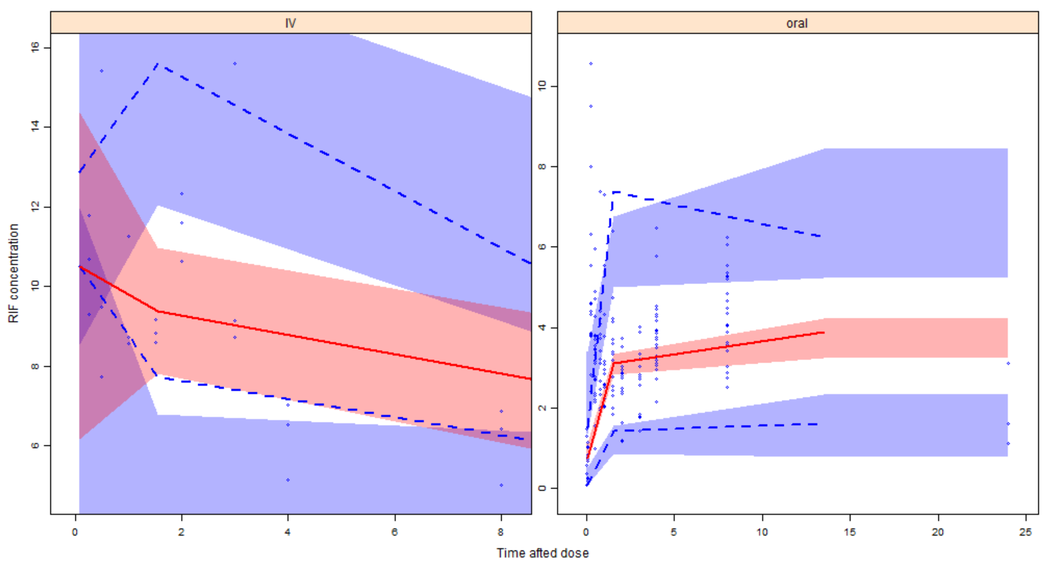

Figure 1. Pred-corrected VPC of the mouse rifampicin POPPK model. Blue circles – observations; red solid line – median of the observations; red dotted lines – 5th and 95th percentile of the observed data; Blue shaded areas- 95% confidence intervals for the 5th percentile and 95th percentiles of simulated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

Bias and imprecision in CL for 3 obs/ time point using naïve pooling approach were 94% and 60% lower, respectively when adding a 24 hr sample (Figure 2).

Using nlme approach, imprecision in all parameters decreased with increasing total number of animals. The imprecision in CL was not affect by the number of samples/animal. Bias in CL was not dependent on number of samples/animal but increased with increasing sample sizes although the bias was generally very low (Figure 3).

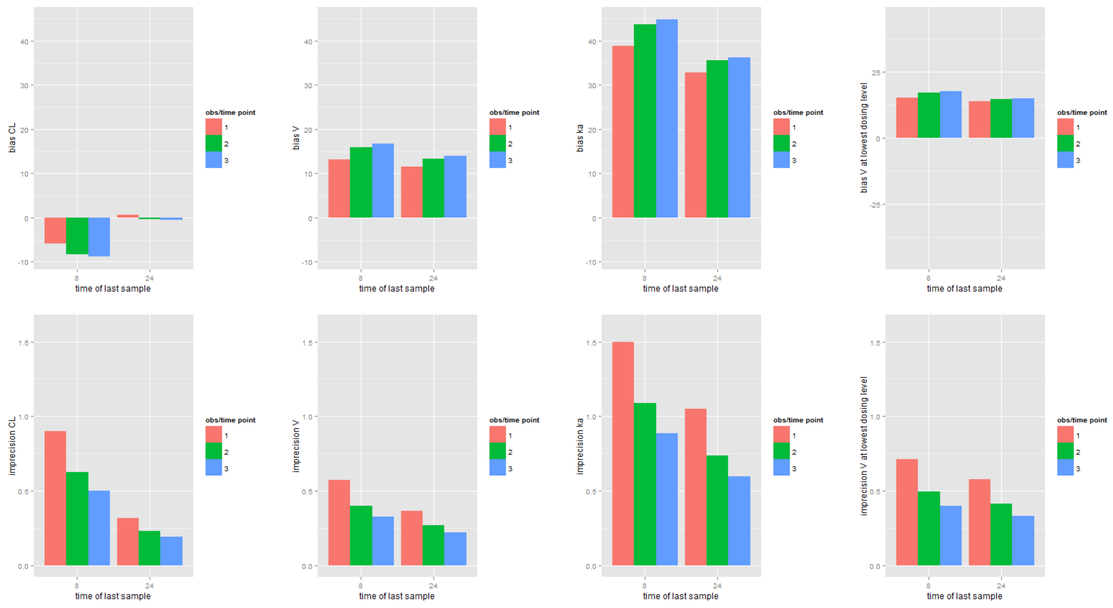

Figure 2. Naïve pooling SSE results with adding one sample at 24 hours and last sample at 8 hours for different total number of animals. Sample sizes are given in Table 1.

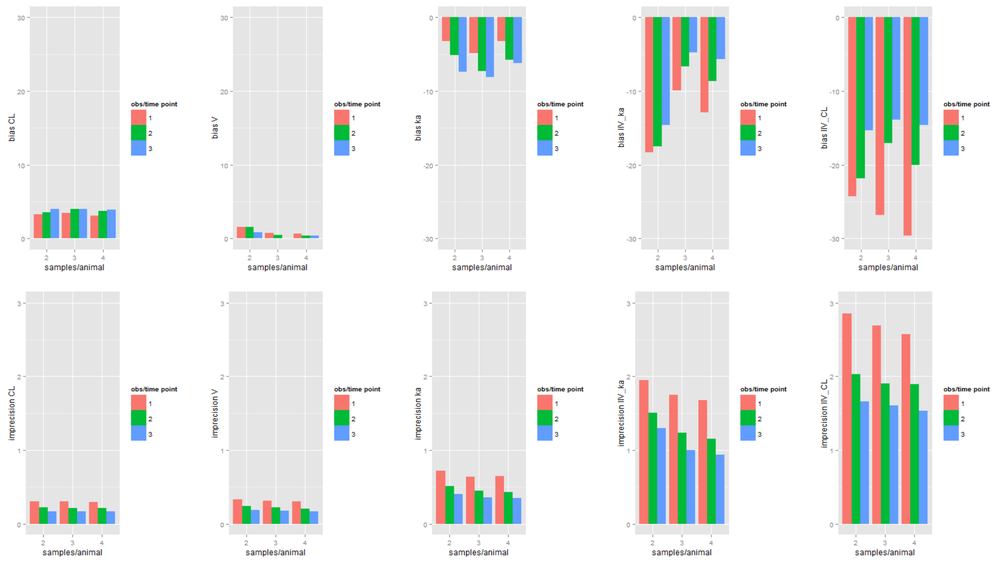

Figure 3. Nonlinear mixed effect approach SSE results for different numbers of samples in each animal (2, 3 and 4 samples) and numbers of observations per time point (1, 2 and 3 observations). Sample sizes are given in Table 1.

Obs / time points	Time of last samples: 8 hrs	Time of last samples: 24 hrs
1	50	55
2	100	110
3	150	165

Obs per time point	Samples / animal: 2	3	4
1	**30**	**20**	**15**
2	**60**	**40**	**30**
3	**90**	**60**	**45**

Table 1. Sample sizes for naïve pooling (left table) and nlme approach (right table)

Conclusions

A linear one compartment model with first–order absorption and elimination and dose nonlinearity in V provided the best fit to the data. With a zipper design of 2 observations per time point and 4 samples per animal (sample size=30), typical values of CL and IIV in CL were well predicted. A zipper design allows for an informative design but still few samples per animal and small total sample sizes.

Ethics

All animal studies were ethically reviewed and carried out in accordance with European Directive 86/609/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals.

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[1]GSK kindly provided rifampicin pharmacokinetic data