A Semi-Mechanistic pharmacokinetic auto-induction model for the characterisation of rifampicin pharmacokinetics in African pulmonary tuberculosis infected adults

Wynand Smythe [1], Helen McIlleron [1], Corinne Merle [2], John Horton [3], Peter Smith [1], and Ulrika SH Simonsson [4]

1 Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa
2 Department of Epidemiology & Population Health, Tropical Epidemiological Group, London School of Hygiene & Tropical Medicine, United Kingdom
3 Tropical Projects, Hitchin, United Kingdom
4 Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Background and Objectives

Rifampicin (RIF) is known to have highly variable absorption [1, 2] and to induce its own metabolism (auto-induction) [3]. These characteristics result in low RIF concentrations in many patients, and may increase the likelihood of treatment failure and emergent drug resistance. The primary objective of this pharmacokinetic analysis was to determine the population pharmacokinetics of RIF at pre-induced and fully auto-induced states amongst African patients with pulmonary tuberculosis using mixed-effects modelling.

Methods

Adults (n=173) with pulmonary tuberculosis received once daily doses of either 450 mg (below 50 kg) or 600 mg (above 50 kg) of RIF 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 sampling was repeated after approximately 28 days (steady state) yielding a total of 998 plasma RIF concentrations. A semi-mechanistic pharmacokinetic model incorporating an enzyme turn over model to address RIF's auto-inductive properties, together with a multiple dosing transit absorption compartment model to describe the drug's highly variable absorption was developed using the first order conditional method with interaction in NONMEM (*Figure 1*).

Results

RIF displayed strong auto-induction properties with an estimated E_{MAX} of 6.18 and an EC_{50} of 5.09 mg*L^{-1} (*Table 1*). The model estimated un-induced CL/F at 5.32 ± 0.33 L*h^{-1}. k_A was set equal to k_{TR} (-36 in OFV), hence RIF absorption was characterized in terms of a mean transit time (MTT). As samples were collected only at pre- and post-induced occasions, the auto-induction turn-over half-life was fixed to approximately 24 hours (k_E fixed to 0.029 h^{-1}) reaching steady state in approximately 1 week [4]. Based on the VPC stratified by occasion (*Figure 2*), the model adequately predicted rifampicin pharmacokinetics both at the pre-induced and induced state.

Parameter	Estimate	RSE (%)	IIV (%)	RSE (%)	IOV (%)	RSE (%)
CL/F (L*h^{-1})	5.32	6.4	32.7	19.9	-	-
V/F (L)	68.4	2.5	24.1	13.0	-	-
Correlation (CL-V)	0.883	14.1			-	-
MTT (h)	1.37	2.5	54.6	15.3	-	-
EC_{50} (mg*L^{-1})	5.09	29.5	74.8	65.1	-	-
E_{MAX}	6.18	11.1	-	-	-	-
F	1 FIX	-	-	-	23.0	7.1
k_E (h^{-1})	0.029 FIX	-	-	-	-	-
NN	1 FIX	-	-	-	-	-
Additive residual error (mg*L^{-1})	1.37	2.5	-	-	-	-
Proportional residual error	0.0448	31.9	-	-	-	-

Table 1. *Parameter estimates for the RIF population PK model. Inter-individual varability (IIV) and inter-occasiotional varability (IOV) together with paramter estimates are summarized above with corresponding percentage relative standard error (%RSE).*

RIF Population PK Model

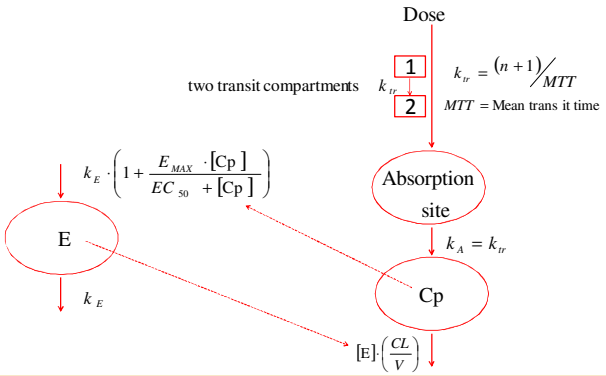

Figure 1. *RIF Population PK model with a transit absorption compartment model in order to describe the variable absorption together with an enzyme (E) compartment to describe single dose (Day 1 on occasion 1) and steady state pharmacokinetics (≈ Day 28 on occasion 2) observed following multiple RIF dosing.*

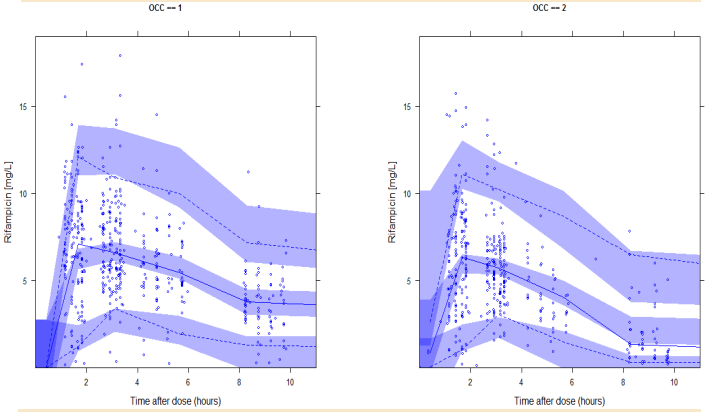

Figure 2. *A visual predictive check (VPC) stratified by occasion. The solid and dashed lines are the median, 5th and 95th percentiles of the observed data respectively. The shaded areas are the 95% confidence intervals for percentiles of simulated data. Blue circles represent the raw data.*

Conclusions

The 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 RIF and the other drug components of the anti-tuberculosis regimens.

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