Population Pharmacokinetics of Voriconazole in Healthy Korean Male with Various CYP2C19 Genotypes

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Objectives: Voriconazole is a first line therapy for invasive fungal infections. Due to its highly variable and nonlinear pharmacokinetic(PK) characteristics, it is difficult to maintain voriconazole concentration in the therapeutic range. The objective of this study was to develop a population PK model of voriconazole in healthy Korean males with various CYP2C19 genotypes to aid personalized therapy of voriconazole.

Methods: Plasma voriconazole concentration – time data in one phase I study were used in population analysis. Subjects whose CYP2C19 genotypes were already known received a single intravenous dose of voriconazole and serial blood samples were collected for 24 hours post-dose. The population PK model was developed using a nonlinear mixed-effects method (NONMEM®, Version:7.3). The first-order conditional estimation with interaction estimation method was implemented and model qualification was performed by bootstrapping and visual predictive checks(VPCs).

Results: A total of 650 voriconazole plasma concentrations from 49 healthy male volunteers with different CYP2C19 genotypes (EM: CYP2C19*1/*1, N=19; IM: CYP2C19*1/*2, *1/*3, *2/*1, N=21; PM: CYP2C19*2/*2, *2/*3, *3/*3, N=9) were included in the population PK analysis. A two-compartment nonlinear elimination model with combined error was chosen as the final PK model. The mean population maximum enzyme activity (Vₘₐₓ) was 36.9 mg/h and substrate concentration at which the reaction rate is half of Vₘₐₓ(Kₘ) was derived by the following equation: Kₘ = TVKₘ· (age/26) mg/L where the TVKₘ is 0.468, 0.742 and 2.43 for CYP2C19 EM, IM and PM, respectively. The mean population central volume of distribution (V₁) was 48.2 · (age/26)-0.759 L and peripheral volume of distribution was 127 L. Model evaluation by bootstrapping and VPCs suggested that the proposed model was adequate and robust with good precision.

Conclusions: The final population PK model adequately described the interindividual variability of plasma voriconazole concentrations among the subjects with different CYP2C19 genotypes. The model-fitted parameter estimates may be applied to develop the personalized therapy of voriconazole.