Population Pharmacokinetic Analysis of Tacrolimus Combined with Wuzhi Capsule in Chinese Kidney Transplant Recipients
Hongwei Peng, Yan Jing, Jinfang Hu, Xiaohua Wei*
* Correspondence: wxh_ndyfy@163.com

Introduction:
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). 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.

Methods:
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 among polymorphisms. Finally, the PPK was established by nonlinear mixed effect model (NONMEM®, Version 7.3).

Results:
The final model was:

\[ CL/F = 19.8 \times (HCT/0.27) - 0.721 \times 0.851 \times e^{-0.0865(POD/14) \times 1.32(haplotype)} \]

where Haplotype = 0 for Haplotype L; Haplotype = 1 for Haplotype R.

Conclusions:
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.

Acknowledgements:
This work was granted by Science and Technology Department of Jiangxi Province (No. 20201BBG71008)and Wu Jieping Medical Foundation (No. 320.6750.19090-36)