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Semi-Mechanistic pharmacokinetic enzyme model for the characterisation of rifampicin pharmacokinetics in South African pulmonary tuberculosis infected adults

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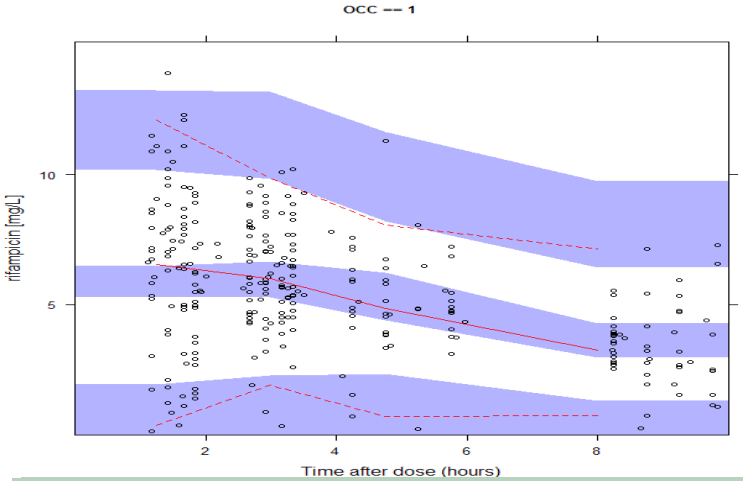
Background and Objectives

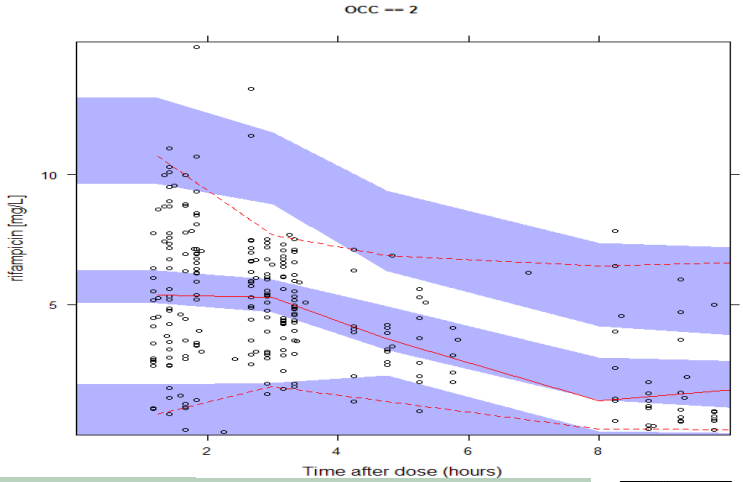
The treatment of *Mycobacterium Tuberculosis* requires the use of multiple drug containing regimens where rifampicin (RIF) is used as part of the first line regimens. RIF is known to have highly variable absorption (Peloquin *et al*. 1997, Wilkins *et al*. 2008) and to induce its own metabolism (Loos *et al*. 1987). These characteristics, coupled with potential drug-drug interactions and low RIF concentrations (Mitchison 2000), may increase the likelihood of treatment failure and the emergence of drug resistance. The primary objective of this pharmacokinetic analysis was to determine the population pharmacokinetics of rifampicin at pre-induced and fully auto-induced state (steady-state) amongst African patients with pulmonary tuberculosis using nonlinear mixed-effects modelling.

Methods and Materials

Pulmonary tuberculosis infected adult patients (n = 101) received once daily doses of either 450 mg (below 50 kg) or 600 mg (above 50 kg) of rifampicin together with isoniazid, pyrazinamide and ethambutol for 6 days of the week. Three blood samples per patient were taken after the first dose (pre-induction) and repeated after approximately 28 days (steady state). A semi-mechanistic pharmacokinetic model (Figure 1) incorporating an enzyme turn over model to address rifampicin auto-inductive properties, together with a multiple dosing transit absorption compartment model to describe the drugs highly variable absorption was developed using the first order conditional method in NONMEM. The enzyme turn-over half-life was fixed to approximately 24 hours (k_{ENZ} fixed to 0.029 h^{-1}) reaching steady state in approximately 1 week (Fromm *et al*. 1996).

Figure 2 : Visual predictive check:
(OCC ==1 = pre-induction, OCC== 2 = induction at steady-state) n = 101





Results

CL/F was predicted approximately 2.5 fold higher at the fully induced state compared to the pre-induced state (Table 1). RIF appeared as potent inducer with an estimated EC_{50} of 0.329 mg/L. The model predicted RIF pharmacokinetics both pre-induced and induced states adequately (Figure 2).

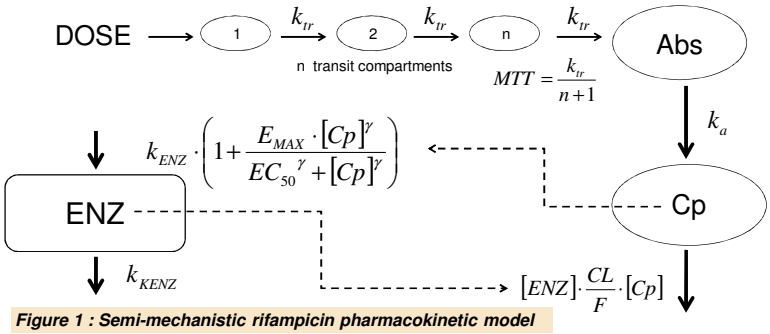


Figure 1 : Semi-mechanistic rifampicin pharmacokinetic model

Parameter	Estimate	RSE %	IIV	RSE %
Oral clearance (CL/F, L/h)	5.28	22.3	-	-
E_{MAX}	2.62	39.3	-	-
EC_{50} (mg/L)	0. 329	26.6	-	-
HILL coefficient	7.22	20.9	-	-
Apparent volume of distribution (V/F, L)	84.9	4.8	-	-
Absorption rate constant (k_a, h^{-1})	6.56	138	-	-
Number of transit compartments (n)	10.3	135	-	-
Enzyme elimination rate constant (k_{ENZ}, h^{-1})	0.029 FIX	-	-	-
Bioavailability (F)	1 FIX	-	0.24	24
Mean transit time (MTT, h)	0.725	35	0.37	98
Additive residual variability (mg/L)	1.97	4.4	-	-
Proportional residual variability (%)	0.0321	498	-	-

Table 1 : Final parameter estimates ***(RSE % = percentage relative standard error)***
(IIV = inter-individual variability)

Conclusion

The developed semi-mechanistic model describing the pharmacokinetics of rifampicin at pre-induced and induced states will be extended to investigate potential drug-drug interactions seen between rifampicin and the other drug components of the anti-tuberculosis regimens.

References

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