Population Pharmacokinetics of Mycophenolic Acid in Liver Transplant Recipients and a Comparison of FOCE and EM Estimation Methods

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Objectives: To characterize the population pharmacokinetics (PK) of mycophenolic acid (MPA) in liver transplant recipients and compare the FOCE and the EM estimation methods

Methods: Eighty-seven adult liver transplant patients received immunosuppressive therapy consisting of MMF (Cellcept®, Roche), tacrolimus (Prograf®, Fujisawa) and corticosteroids. Blood samples were collected at 0 - 12 h after MMF administration during 7 - 30 days post-surgery and the MPA plasma concentrations were determined by HPLC assay. Population PK models of MPA using NONMEM FOCE (first-order conditional estimation) or EM (expectation maximization) methods were developed and compared.

Results: MPA PK profiles was best described by a two-compartment PK model with a first order of absorption using either FOCE or EM methods. No significant difference in MPA PK parameters were observed with the absorption rate constant (Ka±SE), apparent clearance (CL/F±SE), as 0.51 ± 0.08 and 0.49 ± 0.06 hr⁻¹, 22.0 ± 4.8 and 20.1 ± 1.5 L/hr), for the FOCE and EM methods, respectively. There was a lag of MPA absorption in liver transplant recipients with the estimated lag time (ALAG1±SE) of 0.41 ± 0.03 and 0.43 ± 0.00 hr for the FOCE and EM methods, respectively. Some differences in the estimation of apparent volume of distribution for the central (V2/F±SE) and peripheral (V3/F±SE) compartments were noticed with V2/F±SE as 16.3 ± 6.4 and 12.1 ± 2.4 L, V3/F±SE as 460 ± 99 and 556 ± 188 L for the FOCE and EM methods, respectively.

Conclusions: The population PK models developed from our study using the FOCE and EM methods successfully characterized the absorption, distribution, and elimination of MPA in liver transplant recipients. In general, the model estimated standard error (SE) values for PK parameter assessment appeared lower using the EM methods especially for the estimation of CL/F and ALAG1.