A population pharmacokinetic-enzyme model for rifampicin autoinduction and bimodal absorption in pulmonary tuberculosis patients

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Background and Objectives

Unexplained variability in the drug pharmacokinetics of rifampicin (RIF), a crucial component of antimycobacterial drug therapy, has been reported in tuberculosis patients.[1] Autoinduction is one potential source of variability.[2-4]

This study was designed to describe the pharmacokinetics of RIF in South African pulmonary tuberculosis patients on daily treatment with a standard RIF-containing drug regimen, using nonlinear mixed-effects modeling. In addition, the pharmacokinetic model was built to describe the auto-induction of metabolism as well as the interoccasional variability in the drug's pharmacokinetic properties.

Methods

Data was collected from three patient populations (Table 1) in which all patients had been on a RIF-containing regimen for at least 10 days prior to enrolment in the study. All patients received treatment on Monday-Friday with drug holidays over the weekends, the standard therapy in South Africa. RIF plasma concentration-time data were analyzed with nonlinear mixed effects modelling using NONMEM (version V and VI).[5] One- and two-compartment models with first-order linear elimination and zero-order and first-order absorption were fitted to the data. Interindividual variability and interoccasional variability were expressed by exponential variables. Residual variability was described using additive and constant coefficient of variation parameters. The first-order estimation (FO), first-order conditional estimation (FOCE), and FOCE with interaction were tested for the estimation of population pharmacokinetic parameters, interindividual and interoccasional variability in these parameters, and residual variability between observed and predicted plasma concentrations.

A mechanistic model implementing enzyme turnover[6] was constructed to address autoinduction of RIF metabolism. An empirical model implementing a time-dependent nonlinear increase in oral clearance relative to an uninduced baseline value and a fully-induced value was also attempted. In addition, a mixture model comprising two subpopulations with variant absorption rate constants was also evaluated as well as an enterohepatic submodel.

Model selection was achieved by comparison of the change in objective function values between hierarchical models as well as by examination of goodness-of-fit plots and examination of relative standard error (RSE) values.

Table 1. Patient datasets.

Subset	Study Design	*n*	Sampling
1	450-600 mg rifampicin given concurrently with isoniazid and (in some subjects) pyrazinamide and ethambutol. Predominantly fixed-dose combinations (FDCs).	91	3 samples per occasion, at random times between 0 – 12 h post-dose, for a total of 4 occasions spread over 10 days.
2	Series of 3 bioequivalence studies of FDC formulations containing 600mg rifampicin as well as isoniazid and (in some subjects) pyrazinamide.	30	Full pharmacokinetic profiles (at pre-dose and 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0 h post-dose) on 2-4 occasions over 6 weeks.
3	450-600mg rifampicin given concurrently with isoniazid, pyrazinamide and (in some subjects) ethambutol. FDCs and single-drug formulations.	144	Full pharmacokinetic profile (at pre-dose and 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0 h post-dose).

Results

The pooled patient RIF plasma concentration-time data were best described by a mechanistic enzyme pool model, implemented in NONMEM's ADVAN9 subroutine, using the FO estimation method. In the model, the enzyme formation is linearly (SL_{RIF}) dependent on the plasma drug concentration while the enzyme level regulates the drug's clearance. The model was parameterized in terms of oral clearance (CL/F_{drug}), volume of distribution of the central compartment (V_c/F_{drug}), absorption rate constant (k_a), and duration of a zero order absorption input (D). The baseline enzyme level (F_{enz}) and the drug bioavailability (F_{drug}) were fixed to unity. To account for different pre-induced enzymatic levels between patients, interindividual variability (IIV) in the baseline enzyme level was incorporated. Interoccasional variability (IOV) in drug bioavailability was incorporated. A mixture submodel, describing two subpopulations with an almost four-fold difference in absorption rate constant, was included. Equations (1)-(3) describe the final model.

In equation (1), describing the rate of change of drug amount in the absorption compartment, t is time (h) since dose administration, A_1 is the amount of rifampicin (mg) in the absorption compartment at a given value of t, D is the duration of zero order absorption input (h), Dose is the RIF dose (mg), and $k_{a,fast}$ is the absorption rate constant, assumed to be a fast absorber (h^{-1}). In equation (2), describing the rate of change of drug amount in the central compartment, A_2 is the amount of drug (mg) in the central compartment at time t, CL is clearance, V_c is volume of distribution, and A_{enz} is the amount of enzyme in the pool. In equation (3), which describes the rate of change of enzyme, k_{enzi} is the rate constant for first-order degradation of the enzyme (h^{-1}), and SL_{RIF} is the slope of the linear function describing enzyme induction by RIF. IIV was included in CL/F, V_c/F, k_{enz}, $k_{a,fast}$, F_{enz} and D, and F_{drug} variability was split into IIV and IOV; variability terms were not included in equations for space reasons.

$$\frac{dA_1}{dt} = \frac{Dose}{D} - k_{a,fast} \cdot A_1 \quad (1)$$

$$\frac{dA_2}{dt} = k_{a,fast} \cdot A_1 - \left(\frac{CL}{V_c}\right) \cdot A_2 \cdot A_{enz} \quad (2)$$

$$\frac{dA_{enz}}{dt} = k_{enz} \cdot \left[1 + SL_{RIF} \cdot \frac{A_2}{V_c}\right] - k_{enz} \cdot A_{enz} \quad (3)$$

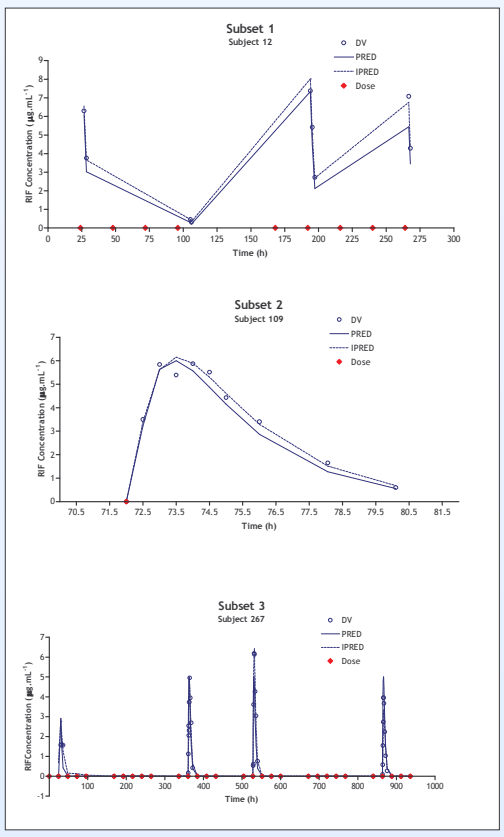

Figure 1. Representative individual plasma rifampicin concentration versus time plots. DV=observed concentration; PRED= typical predicted concentration; IPRED= individual predicted concentration.

Table 2. Final parameter estimates.

Parameter	Estimate	%CV
Oral clearance (CL/F, mg.L^{-1})	6.4	18.4
Apparent volume of distribution (V_c/F, L)	50.4	4.74
Absorption rate constant (fast absorbers, $(k_a)_{fast}$, h^{-1})	1.69	3.39
Absorption rate constant (delayed absorbers, $(k_a)_{slow}$, h^{-1})	0.447	3.31
Duration of zero-order absorption input (D, h)	0.409	2.67
Slope of the linear function describing enzyme induction by rifampicin (SL_{RIF})	1.88	24.6
Elimination rate constant of enzyme (k_{enz}, h^{-1})	0.0246	9.35
Fraction of smooth absorbers (P_{abs})	0.509	8.04
Interindividual Variability (IIV)		
Oral clearance (CL/F)	0.481	17.5
Apparent volume of distribution (V_c/F)	2.49x10^{-4}	12 972
First-order absorption rate constant, fast absorbers, $(k_a)_{fast}$)	2.57	22.4
Duration of zero-order absorption input (D)	2.13	18.8
Enzyme level at baseline (F_{enz})	33.7	104.2
Drug bioavailability (F_{drug})	0.0992	47.7
Elimination rate constant of enzyme (k_{enz})	1.46	43.5
Interoccasional Variability (IOV)		
Drug bioavailability (F_{drug})	0.199	16.4
Residual variability		
Additive (ε_{add})	0.180	3.35
Constant coefficient of variability (ε_{ccv})	0.263	4.75

Discussion and Conclusions

This is the first study to describe the population pharmacokinetics of rifampicin based upon data collected from South African pulmonary tuberculosis patients as well as the known physiological characteristics describing ß-esterase autoinduction by the drug. We have, further, characterised the existence of two distinct subpopulations of subjects with vastly differing absorption profiles.

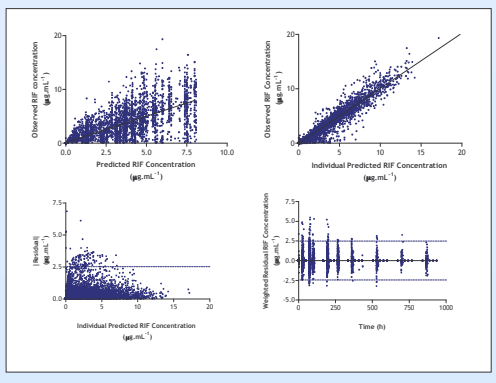

Figure 2. Goodness-of fit plots.

Rifampicin is an extremely effective weapon in the treatment of tuberculosis. However, its highly variable pharmacokinetics may affect clinical outcomes, which in a tuberculosis-endemic region like sub-Saharan Africa is a very serious problem. Further research should address the influence of covariate relations on rifampicin pharmacokinetics in tuberculosis patients.

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