Population Pharmacokinetic Analysis of Once Daily Formulation of Tacrolimus in Kidney Transplantation Patients

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Objectives: Tacrolimus is a calcineurin inhibitor that is used to prevent graft rejection after kidney transplantation [1]. Advagraf®, a prolonged-release tacrolimus formulation, allows once-daily dosing to improve adherence [2]. The aim of this study was to develop a population pharmacokinetic (PK) model for Advagraf® in kidney transplantation patients.

Methods: A total of 272 tacrolimus whole blood concentrations from 25 patients (age 21-66 years, body weight (WT) 41.15-84.90 kg) who had received kidney transplantation in Seoul National University Hospital were analyzed to develop a population PK model using the nonlinear mixed-effects method using NONMEM (Version: 7.3). Subjects received dose-adjusted oral Advagraf® once-daily and blood samples were collected at steady-state. The first-order conditional estimation with interaction estimation method was implemented. The adequacy of model was evaluated using standard goodness-of-fit diagnostics and visual predictive checks.

Results: A two compartment linear PK model, first-order absorption with lag time best described the data. Covariate included in the final model was dose on relative bioavailability (F1). The mean population PK parameters (interindividual variability, CV%) of clearance, central volume of distribution, peripheral volume of distribution, intercompartmental clearance, absorption lag time and relative bioavailability were 27 L/h (7.4%), 358 L (44.3%), 527 L (0 fixed), 51.9 L/h (0 fixed), 0.443 h (0 fixed) and ((DOSE/10)^-0.92) (21.5%), respectively.

Conclusions: As the oral dose of Advagraf® increased, the relative bioavailability (F1) was decreased. This result implies that absorption of Advagraf® in kidney transplantation patients might be non-linear and should be considered when physician adjust dose of Advagraf®. The model-fitted parameter estimates may be applied to determine the optimal dosage regimens of Advagraf® in kidney transplantation patients.

References: