Impact of SLCO1B1 Genotype and Single Nucleotide Polymorphism on Rifampin Pharmacokinetics using Linkage Analysis and Physiologically-based Pharmacokinetic (PBPK) Modeling Approach

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ABSTRACT

Background. A single nucleotide polymorphisms (SNP) in the solute carrier gene (SLCO1B1) encoding OATP1B1 (rs11045819) is associated with lower plasma rifampin exposures. In this work, we evaluated SLCO1B1 genotype SNPs and their association with rifampin plasma exposures in various tissue compartments.

Methods. All SNPs identified in SLCO1B1 identified by whole exome sequencing were identified for each study subject. A physiologically-based pharmacokinetic (PBPK) model for rifampin was extended to include an effect of a previously identified SNP as a categorical covariate on SLCO1B1 transport kinetics parameter. Population simulations were performed for lung and brain compartments in order to compare area under the concentration-time curve (AUC) for different compartments.

Results. The PBPK model demonstrated a 3% proportional increase in SLCO1B1 $Vmax_{OATP1B1}$ among patients with heterozygous rs11045819. Simulated plasma concentrations-time profile agreed with observed data in the model-building and evaluation datasets (R^2=0.96 and 0.93, respectively). In exploratory analysis, rs4149080 SNP was associated with low rifampin maximum concentrations (C_{max}) independent of rs11045819 (D 3.68e-03, D' 6.37e-02, p-value 0.60).

Discussion. The previous observations of lower rifampin exposures in patients with heterozygous rs11045819 SNP in literature were confirmed by our study. In addition, our study suggested an independent association of heterozygous rs4149080 with lower rifampin exposures.

INTRODUCTION

Rifampin is the key drug responsible for sterilizing activities in the first-line regimen for the treatment of tuberculosis (TB), and it is likely that current dosing regimens lead to exposures at the lower end of the dose-response curve. Pharmacokinetic variability has been identified as a key mediator of the rate of sterilizing effect and the emergence of new drug resistance mutations during tuberculosis therapy.

Rifampin is a substrate of organic anion transporter polypeptides family member 1B1 (OATP1B1) which is expressed on the sinusoidal membrane of hepatocytes and is encoded by the SLCO1B1 gene. Population pharmacokinetic studies have identified an SNP in SLCO1B1 that contributes to rifampin PK variability, with higher systemic (plasma) concentrations observed among individuals with the variant SNP, compared to wild-type. Mechanistically, these clinically significant SNPs in SLCO1B1 may be associated with altered functionality of SLCO1B1 transporters[3]. In this analysis, we evaluated SNPs in SLCO1B1 and their possible association with rifampin PK among a cohort of HIV/TB patients in Botswana, including a modification of a previously published PBPK model of rifampin exposures in target tissues during TB treatment.

METHODS

All SNPs identified in SLCO1B1 recognized in the study were evaluated for each subject. Contingency tables and plots were prepared to identify which SLCO1B1 SNPs were consistently associated with lower C_{max} across patients. Linkage disequilibrium analysis was performed to characterize the association between different SLCO1B1 SNPs in our dataset.

Pharmacokinetic (PK) concentration-time profile after single oral doses of rifampin 600 mg to patients with TB was digitized from a previously published study of 72 adults with pulmonary tuberculosis from Africa, North America, and Spain[9]. The study population was grouped in either SLCO1B1 c.463CC (rs11045819 wildtype) or c.463CA (rs11045819 heterozygous) genotype groups[9]. A previously developed rifampin PBPK model using PK-Sim® (Suite 7.2.1) was obtained and adjusted for oral administration[2].

Next, we added and evaluated the effect of a categorical covariate, SLCO1B1 rs11045819 wild-type vs. heterozygous, on the rifampin kinetics by fitting to data from literature using the following equation in Mobi®.

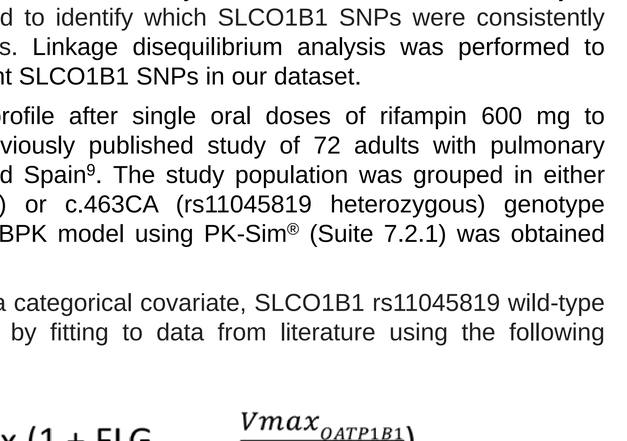
$$Kcat = \frac{Vmax_{OATP1B1}}{Conc_{OATP1B1}} \times (1 + FLG_{hetero} \frac{Vmax_{OATP1B1}}{Conc_{OATP1B1}})$$

The updated PBPK model was evaluated by overlaying population simulations over population data collected in our study[7] for both SNP categories. Additionally, the sensitivity of the estimates in exposure metrics (area under the plasma concentration-time curve (AUC), C_{max}, and half-life) following 10% variation in selected parameters (absorption and clearance related parameters) was calculated. Once the robustness of the model was demonstrated under these conditions, population simulations for lung tissue compartment were conducted and lung tissue $AUC_{0-\infty}$ was reported.

RESULTS

- Total of 32/40 patients had at least 1 heterozygous SNP.
- Four patients had heterozygous rs11045819, which was previously associated with lower rifampin C_{max}.
- We identified other SNPs that were possibly associated (r^2>0.50) with rs11045819 via linkage disequilibrium analysis.
- Two patients who did not have heterozygous rs11045819 SNP, but one or more associated SNP also had lower rifampin C_{max} values in our dataset. Additionally, two patients who had heterozygous rs4149080 had lower rifampin C_{max}.
- Previously, Sloan 2017 observed rs4149032 to be possibly associated with lower rifampin exposure; however, our study did not demonstrate similar finding. Patients who had rs11045819 heterozygous SNP were flagged in our dataset for evaluation of the PBPK model.

Figure 1. Observed C_{max} Stratified by SLCO1B1 SNP Groups



- A previously developed and evaluated whole body PBPK model was adapted to describe lower rifampin exposure in patients with few identified heterozygous SNPs.
- Simulated plasma concentrations-time profile agreed well with observed data (R^2=0.96 and 0.93, respectively, p-value<0.0001) for both datasets (Figure 3 and 4, respectively).

Figure 2. Linkage Disequilibrium Heatmap for SLCO1B1 SNPs

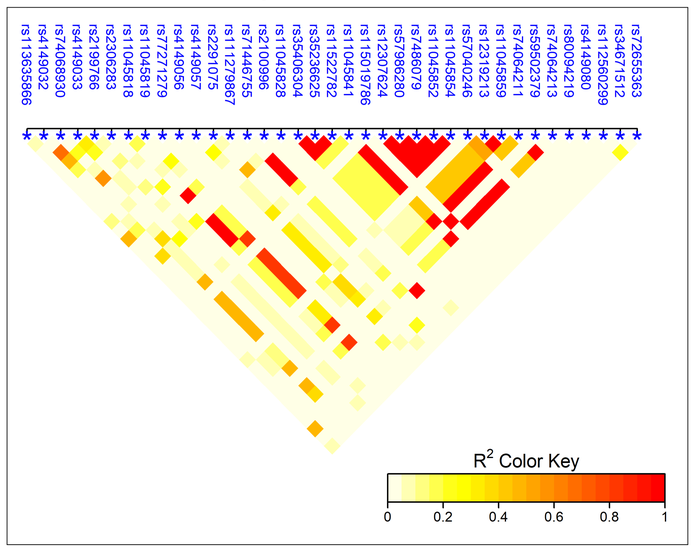


Table 1. List of SLCO1B1 SNPs Associated with RS11045819

SLCO1B1 SNPs	rs11045819 (r^2)
rs11045841	0.82
rs11045852	0.82
rs11045854	0.82
rs12307624	0.82
rs57986280	0.82
rs74064211	0.82
rs74064213	0.82
rs74068930	0.57
rs7486079	0.82

Figure 3. Model Fitting Results: Rifampin Plasma Concentrations vs. Time Profile for Model Fitting Dataset: Observed and Simulated Overlay.

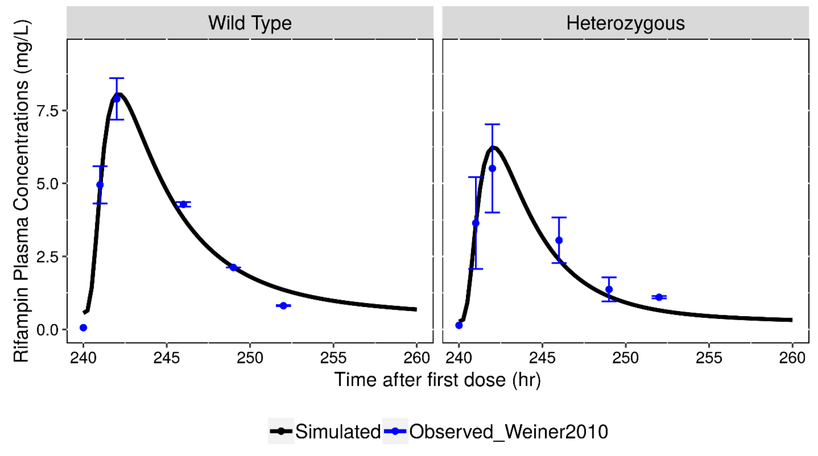


Figure 4. External Validation of the Model: Rifampin Plasma Concentrations vs. Time Profile with Observed and Simulated Overlay

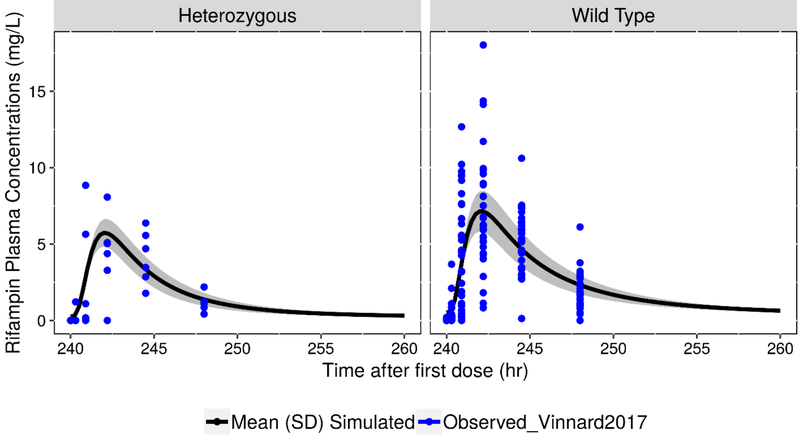
- Sensitivity for key PK parameters was low (between -1 to 1), confirming reliability of the model.
- The model was then used to predict rifampin concentrations at the site of action, lung tissue. Figure 5 shows mean and standard errors of predicted concentrations for venous plasma and lung tissue compartments. Mean AUClung : AUCplasma ratio was predicted to be approximately 0.4 for both wild type and heterozygous groups.

DISCUSSION

Development of resistance to rifampin is still a major issue in TB treatment. Lower rifampin exposures have been linked to development of the resistance and treatment failure. Prior work have linked SLCO1B1 heterozygous SNP rs11045819 to lower rifampin exposure[9]. A whole-body PBPK model was previously developed using an open-source platform, PK-Sim, for intravenous rifampin.

Our work extended the model to allow simulations following oral administration of rifampin and to include the effect of SLCO1B1 heterozygous SNP rs11045819 on $Vmax_{OATP1B1}$. Our model suggested a 3% proportional increase in SLCO1B1 Vmax among patients with heterozygous rs11045819. Additionally, our study identified that heterozygous rs4149080 could possibly be associated with lower rifampin exposure; however, this finding needs to be confirmed in additional studies due to low prevalence of this SNP in our dataset.

Figure 5. Predicted Rifampin Area under Curve (AUC) for Venous Plasma and Site of Action



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