M-07

Population Pharmacokinetics of Mycophenolic Acid and its Glucuronide Metabolite in Lung Transplant Recipients with and without Cystic Fibrosis

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Objectives: The objective of this work was to characterize the population pharmacokinetics (PK) of mycophenolic acid (MPA), an immunosuppressant, and its glucuronide metabolite (MPAG) in adult lung transplant recipients with cystic fibrosis (CF) and without the disease (NCF) following repeated oral administration of the prodrug mycophenolate mofetil (MMF).

Methods: Three separate 12-hour PK visits were conducted in CF and NCF lung transplant patients following repeated MMF treatment, with at least 2 weeks between the visits. A population PK model was developed, with simultaneously modeling of MPA and MPAG, using nonlinear mixed effects modeling and considering the contribution of physiological and pathological factors, and enterohepatic recirculation (EHC).

Results: Plasma MPA and MPAG concentration-time data after MMF oral administration were adequately described by a three-compartment model, which included EHC. CF patients had elevated values for both the apparent total clearance of MPA (CL/F = 17.18 L/h) and apparent elimination clearance of MPAG (CLₘ/F = 2.18 L/h) compared to NCF patients (CL/F = 9.98 L/h and CLₘ/F = 1.22 L/h). The systemic appearance rate constant of MPA in CF patients (KA = 1.35 h⁻¹) was slower than that in NCF patients (KA = 2.90 h⁻¹).

Conclusions: The population PK model developed from our study successfully characterized the absorption, distribution, and elimination of MPA and its major metabolite MPAG in lung transplant recipients with or without CF. The decrease of MPA systemic appearance rate and increase of both CL/F and CLₘ/F in CF patients suggests the importance of MPA therapeutic monitoring for this group.