Metabolic Disposition of Chlorpropamide in Relation to *CYP2C9* and *CYP2C19*

Ji-Hong Shon, Young-Ran Yoon, Kyung-Ah Kim, In-June Cha, Jae-Gook Shin

Dept of Pharmacology, Inje Univ Coll Med and Clinical Pharmacology Center, IJUPH

Chlorpropamide is a sulfonylurea hypoglycemic drug which shows wide interindividual variations in pharmacokinetics. It is chemically similar to tolbutamide. We evaluated whether CYP2C9 and CYP2C19 were involved in the metabolism of chlorpropamide. In Addition, we evaluated the possibility that CYP2C19 might participate in the metabolism of tolbutamide in vivo.

We conducted single blind ramdomized crossover chlorpropamide and tolbutamide single oral administration study in 5 EM and 4 PM of CYP2C19, and 2 $Ile^{359}Leu$ heterozygous mutants of CYP2C9. We collected blood samples upto 4 days and urine sample upto 24 hours after single oral administration of chlorpropamide or tolbutamide. To evaluate the effects of drugs, We measured serum glucose level after 100g dextrose oral administration in placebo and each study day. The concentration of plasma chlorpropamide, tolbutamide, and hydroxytolbutamide were measured using HPLC. Pharmacokinetic parameters were estimated by one-compartment analysis using PC NONLIN.

Pharmacokinetic data of chlorpropamide and tolbutamide did not show any significant differences among genotypic groups of CYP2C9 and CYP2C9. But, tolbutamide AUC/ hydroxytolbutamide AUC ratio was lower in heterozygous mutants than in wild type group of CYP2C19. In the glucose level test, in the heterozygous mutants, the AUC of plsma glucose concentration-time after chlorpropamide and tolbutamide were much decreased than wild type of CYP2C9.

This work has not clearly identified the enzymes which involved in metabolism of chlorpropamide and could not comfirm whether CYP2C19 was related in the metabolism of tolbutamide *in vivo*.