Population Pharmacokinetics of Mycophenolic Acid and its Metabolites in Liver Transplant Recipients

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Objectives: Mycophenolic acid (MPA) is an immunosuppressant, which is commonly used in liver transplant recipients. The objective of this work was to characterize the population pharmacokinetics (PK) of MPA, and its glucuronide metabolite (MPAG) and acyl-glucuronide metabolite (AcMPAG) in adult Chinese liver transplant recipients following repeated oral administration of the prodrug mycophenolate mofetil (MMF, Cellcept®, Roche).

Methods: Sixty-four adult liver transplant patients (52 males, 12 females) received liver transplantation received immunosuppressive therapy consisting of MMF, tacrolimus (Prograf®, Fujisawa) and corticosteroids. Serial blood samples were collected following oral MMF treatment after the liver transplantation. A population pharmacokinetic (PK) model with simultaneous characterization of the plasma PK profiles of MPA, MPAG and AcMPAG was developed using nonlinear mixed effects modeling.

Results: Plasma MPA, MPAG and AcMPAG concentration-time data after MMF oral administration were adequately described by a five-compartment model including EHC. The apparent total clearance of MPA and the apparent elimination clearance of the metabolites MPAG and AcMPAG were quantified (CL\textsubscript{MPA}/F = 18.71 L/h, CL\textsubscript{MPAG}/F = 1.22 L/h, CL\textsubscript{AcMPAG}/F = 5.44 L/h, respectively).

Conclusions: The population PK model developed from our study successfully characterized the absorption, distribution, and elimination of MPA and its major metabolites in liver transplant recipients. A good description of the metabolites of MPA may provide a useful tool in predicting some MPA-related side effects.