Tacrolimus Population Pharmacokinetic-Pharmacogenetic Analysis and Bayesian Estimation in Renal Transplant Recipients

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Résumé en anglais	Objectives: The aims of this study were (i) to investigate the population pharmacokinetics of tacrolimus in renal transplant recipients, including the influence of biological and pharmacogenetic covariates; and (ii) to develop a Bayesian estimator able to reliably estimate the individual pharmacokinetic parameters and inter-dose area under the blood concentration-time curve (AUC) from 0 to 12 hours (AUC12) in renal transplant patients. Methods: Full pharmacokinetic profiles were obtained from 32 renal transplant patients at weeks 1 and 2, and at months 1, 3 and 6 post-transplantation. The population pharmacokinetic analysis was performed using the nonlinear mixed-effect modelling software NONMEM® version VI. Patients' genotypes were characterized by allelic discrimination for PXR −25385C>T genes. Results: Tacrolimus pharmacokinetics were well described by a two-compartment model combined with an Erlang distribution to describe the absorption phase, with low additive and proportional residual errors of 1.6 ng/mL and 9%, respectively. Both the haematocrit and PXR −25385C>T single nucleotide polymorphism (SNP) were identified as significant covariates for apparent oral clearance (CL/F) of tacrolimus, which allowed improvement of prediction accuracy. Specifically, CL/F decreased gradually with the number of mutated alleles for the PXR −25385C>T SNP and was inversely proportional to the haematocrit value. However, clinical criteria of relevance, mainly the decrease in interindividual variability and residual error, led us to retain only the haematocrit in the final model. Maximum a posteriori Bayesian forecasting allowed accurate prediction of the tacrolimus AUC12 using only three sampling times (at 0 hour [predose] and at 1 and 3 hours postdose) in addition to the haematocrit value, with a nonsignificant mean AUC bias of 2% and good precision (relative mean square error = 11%). Conclusion: Population pharmacokinetic analysis of tacrolimus in renal transplant recipients showed a significant influence of the haematocrit on its CL/F and led to the development of a Bayesian estimator compatible with clinical practice and able to accurately predict tacrolimus individual pharmacokinetic parameters and the AUC12.
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