Effect of Various Meals on the Population Pharmacokinetics of Rifapentine

SP Zvada[1], JS Van Der Walt[1,2], PJ Smith[1], P B Fourie[3], G Roscigno[4], D Mitchison[5], USH Simonsson[2], HM McIlleron[1]

1 Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa, 2 Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden, 3 Medicine in Need South Africa, Pretoria, South Africa, 4 Foundation for Innovative New Diagnostics, Geneva, Switzerland, 5 St. George's Hospital Medical School, London, United Kingdom

Background and Objectives

Experimental murine studies have shown dose dependant activity of rifapentine (RFP) against *Mycobacterium tuberculosis* [1]. In humans, administration of RFP after a high-fat meal increased RFP bioavailability by 50% [2]. The objective of this study was to describe the population pharmacokinetics (PK) of RFP and its active metabolite, 25-desacetyl rifapentine (25-DRFP), in the fasting and fed states.

Methods

Thirty-five male healthy volunteers were enrolled in an open-label, randomized, sequential, five-way crossover study. Participants received a single 900 mg dose of RFP after meals with high fat (meal A), bulk and low fat (meal B), bulk and high fat (meal C), high fluid and low fat (meal D) content, or with 200 mL of water (meal E). Venous blood samples were collected 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 36, 48, 72 h after the dose. Plasma concentrations of RFP and 25- DRFP were determined using a validated high-performance liquid chromatography (HPLC) method [3]. Concentration-time data for RFP and 25-DRFP were analysed in an integrated model using nonlinear mixed-effect modeling in NONMEM IV version 2 (FOCE INTER). First the RFP model was developed. A time-varying clearance was implemented using a step-function (Eq. 1). The fixed and random effects estimates of oral clearance (CL/F), volume of distribution (V/F), first-order absorption rate constant (k_a), mean transit time (MTT), oral bioavailability (F) and number of hypothetical transit compartments (NN) were fixed and the 25-DRFP model was developed using all data assuming RFP was completely metabolized to 25-DRFP. Interindividual (IIV) and interoccasional (IOV) variability were described using an exponential model.

Results

The population PK of RFP were best described by a one-compartment model with first order absorption rate constant and time-varying clearance. Absorption delay was described using hypothetical transit compartments. 25-DRFP data were described by a two-compartment model with time-varying clearance (Figure 1 and Figure 2). Meal effects were investigated as categorical covariates and were found to be significant on the oral bioavailability (Table 1). Similar trends were observed for 25-DRFP. Meal A had the greatest effect on RFP oral bioavailability, increasing it by 86% relative to fasting condition. Meals B, C and D gave 33%, 46%, and 49% increases in RFP oral bioavailability, respectively.

Parameter	Typical value	%RSE	IIV (%CV)	%RSE	IOV (%CV)	%RSE
Rifapentine						
CL/F (L/h) before MTIME	2.14	13.6	0.0367 (19%)	48.5	0.015 (12%)	18.1
CL/F (L/h) after MTIME	3.22	11.9	0.0367 (19%)	48.5	0.015 (12%)	18.1
MTIME (h)	43	2.6	-	-	-	-
V/F (L)	60.6	9.2	-	-	-	-
F	1 (fixed)	-	0.0458 (21%)	70.5	0.0586 (24%)	26.8
k_a (/h)	1.66	13.1	-	-	-	-
MTT(h)	1.45	10.8	0.0090 (10%)	174	0.0839 (29%)	33.1
NN	10.9	9.6	-	-	-	-
Additive error (mg/L)	0.206	12.3	-	-	-	-
Proportional error (%)	10.6	1.8	-	-	-	-
25-Decyatyl rifapentine						
CL/F (L/h) before MTIME	1.81	8. 7	0.0569 (24%)	24	0.0912 (30%)	10.6
CL/F (L/h) after MTIME	4.63	8.1	0.0569 (24%)	24	0.912(30%)	10.6
MTIME (h)	46.8	0.3	-	-	-	-
Central volume V/F (L)	6.52	5.8	-	-	-	-
Peripheral volume (V/F (L)	22.1	4.8	-	-	-	-
Q (L/h)	4.4	6.9	-	-	-	-
Additive error (mg/L)	0.211	9.7	-	-	-	-
Proportional error (%)	19.1	0.70	-	-	-	-

Table 1. *Final parameter estimates for rifapentine and 25-desacetyl rifapentine.*

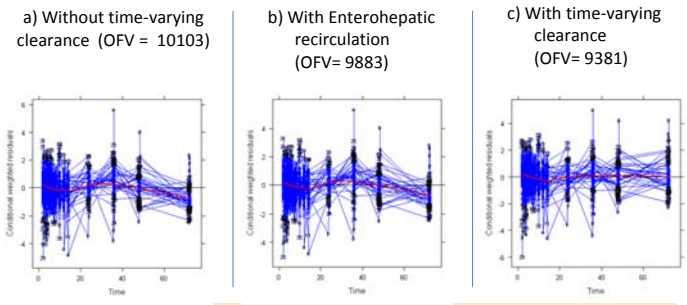

Figure 1. *The Conditional weighted residual plot parent-metabolite model a) without time-varying clearance, b) incorporating enterohepatic recirculation, and c) time-varying clearance .*

Equation 1:

$$CL_i = TV(\frac{CL_1}{F}).\exp\left(\eta_{i_{.}}^{\frac{CL_1}{F}} + \kappa_i^{\frac{CL_1}{F}}\right).(1 - mpast(i)) + TV(\frac{CL_2}{F}).\exp\left(\eta_i^{\frac{CL_2}{F}} + \kappa_i^{\frac{CL_2}{F}}\right).mpast(i)$$

Where CL_i the oral clearance for the i^{th} individual, $TV(CL_1/F)$ is the typical oral clearance which later changes to $TV(CL_2/F)$ at model event time (MTIME), $mpast(i)$ remains zero until MTIME when it changes to 1, η_i represents IIV and κ_i represents IOV.

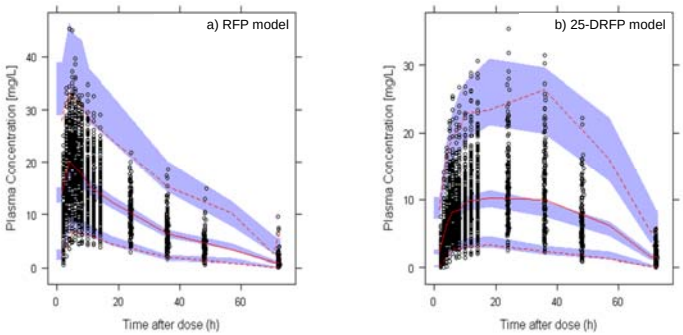

Figure 2. *Visual Predictive Check for the final a) parent- and b) metabolite models. The solid lines; lower, middle and upper are 5th, 50th, 95th percentiles of the observed data, respectively. The shaded areas around each percentile indicate the 95% confidence interval from model prediction. The small open circles are the observed concentration-time data points.*

Conclusions

The population PK of RFP were best described by a transit compartment absorption model with a one-compartment disposition model for RFP and a two-compartment disposition model for 25-DRFP. Time-varying clearance, suggestive of auto-induction, improved the model fit. Food increased RFP oral bioavailability in comparison to fasted state. While higher RFP exposure may be beneficial in enhancing the efficacy of regimens, there is concern of increased risk of adverse events. Thus future trials, aiming to investigate optimal dosing regimens, should consider both safety and efficacy when RFP is taken with and without food as is likely to occur under clinical conditions.

Acknowledgements

At the time of the study, PB Fourie was attached to the Tuberculosis Research Program of South Africa MRC, which financially supported the work through a grant from Hoechst Marion Roussel, France. SP Zvada is supported by the Wellcome Trust, UK [grant number: WT081199/Z/06/Z].

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