Population Pharmacokinetics of Mycophenolic Acid in Liver Transplant Patients and the Limited-Sampling Strategy in Therapeutic Monitoring

X. Wang 1, B. Chen 2, D. E. Smith 1, M. R. Feng 1
1 University of Michigan, 2 Shanghai Jiao Tong University

Purpose
Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid (MPA), an immunosuppressive agent used for the prevention of acute rejection after solid organ transplantation. The objective of this work is to develop a population pharmacokinetic (POPPK) model for MPA in Chinese adult liver transplant recipients following oral administration of MMF and a limited-sampling strategy (LSS) in therapeutic monitoring.

Methods
The POPPK model was established using plasma concentration data from 64 adult liver transplant patients following repeated daily oral dose of MMF. The data were analyzed by nonlinear mixed effects modeling (NONMEM) and the contribution of physiological (age, weight, gender) and pathological (total bilirubin, albumin, clearance of creatinine) covariates was evaluated. LSS was explored using a combination of multi-linear regression (MLR) and NONMEM based on prediction of the area under the concentration-time curve (AUC0-12hr) of MPA.

Results
The MPA concentration data were best described by a two-compartment disposition model with lag time. The model was evaluated using goodness of fit plots and relative error measurements. The final POPPK parameters for MPA are: CL/F = 21.9 L/hr, V1/F = 14.6 L, V2/F = 218 L, Ka = 0.487 hr⁻¹, lag time = 0.477 hr, and Q/F = 18.4 L/hr. Statistical analysis indicated that none of the physiological or pathological covariates significantly contributed to POPPK parameter estimation. A limited-sampling model using three data points (2, 4 and 10hr postdose) was developed based on results from both MLR and NONMEM analysis with great correlation (r² = 0.944) of AUC0-12hr values between the full and LSS data sets. The LSS data set was also well fitted by a two-compartment model [CL/F= 19.7 L/hr, V1/F = 8.96 L, V2/F = 239 L, and Q/F = 11.3 L/hr] comparable to those calculated from the full data set.

Conclusion
The POPPK models and the LSS developed in this study could be used to optimize MPA dose in individual liver transplant recipient and to project MPA concentration-time profile in future therapeutic monitoring.