Title: Arylacetamide deacetylase (AADAC) gene polymorphism and HIV infection affect the exposure of Rifapentine: a population pharmacokinetics analysis.

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ABSTRACT

Rifapentine is a rifamycin used to treat tuberculosis. As for rifampicin, plasma exposures of rifapentine are associated with treatment response. While concomitant food intake and HIV infection explain part of the pharmacokinetic variability associated with rifapentine, few studies have evaluated the contribution of genetic polymorphisms. We evaluated the effects of functionally significant polymorphisms of the genes encoding OATP1B1, PXR, CAR, and AADAC on rifapentine exposure. Two studies evaluating novel regimens amongst Southern African patients with drug-susceptible pulmonary tuberculosis were included in this analysis. In RIFAQUIN, rifapentine was administered in the continuation phase of antituberculosis treatment in 1200mg once-weekly or 900mg twice-weekly doses. In Daily-RPE 450 or 600mg were given daily during the intensive-phase of treatment. Nonlinear mixed-effects modelling was used to describe the pharmacokinetics of rifapentine and to identify significant covariates. A total of 1144 drug-concentration measurements, from 326 patients, were included in the analysis. Pharmacogenetic information was available for 162 patients. A one-

compartment model with first-order elimination and transit compartment absorption described the data well. In a typical patient (body weight of 56kg, fat-free-mass of 45kg), the values of clearance and volume of distribution were 1.33L/h and 25L, respectively. Patients carrying the AA variant (65.4%) of *AADAC* rs1803155 were found to have 10.4% lower clearance. HIV+ infected patients had 21.9% lower bioavailability. Once weekly doses of 1200 mg were associated reduced clearance (-13.2%), compared to more frequently administered doses. Bioavailability was 23.3% lower amongst patients participating in the Daily-RPE study compared to RIFAQUIN. This is the first study to report the effect of *AADAC* rs1803155AA on rifapentine clearance. The observed increase in exposure is modest and unlikely to be of clinical relevance. The difference in bioavailability between the two studies is probably related to the different food concomitant to the dose. HIV coinfected patients had lower rifapentine exposures.

INTRODUCTION

Rifamycins play a key role in the multidrug treatment of tuberculosis. Their sterilizing activity is exposure-dependent (1-3). Rifapentine, was approved by the Food and Drug Administration (FDA) in 1998 for the treatment of pulmonary tuberculosis (3,4). Rifapentine pharmacokinetics are influenced by age, weight, dosing pattern, human immunodeficiency virus (HIV) infection, and sex (5,6). Rifapentine is less rapidly absorbed than rifampicin, with peak plasma concentrations reached within 5 hours. Concomitant food markedly increases its absorption; the extent of rifapentine absorption increased by 33-86% when given with meals (7). Rifapentine has a half-life of approximately 12 hours in humans (8,9). With its long half-life and excellent sterilizing activity, rifapentine is an attractive alternative to rifampicin and is increasingly used to treat active tuberculosis and latent infection. However,

there is marked interpatient variability in rifamycin pharmacokinetics (10). The primary metabolic pathways for rifapentine involve deacetylation to the primary enzymatic metabolite 25-desacetyl rifapentine, which is mediated by human arylacetamide deacetylase (*AADAC*) and non-enzymatic hydrolysis resulting in formation of the secondary metabolites 3-formyl rifapentine and 3-formyldesacetyl rifapentine (11). Protein binding of rifapentine is estimated to be about 98% (3,12). Like other rifamycin's, rifapentine induces its own metabolism (9).

Previously published data indicate that single nucleotide polymorphisms (SNPs) in the solute carrier organic anion transporter 1B1 (*SLCO1B1*) gene encoding the OATP1B1 transmembrane receptor affect rifampicin concentrations (13,14). *SLCO1B1* rs4149032 C>T polymorphism, found in 70% of South Africans with tuberculosis living in Cape Town, was associated with 20% and 28% reductions in rifampicin bioavailability in heterozygotes and homozygotes, respectively (14). Rifamycins are also substrates of the drug efflux pump P-glycoprotein coded for by the polymorphic *ABCB1* gene (15) and are metabolized mainly by polymorphic human arylacetamide deacetylase (*AADAC*) (16). Human rifamycin exposures are also modulated by the pregnane X receptor (*PXR*) and constitutive androstane (*CAR*) nuclear receptors (17). Since the development of resistance to rifamycins and their bactericidal effects are related to rifamycin concentrations, SNPs substantially influencing rifamycin concentrations may be of therapeutic importance. Little is known about the pharmacogenetic correlates of rifapentine pharmacokinetics, which may potentially help in finding the optimal dose of rifapentine. Therefore, the aim of this study was to determine the effect of polymorphisms of *SLCO1B1*, *PXR*, *CAR*, and *AADAC* on rifapentine pharmacokinetics.

RESULTS

A total of 326 patients were included in the study and contributed a total of 1151 concentrations-time points. Only 7 concentrations were below the LLOQ and were omitted from the analysis. The median body weight and age of the study participants were 56 kg and 32 years respectively. All demographic characteristics are summarized in Table 1.

The population pharmacokinetics of rifapentine was well described by a one-compartment model with first-order elimination and transit compartment absorption. Fat-free-mass(FFM) was found to be the best size descriptor for clearance (ΔOFV 93 points, $p<0.001$ when including FFM for allometric scaling on clearance and 23 points better than using body weight) and total body weight for volume of distribution (ΔOFV 20, $p<0.001$). The absorption of rifapentine was described using a series of transit compartments, which significantly improved the model with respect to simple first-order absorption (ΔOFV 421, $p<0.001$). In a typical patient (46 kg FFM and 56 kg weight), the values of clearance and volume of distribution were 1.33 L/h and 25 litres. Final parameter estimates (shown in Table 3) were in agreement with the previously published results (6,18) and a VPC of the final model is shown in Figure 1.

Of 326 patients, pharmacogenetic data was available for 162 (49.7%) all of whom were enrolled from South African sites. The distribution of genotype and allele frequencies are presented in Table 2. *SLCO1B1* rs2306283 and *AADAC* rs1803155 variant alleles were found in 82% of patients whereas the *NR1I2* rs2472677 and *NR1I2* rs1523130 variant alleles existed at a low overall frequency of 33.5% and 16.4% respectively. In keeping with our previous findings among South Africans in Cape Town (14), the *SLCO1B1* rs4149032 variant allele frequency was found to be 0.75 (Table 2).

After screening and inclusion of genetic information (and imputation of missing genotype with a mixture model), patients homozygous for *AADAC* rs1803155 AA polymorphism were

found to have 10.4% lower clearance of rifapentine compared to subjects that were rs1803155 GG or GA (ΔOFV 6.2, p=0.013). Initially the three categories of rs1803155 (AA, GA, GG) were analysed as separate groups to estimate the respective effects of GA and GG. However, the estimated effects were similar for GG & GA, and when combined the model goodness of fit was not affected. Using the principle of parsimony, we decided to use the simpler model, as the effects of GG and GA were not statistically significant. The other pharmacogenetic variants did not affect the pharmacokinetic parameters.

Patients infected with HIV infection were found to have 21.9% lower bioavailability (ΔOFV 42, p<0.001). The patients who were treated with high 1200 mg doses of rifapentine tended to have clearance reduced by 13.2% compared to other dose groups (ΔOFV 17, p<0.001). The pharmacokinetic differences between the two studies were explored and it was found that the bioavailability of rifapentine in the Daily RPE study was 23.3% lower than in the RIFAQUIN study (Δ OFV 59, p<0.001). The pharmacogenetic covariates other than *AADAC* rs1803155 polymorphism didn't have significant effects on the pharmacokinetic parameters.

DISCUSSION

The present study is the first to investigate the influence of various plausible physiologically-relevant candidate gene polymorphisms on rifapentine pharmacokinetics. We developed a population pharmacokinetic model of rifapentine, which was consistent with previous reports, and tested the effect of genotype information on the pharmacokinetic parameters. We showed that the *AADAC* rs1803155 polymorphism is associated with rifapentine clearance. Subjects carrying the AA genotype had 10.4% lower clearance than those carrying AG or GG, thus leading to increased rifapentine exposure. The low clearance due to this polymorphism is consistent with previous studies reporting decreased activity of *AADAC* activity due to the presence of the variant allele (19). The majority of patients in our study had the *AADAC*

rs1803155 AA variant allele which occurred at a frequency of 0.82, and 65% were homozygous for the single nucleotide polymorphism, which could, in part, account for the relatively high rifapentine exposures described. The polymorphism occurs at lower frequencies of 0.50 to 0.64 in European American, African American, Korean, and Japanese populations (19). Another study identified lower rifapentine concentrations in black Africans but the influence of pharmacogenetic factors, which might account for the difference in the genotype frequencies between the populations, was not explored (20), whereas Sloan *et al.*, who explored the influence of *AADAC* gene polymorphisms on rifampicin pharmacokinetics in Malawian patients, did not identify a significant relationship (21).The prevalence of variant genotypes is different between African ethnic groups and may be the reason for this contrasting effect. As only 3 of 162 patients had rs1803155 GG, no meaningful separate estimate of clearance for this genotype could be obtained. In further attempts to explain variability in rifapentine pharmacokinetics, we explored the effects of several polymorphisms of drug transporters and transcriptional regulators. The choice of polymorphisms was based on those previously described to affect drug disposition, and also by previous pharmacogenetic studies conducted on rifampicin. Interestingly, we could not detect the effect *SLCO1B1* rs4149032 polymorphism on pharmacokinetics of rifapentine, even with a carrier, no carrier approach. The frequency of *SLCO1B1* in our cohort was 0.75, which is in agreement with previous finding in South African patients from the Cape Town region. Similarly, we did not find a statistically significant effect associated with *SLCO1B1* rs2306283, which existed in our study population at a frequency of 0.82. *SLCO1B1* polymorphisms have been reported to be associated with low rifampicin levels (13,14) and the lack of effect on rifapentine may suggest differences in the ADME of the two drugs. It may be that this transporter does not play a major role in the pharmacokinetics of rifapentine, or that the variant allele is associated with greater induction by rifampicin. We did not

observe an effect due to polymorphisms of the transcriptional regulators. This could be due to activation of PXR or CAR by rifapentine, which may have overridden any constitutive effects.

Additionally, we found that HIV infected patients have lower bioavailability of rifapentine. While the association of HIV infection with antituberculosis drug exposures is inconsistent, our findings for rifapentine are consistent with recent studies (22-24). The data available was not sufficient to identify potential drug-drug interactions with the various antiretroviral drugs prescribed concomitantly.

Patients in the higher dose group (1200 mg given once weekly) had increased exposure in the current study contrary to the findings by Savic *et al*., which describes a decrease in the bioavailability of rifapentine with increased dose (6). The reduced dosing frequency in this group, may have led to reduced auto-induction and thus increased exposure.

Previous reports demonstrate that exposure to rifamycins is reduced in males due to a higher FFM: body weight ratio (25). The study by Langdon *et al.* described a 35% reduction in the clearance of 25-desacetyl rifapentine amongst females (5). In the present analysis, as allometric scaling with FFM accounted for the variability associated with sex, we did not observe any outstanding effects of sex. There was a difference in bioavailability between the two studies included in this analysis. This may be due to differences in food intake with the dose. Rifapentine absorption is strongly enhanced when it is administered with food (7). The finding that the Daily RPE study had a lower bioavailability may arise from the fact that meals with the dose were not standardized, in contrast to the RIFAQUIN study where a standard meal was provided throughout the study.

To conclude, our study is the first to show that the *AADAC* rs1803155 (AA) genotype is associated with lower rifapentine clearance, leading to increased rifapentine exposure. This

effect should be confirmed in a larger independent analysis. The pharmacogenetic association was modest compared to the study effect, which is likely linked to differences in the pattern of food use across the studies and highlights the importance of food recommendations both when the drug is used in a programmatic setting and when its pharmacokinetics is investigated. Additionally, we found that rifapentine exposure was lower in HIV infected patients, a finding consistent with previous studies and warranting further investigation to assess whether dose adjustment strategies should be considered. Lastly, patients dosed with 1200 mg once weekly doses had lower clearance, possibly as a result of less pronounced autoinduction.

MATERIALS AND METHODS

Study population: This analysis was performed on patients diagnosed with pulmonary TB from two clinical studies: The Phase III RIFAQUIN study (ISRCTN44153044) (26) and two-stage activity-safety study of daily rifapentine (27), hereinafter "Daily RPE" (NCT00814671). A subset of participants from these studies provided their consent to assess the effect of genetic polymorphisms of nuclear receptors, drug metabolizing enzymes, and drug transporters on the pharmacokinetics of rifapentine.

The RIFAQUIN study included two experimental arms in which patients were dosed with daily moxifloxacin, rifampicin, pyrazinamide, and ethambutol for 2 months followed by a continuation phase with either 4 months of once weekly 1200 mg rifapentine together with 400 mg moxifloxacin, or 2 months of 400 mg moxifloxacin twice weekly with 900 mg of rifapentine. The RIFAQUIN study was conducted at sites in the Western Cape and Gauteng regions of South Africa and in Harare, Zimbabwe. The doses of rifapentine and moxifloxacin were taken with 240 mL of water 15 minutes after a light meal of 2 hard-boiled eggs with

bread. During the 4th month of treatment, blood samples were drawn for determination of plasma rifapentine concentrations. The pharmacokinetic assessment involved rich (with a pre-dose and samples at 1, 2, 3, 5, 7, 10, 12, 26, and 50 h after dosing) or sparse sampling (samples drawn around 2, 5, and 24 or 48 h after dosing).

The Daily RPE study was open-label and had two experimental arms. Patients with pulmonary tuberculosis were randomized to 450 or 600 mg rifapentine daily, which replaced 600 mg rifampicin during the intensive phase of standard therapy. The study participants were recruited in the Western Cape, South Africa. The patients were advised to take the required Rifapentine dose with food, but no standardised meal was provided during the study and no accurate details about food intake with the dose were recorded. Pharmacokinetic sampling was performed at approximately one month after starting therapy and samples were obtained either with intensive (with samples pre-dose and at 0.75, 1.5, 3.5, 5, 12, and 24 h after dose), or sparse sampling (0.5-2 h and 5-8 h after dose). Separate written informed consent for the pharmacogenetic study was obtained from participants retrospectively. The pharmacogenetic study was reviewed and approved the Research Ethics Committee of the University of Cape Town and the University of the Witwatersrand.

Drug determination: Plasma rifapentine concentrations were determined with a validated liquid chromatography-tandem mass spectrometry assay developed in the Division of Clinical Pharmacology, University of Cape Town. Samples were processed with a protein precipitation extraction method using rifaximin as internal standard, followed by high performance liquid chromatography with MS/MS detection using an AB SCIEX API 3200 instrument. The analyte and internal standard were monitored at mass transitions of the protonated precursor ions m/z 877.3 and m/z 786.3 to the product ions m/z 845.4 and m/z 754.1 for rifapentine and rifaximin, respectively. The calibration curves fit quadratic (weighted by 1/concentration) regressions over the ranges 0.156 – 40.0 mg/L for rifapentine.

242 The accuracies for the rifapentine assay were 103.9%, 102.8%, and 97.5% at the low,
243 medium, and high QC levels, respectively, during inter-batch validation. The lower limit of
244 quantification (LLOQ) was 0.156 mg/L.

245 **SNP genotyping:** Genomic DNA was extracted from 200 µL whole blood using QIAamp
246 DNA Mini Kit (Qiagen, Inc., Valencia, California) in accordance with the manufacturer's
247 protocol. DNA was quantified spectrophotometrically using NanoDrop (Thermo Fisher
248 Scientific Inc., Wilmington, Delaware) before storage at −20°C. Genotyping was performed
249 by real-time polymerase chain reaction (PCR) on a DNA Engine Chromo4 system (Bio-Rad
250 Laboratories, Inc., Hercules, California). The PCR protocol involved an initial denaturation
251 step at 95°C for 15 min, followed by 50 cycles of amplification at 95°C for 15 s and final
252 annealing at 60°C for 1 min. TaqMan Genotyping Master Mix and assays for *SLCO1B1*
253 rs2306283 (SNP ID: C_1901697_20), *SLCO1B1* rs4149032 (C_1901709_10), *NR1I2*
254 rs2472677 (C_26079845_10), *NR1I2* rs1523130 (C_9152783_20), and *AADAC* rs1803155
255 (C_8911003_1_) were obtained from Thermo Fisher Scientific (Waltham, Massachusetts).
256 Allelic discrimination plots and genotype assignments were performed using Opticon
257 Monitor, version 3.1 from Bio-Rad Laboratories.

258 **Pharmacokinetic analysis**: Rifapentine plasma concentration-time data was analysed using a
259 nonlinear mixed-effects model implemented in NONMEM 7.4.2 (28). The execution of runs
260 was through Perl-speaks-NONMEM, Pirana and graphical diagnostics were created using
261 Xpose 4.6.0 and R (29,30). Estimation of typical population pharmacokinetic parameters,
262 along with their random inter-individual (IIV) and inter-occasion (IOV) variability was
263 performed using first-order conditional estimation method with ε-η interaction (FOCE
264 INTER). A lognormal distribution was assumed for IIV and IOV and a combined additive
265 and proportional model for the residual unexplained variability (RUV) was evaluated.
266 Various structural models were tested including one or two-compartment distribution with

first-order elimination and first–order absorption with or without lag time or transit compartment absorption (31). The influence of genetic polymorphisms on rifapentine pharmacokinetics for patients with unknown genotype was identified using mixture modelling (32). The effect of the genotype was first tested using method *EXTRA* which estimates the association only for the patients with available genetic information but also estimating an additional covariate effect for the unknown genotype. Subsequently, the *MIX* method to impute values using mixture modelling was applied to include the patient with unknown genotype to strengthen the robustness of the findings (32). Model selection was based on changes in the NONMEM objective function value (ΔOFV), and visual inspection of conditional weighted residuals (CWRES) versus time, visual predictive checks (33), and basic goodness of fit plots (GOF). During model development, physiological plausibility and the precision of the parameter estimates were also considered. The model parameters of the final model were evaluated for their precision using sampling importance resampling method (SIR) (34).

Allometric scaling was applied on clearance (CL), and volume of distribution (V) to adjust for the effect of body size, according to Anderson and Holford (35). Fat-free mass (FFM), and fat mass (FAT) were tested as alternative size predictors through allometric scaling instead of total body weight (35,36). After the inclusion of allometric scaling, potential demographic, study site specific and pharmacogenetic covariates were screened inspecting parameter versus covariate plots and then tested in the model using drops in objective function value (assumed to be χ-square distributed and thus using 3.84 points drop as significant at $p<0.05$ for the inclusion of a single parameter), while scrutinising the physiological plausibility of the effect (37).

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Table 1: Demographic and clinical characteristics of patients

Demographic & Clinical Characteristics	Daily RPE 450 mg group (N=44)	Daily RPE 600 mg group (N=41)	RIFAQUIN 900 mg group (N=116)	RIFAQUIN 1200 mg group (N=125)	Overall (N=326)
No. of PK samples	166	130	416	432	1144
Sex (male/female)	(33/11)	(32/9)	(72/44)	(81/44)	(218/108)
Number of HIV+ patients	6 (13.6%)	7 (17.1%)	30 (25.9%)	16(12.8%)	59(18.1%)
Median age, range (yrs)	29 (19-61)	29 (18-63)	31 (19-64)	34 (19- 80)	32 (18-80)
Median weight in kg (range)	55 (45-79)	55 (45-94)	55 (38-77)	57 (38- 78)	56 (38-94)
Median FFM in kg (range)	47 (32-58)	47 (32-56)	45 (27-62)	45 (27-60)	45 (27-62)

Table 2: Observed genotype and allele frequency of Single nucleotide polymorphisms in the study (N=162)

Genotype	Genotype frequency (%)			Allele frequencies	
SLCO1B1 A>G	AA	AG	GG	A	G
rs2306283	8 (4.94)	43 (26.5)	111 (68.5)	0.18	0.82
SLCO1B1 C>T	CC	CT	TT	C	T
rs4149032	15 (9.26)	52 (32.1)	95 (58.6)	0.25	0.75
*NR1I2 C>T	CC	CT	TT	C	T
rs2472677	71 (44.1)	72(44.7)	18 (11.2)	0.67	0.34
NR1I2 T>C	TT	CT	CC	T	C
rs1523130	116 (71.6)	39 (24.1)	7 (4.3)	0.84	0.16
AADAC G>A	GG	GA	AA	G	A
rs1803155	3 (1.85)	53 (32.7)	106 (65.4)	0.18	0.82

*The data available only for 161 patients

Table 3: Final parameter estimates for rifapentine population pharmacokinetic model

Parameter	Estimate	95% CI	IIV[+] or IOV[++]	95% CI
CL[a] (L/hr)	1.33	1.14;1.54	23.0%[+]	17.7;28.6
V[a] (L)	25	21.9;28.4	12.8%[+]	8.8;17.4
ka (hr^{-1})	0.814	0.568;1.26	48.9%[++]	36.4;59.8
MTT (hr)	1.47	1.20;1.78	37.4%[++]	28.3;48.6
NN	10.2	6.70;14.0	-	-
F	1 FIXED		20.3%[++]	14.9;26.4
Proportional residual error (%)	9.56	7.09;13.2	-	-
Additive residual error (mg/L)	0.247	0.143-0.401	-	-
HIV+ effect on F (%)	-21.9	-33.2; -6.64	-	-
Group on 1200 mg dose in RIFAQUIN study on CL (%)	-13.2	-22.8; -4.36	-	-
Daily RPE study on F (%)	-23.3	-35.6: -9.25	-	-
AADAC rs1803155 (AA) effect on CL (%)	-10.4	-17.3; -3.53	-	-

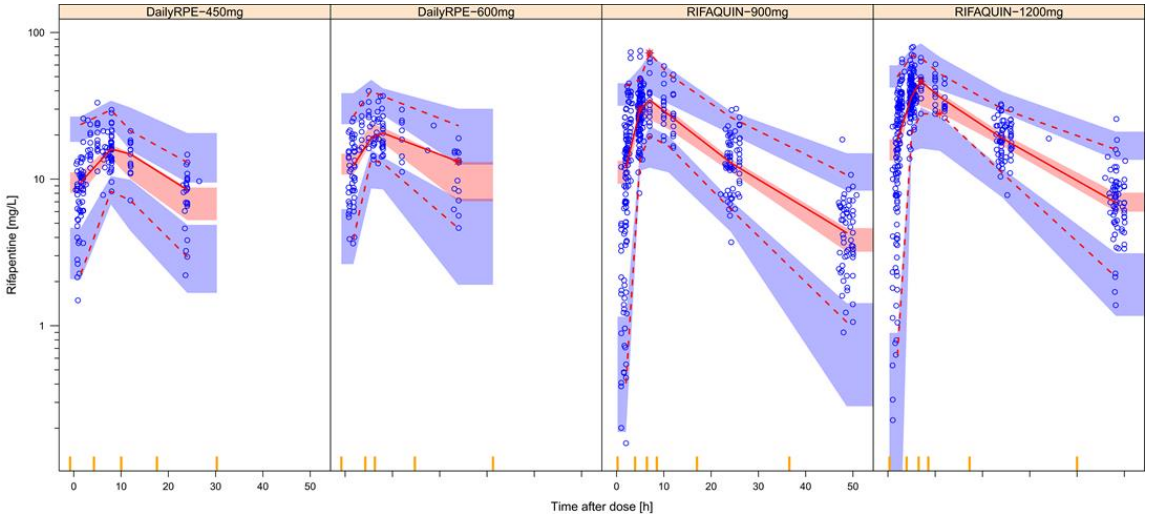
CL-oral clearance; V-apparent volume of distribution in the central compartment; k_a-first-order absorption rate constant; MTT- absorption mean transit time; NN- number of hypothetical transit compartments; F- oral bioavailability; HIV+ - Human immunodeficiency

virus positive; *AADAC*- arylacetamide deacetylase. IIV- inter-individual variability, and IOV- inter-occasional variability are expressed as percent coefficient of variation (% CV).

a - The typical values of clearance and volume of distribution reported for a patient with body weight 56 kg and FFM of 46 kg.

95% CI of parameter estimates obtained with Sampling importance resampling (SIR) n=1000 of the final model.

Figure 1: Visual predictive check (VPC) for the final rifapentine population pharmacokinetic model in log scale, stratified according to different dose groups in the analysis.



The lower, middle, and upper solid lines are the 2.5th, 50th, and 97.5th percentiles of the observed plasma concentration. The shaded areas are the 95% confidence intervals for the same percentiles, obtained from re-simulations of the same trial.