Poster

[P27-2] P27-2: Anti-infective drugs (7): Antifungals

Chair: Yoh Takekuma, Japan

Wed. Sep 27, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Wed. Sep 27, 2017 12:30 PM - 1:30 PM Annex Hall)

[P27-2-6] Impact of CYP2C19 genotype and liver function on voriconazole pharmacokinetics in renal transplant recipients

Miao Yan[1], Feng Wang[2], Zi-Wei Li[3], Feng-Hua Peng[4], Wu Liang[5], Bi-Kui Zhang[6] (1.The Second Xiangya Hospital, Central South University, 2.The Second Xiangya Hospital, Central South University, 3.The Second Xiangya Hospital, Central South University, Rui Jin Hospital, Shanghai Jiao Tong University, 4.Beijing Dryas Pharma-Tech Co., LTD, 5.The Second Xiangya Hospital, Central South University, 6.The Second Xiangya Hospital, Central South University)

Keywords: voriconazole, population pharmacokinetics, renal transplant recipients, CYP2C19 genotype

Background

Invasive fungal infection (IFI) is the main cause of early death in renal transplant recipients (RTRs). Voriconazole (VRC) is the first-line drug of IFI. VRC is with wide individual variability and narrow therapeutic range. But the factors influencing pharmacokinetic variability is incompletely understood. This manuscript performed a population pharmacokinetics (PPK) of VRC for personalized medicine.

Methods

A total of 125 trough concentrations (C_{min}) from 56 patients were enrolled retrospectively. Nonliner mixed effect mode (NONMEN) was used to describe a PPK model that was internally validated by Bootstrap method. Potential covariants included demographic characteristics, physiological and pathological data, concomitant medications and CYP2C19 genotype.

Results

A one-compartment model with first-order absorption and elimination was applied to characterize the VRC pharmacokinetics in RTRs. Aspartate transaminase (AST) had a significant influence on clearance (CL) while CYP2C19 genotype had a major impact on volume of distribution (V). The parameters of CL and V were 4.76 $L{\cdot}h^{-1}$ and 22.47 L, respectively. The final model were V(L) = 22.47 ×[1 + 2.21 ×(EM=1)] ×[1+ 4.67 ×(IM=1)] × [1 + 3.30 ×(PM=1)] ×exp (0.96); CL (L/h) = 4.76 ×(AST / 33) ^(-0.23) ×exp (0.14). The C_{min} of VRC in intermediate metabolizers was significantly higher than inextensive metabolizers.

Conclusions

Liver function and CYP2C19 polymorphism are major determinants of VRC pharmacokinetic variability in RTRs. Genotypes and clinical biomarkers can determine the initial scheme. Subsequently, therapy drug monitoring can optimize clinical success and minimize toxicity. Hence this is a feasible way to facilitate the individual's management of their treatment plan in RTRs. Nevertheless, it’ s the first report about PPK of VRC in RTRs.