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Pharmacokinetics of First-Line Tuberculosis Drugs in South African Patients from Kwazulu-Natal: Effects of Pharmacogenetic Variation on Rifampicin and Isoniazid Concentrations

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Abstract : Background: Despite efforts to introduce new drugs and shorter drug regimens for drug-susceptible tuberculosis (TB), the standard first-line treatment has not changed in over 50 years. Rifampicin, isoniazid, and pyrazinamide are critical components of the current standard treatment regimens. Some studies suggest that microbiologic failure and acquired drug resistance are primarily driven by low drug concentrations that result from pharmacokinetic (PK) variability independent of adherence to treatment. Wide between-patient pharmacokinetic variability for rifampin, isoniazid, and pyrazinamide has been reported in prior studies. There may be several reasons for this variability. However, genetic variability in genes coding for drug metabolizing and transporter enzymes have been shown to be a contributing factor for variable tuberculosis drug exposures. Objective: We describe the pharmacokinetics of first-line TB drugs rifampicin, isoniazid, and pyrazinamide and assess the effect of genetic variability in relevant selected drug metabolizing and transporter enzymes on pharmacokinetic parameters of isoniazid and rifampicin. Methods: We conducted the randomized-controlled Improving retreatment success TB trial in Durban, South Africa. The drug regimen included rifampicin, isoniazid, and pyrazinamide. Drug concentrations were measured in plasma, and concentration-time data were analysed using nonlinear-mixed-effects models to quantify the effects of relevant covariates and single nucleotide polymorphisms (SNP's) of drug metabolizing and transporter genes on rifampicin, isoniazid and pyrazinamide exposure. A total of 25 SNP's: four NAT2 (used to determine acetylator status), four SLCO1B1, three Pregnane X receptor (NR1), six ABCB1 and eight UGT1A, were selected for analysis in this study. Genotypes were determined for each of the SNP's using a TaqMan® Genotyping OpenArray™. Results: Among fifty-eight patients studied; 41 (70.7%) were male, 97% black African, 42 (72.4%) HIV co-infected and 40 (95%) on efavirenz-based ART. Median weight, fat-free mass (FFM), and age at baseline were 56.9 kg (interquartile range, IQR: 51.1-65.2), 46.8 kg (IQR: 42.5-50.3) and 37 years (IQR: 31-42), respectively. The pharmacokinetics of rifampicin and pyrazinamide was best described using one-compartment models with first-order absorption and elimination, while for isoniazid two-compartment disposition was used. The median (interquartile range: IQR) AUC (h·mg/L) and Cmax (mg/L) for rifampicin, isoniazid, and pyrazinamide were; 25.62 (23.01-28.53) and 4.85 (4.36-5.40), 10.62 (9.20-12.25) and 2.79 (2.61-2.97), 345.74 (312.03-383.10) and 28.06 (25.01-31.52), respectively. Eighteen percent of patients were classified as rapid acetylators, and 34% and 43% as slow and intermediate acetylators, respectively. Rapid and intermediate acetylator status based on NAT 2 genotype resulted in 2.3 and 1.6 times higher isoniazid clearance than slow acetylators. We found no effects of the SLCO1B1 genotypes on rifampicin pharmacokinetics. Conclusion: Plasma concentrations of rifampicin, isoniazid, and pyrazinamide were low overall in our patients. Isoniazid clearance was high overall and as expected higher in rapid and intermediate acetylators resulting in lower drug exposures. In contrast to reports from previous South African or Ugandan studies, we did not find any effects of the SLCO1B1 or other genotypes tested on rifampicin PK. However, our findings are in keeping with more recent studies from Malawi and India emphasizing the need for geographically diverse and adequately powered studies. The clinical relevance of the low tuberculosis drug concentrations warrants further investigation.

Keywords : rifampicin, isoniazid pharmacokinetics, genetics, NAT2, SLCO1B1, tuberculosis
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