Poster

[P26-6] P26-6: Immunosuppressive drugs (5): Clinical practice

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[P26-6-6] Population pharmacokinetics and its clinical application of Mycophenolate Mofetil in renal transplantation patients

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Background

The pharmacokinetic of mycophenolate mofetil (MMF) shows great intra- and inter-individual variability, and that combined with a narrow therapeutic window making therapeutic drug monitoring of MMF been mandatory[1]. Clinical results of MMF are closely related to its metabolite-mycophenolic acids (MPA)[2]. The population pharmacokinetic program of NONMEM® predicts individual pharmacokinetic parameters of MPA based not only on individual patient measurements but also on the patient’ s covariates and population characteristics[3,4]. This study aims to establish an appropriate model for potentially use of individual drug delivery to optimize MMF dosing in renal transplantation patients

Methods

HPLC fluorescence method is established to measure the plasma concentration of MPA. Covariates such as age, gender, body weight, postoperative time (weeks), serum creatinine (Scr) and blood urea nitrogen (BUN) are considered. The population pharmacokinetic model of MPA has been developed with NONMEM® using 12-hour pharmacokinetic profiles from 102 renal transplant recipients. Internal validation of the model was based on data splitting and Boostrap methods. In addition, the model was validated for its clinical applicability and stability compares with Bayesian feedback method.

Results

The chromatographic conditions are as follows: acetonitrile and glycine buffer (32 mmol/L) is at the ratio of 17:83 (volume) as the mobile phase (pH=9.2); the optimal fluorescence excitation and emission wavelengths are 342 and 425 nm respectively. The model that best described the MPA data was a one-compartment model with first-order absorption process. Two covariates including postoperative time (POT) and total bilirubin (TBil) had significant effect on pharmacokinetic parameters. Whether combined medicine is a significant covariate in the model need to be clarified by massive clinical samples.

The final model equation: CL=55.9*EXP (ETA (1));

V=10600** (POT/15) **1.25*(TBIL/12) **0.230*EXP (ETA (2)) (Fig 1);

(n=12, r=0.999, extraction recovery rate=94.63±2.18%; accuracy=100.69%-110.57%); External validation showed that the model was able to predict MPA concentrations in the 12 new patients with an average predictive error of 6.1% when the standard sample concentrations were given from the previous week.

Zoom image

Fig 1. The individual variation of CL and V (ETA1， ETA2)

Conclusions

The HPLC method for MPA measurement is simple and practicable, and the NONMEM® pharmacokinetic model for MPA is successfully developed. The model showed good predictability in a new patient cohort and may be applicable as a clinical tool for optimizing MMF dosing in renal transplantation patients during perioperative period after further clinical validation.