Title: Population Pharmacokinetic analysis of tacrolimus combined with Wuzhi capsule in Chinese kidney transplant recipients

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Tacrolimus (TAC) is a critical constituent of immunosuppressive regimens in kidney transplant recipients (KTRs).TAC is mainly metabolized by the cytochrome P450 enzymes (CYP3A4 and CYP3A5) in vivo, and it is also the substrate of multidrug resistance efflux transporter P-glycoprotein (MDR1, encoded by ABCB1 gene). Pregnane X receptor (PXR) is encoded by NR1I2, which is responsible for the upstream regulation of drug-metabolizing enzymes and transporters, including the CYP3A4/3A5 and MDR1. Wuzhi capsule (WZC) was a Traditional Chinese Medicine (TCM), which was widely used as a TAC-sparing agent in China. WZC is also the substrates of CYP3A and P-gp. Due to the narrow therapeutic window of TAC, cytochrome P450 mediated drug interactions, and the individual variability in pharmacokinetics (PK) and pharmacogenomics (PG), it is necessary to monitor the steady-state trough concentration of TAC. Population pharmacokinetics (PPK) uses the scattered, routine therapeutic drug monitoring (TDM) data of patients to calculate relevant PPK parameters. Our study aimed to establish a PPK model and analysis the influence of drug co-administration as well as PK and PG factors in TAC metabolism. The medical records of 211 adult KTRs and their 824 TAC steady-state trough concentrations were reviewed. Each patient generally has 3 to 4 TAC trough concentration points. According to the patients' immunosuppressant regimen, KTRs were divided into two cohorts retrospectively, TAC + WZC cohort (107 cases), and TAC cohort (104 cases). MASSARRAY assay help us test the genotypes of twelve single-nucleotide polymorphisms (SNPs). The online platform SHEsis (http://shesisplus.bio-x.cn/tmp/184971.html) was used for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism. Finally, the PPK was analysed by nonlinear mixed effect model (NONMEM®, Version 7.3). CYP3A5 (rs776746)-CYP3A4 (rs4646437)-PXR (rs2276707) polyploid was found to be the main factor affecting TAC metabolism. Slow metabolizers carry polyploid rs776746-rs4646437-rs2276707 (CC/GG/CC) showed high TAC C0/D in posttransplant periods of 7, 14, and 21 days. The final model showed that the hematocrit (HCT), postoperative-time (POD), WZC, and CYP3A5 (rs776746)-CYP3A4 (rs4646437)-PXR (rs2276707) polyploid were the main factors affecting TAC clearance. The estimated clearance (CL/F) of TAC was 19.8 L/h. Above all, this was the first study that thoroughly evaluated the impact of WZC co-administration as well as variable SNPs by PPK analysis in KTRs, which may provide a rational consideration and medication adjustment suggestion for busy clinicians.

Biography

Jing Yan is a postgraduate majoring in pharmacology at Nanchang University. She was awarded the honorary titles of "Outstanding Student Cadre" and "Outstanding League Member." At the same time, she is a student who was published one Chinese core paper and applied for two patents.

Hongwei Peng is a senior pharmacist major in clinical pharmacy in fields of solid organ transplantation and leukemia. She is awarded Jiangxi provincial outstanding hospital pharmacist. The work was granted by the China National Sciences Foundation Committee (NO. 81860035) and Jiangxi Provincial Sciences Foundation Committee (20201BBG71008).

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