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Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations



Tenofovir population pharmacokinetics in HIV-infected children and adolescents

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Background: Tenofovir (TDF), at a fixed dose of 300 mg once daily, is commonly used in combination with other antiretrovirals to treat human immunodeficiency virus (HIV) in adults, adolescents and children. Yet, factors affecting pharmacokinetic variability of TDF in HIV-infected children and adolescents have not been evaluated.

Materials & Methods: Data for this analysis were collected from a multicenter study conducted through the International Maternal, Pediatric and Adolescent AIDS Clinical Trials Group (IMPAACT) Protocol P1058 which evaluated the pharmacokinetics of TDF 300 mg once daily in combination with efavirenz (EFV), darunavir/ritonavir (DRV/r) or atazanavir/ritonavir (ATV/r) in 47 HIV-infected patients 8 to 18 years of age. Fifty-two intensive pharmacokinetic data sets for TDF were available. Nonlinear mixed effects modeling (NONMEM® VI) was used to develop the population pharmacokinetic model and explore the influence of demographic covariates (age, sex, weight, height, body surface area, tanner stage) and concomitant medication (EFV, DRV/r or ATV/r) on TDF pharmacokinetics.

Results: Median (range) age, weight and creatinine clearance of patients were 14 (8-17) years, 48.1 (32.6-102.6) kg and 154 (74.8-267.6) ml/min/1.73m², respectively. A two-compartment model with first-order absorption described TDF pharmacokinetics. Allometric scaling of subject size improved the model over a linear weight model and this approach limited the impact of age on TDF CL/F. Typical population estimates of apparent central distribution volume (V_c/F), peripheral distribution volume (V_p/F) and intercompartmental clearance (Q/F) for a 50 kg individual with a CRCL of 156.44 ml/min/1.73m² were 923 L, 1400 L, and 253 L/hr, respectively. The model for the typical value of clearance (L/hr) was (65.3 + 0.377*CRCL)*(wt/70)**0.75. The model was further improved by allowing subjects to be classified as slow absorbers (final estimate of 0.43 hr⁻¹) or rapid absorbers (final estimate of 18 hr⁻¹). The estimated inter-subject variabilities for CL/F and V_c/F were 28.4% and 78.3%, respectively. The correlation between CL/F and V_c/F was 0.612. The residual variability included a proportional component with a CV of 25.9% and an additive component with a standard deviation of 0.0298 ng/mL. A predictive check assessment indicated satisfactory model performance without any systematic bias.

Conclusions: A population pharmacokinetic model satisfactorily described TDF pharmacokinetics, including effects of known covariates. Apparent plasma TDF clearance (96.2 L/hr) was slightly higher in our subjects compared with adults (90.9 L/hr) and affected by CrCL. Differences in rate of absorption were likely a result of food intake with medication administration. Age, sex, tanner stage and concomitant medications did not affect tenofovir clearance or volume of distribution.

No conflict of interest