일반연제 3

Genotype-Phenotype Associations for CYP3A5 Genotype in the Basal, Inhibited, and Induced Metabolism of Midazolam in Healthy Koreans

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Backgrouds: The CYP3A subfamily is the most abundant cytochrome P450 in human liver and intestine and plays very important role in xenobiotic metabolism. CYP3A5 is polymorphically expressed in 10 to 30% of whites and Orientals. The most frequent *CYP3A5*3* allele is responsible for this polymorphism. In this study, we evaluated the effect of the *CYP3A5* genotype on the pharmacokinetics of intravenous midazolam (MDZ) in healthy Korean subjects after administration of itraconazole and rifampicin.

Methods: A single 1 mg of MDZ was administered intravenously to 9 healthy subjects who were classified to three genotypes, *CYP3A5*1/*1*, *CYP3A5*1/*3*, and *CYP3A5*3/*3*. After administration of itraconazole (200mg daily) for 4 days and rifampicin (600 mg daily) for 10 days, 1mg and 2mg of MDZ, respectively, were administered. Plasma concentrations of MDZ, 1-(OH) MDZ, 4-(OH) MDZ were determined by validated LC/MS/MS methods and data were analyzed by using non-compartmental linear PK methods. The genotypes of *CYP3A5* were determined by PCR-RFLP.

Results: The systemic clearance (CL) of MDZ was not statistically different among three *CYP3A5* genotypes. In contrast, CL of MDZ after daily administration of itraconazole for 4 days were 13.5±2.7, 11.5±4.5, and 8.5± 3.8 L/hr in *CYP3A5*1/*1*, **1/*3*, and **3/*3* genotypes, respectively. Furthermore, the percent-change in CL of MDZ and the AUC ratio of 1-(OH)MDZ to 4-(OH)MDZ were greater in homozygous *CYP3A5*3* carriers compared to homozygous wild-type subjects, and trends consistent with a gene dose effect were apparent. However, after daily administration of rifampicin for 10 days, the absolute value and the percent-increase in CL of MDZ were not different among three genotype carriers.

Conclusion: In the itraconazole-inhibited metabolism of midazolam, the systemic midazolam clearance and the extent of inhibition were associated with *CYP3A5* genotypes, such as *CYP3A5*1/*1*, **1/*3*, and **3/*3*, although no genotype-phenotype associations were not noted in the basal and rifampicin-induced metabolism of midazolam.

Key Words: midazolam, *CYP3A5* genotype, itraconazole, rifampicin, pharmacokinetics