P-86

INVOLVEMENT OF CYP2C9 ON CHLORPROPAMIDE 2-HYDROXYLATION IN HUMAN: *IN VITRO* AND *IN VIVO* EVIDENCE.

Ji-Hong Shon, Young-Ran Yoon, Min-Jung Kim, In-June Cha, and Jae-Gook Shin

Dept. of Pharmacol., Inje Univ., Coll. of Med. and Clin. Pharmacol. Center, Pusan Paik Hosp., Pusan, Korea
E-mail: phshon@ijnc.inje.ac.kr

No report has been addressed to the CYP isoforms catalyzing chlorpropamide, a structural analogue of tolbutamide. To evaluate enzyme(s) mediating formation of 2-hydroxychlorpropamide, a major metabolite and identified by LC/Mass and NMR, incubation studies using human liver microsomes and cDNA expressed CYP were performed on the presence or absence of selective inhibitors of each CYP isoform. We also compared the disposition of chlorpropamide and formation of 2-hydroxy metabolite between subjects with CYP2C9*1/*1 and *1/*3, and EM and PM of CYP2C19 genotype. Formation of 2-hydroxy metabolite was well fitted to Michaelis-Menten kinetics (K_m=78.78uM, V_{max}=8.89 pmol/min/mg). The formation of this metabolite was almost wiped out by the presence of 10uM sulphaphenazole. Furafylline, quinidine ketoconazole, s-mephenytoin showed no inhibition. 2-hydroxy metabolite was also formed in cDNA expressed CYP2C19 as well as CYP2C9, suggesting the possible involvement of CYP2C19 *in vitro*. There was a significant difference of Clnr (2.39±0.27 and 1.68± 0.66 ml/hr/kg) and MR (chlorpropamide/ 2-hydroxychlorpropamide in urine: 0.59±0.37and 1.04± 0.48) between CYP2C9*1/*1 and CYP*1/*3 groups, whereas no difference between EM and PM of CYP2C19. These results suggest that CYP2C9 is major CYP isoform catalyzing the chlorpropamide 2-hydroxylation in human *in vivo*, and CYP2C19 contributes less to the *in vitro* disposition of chlorpropamide and its metabolite formation.