P-83

IN VITRO INHIBITION BY TRICYCLIC ANTIDEPRESSANTS OF PHENYTOIN *p*-HYDROXYLATION: MECHANISTIC APPROACH

Ji-Young Park, Min-Jung Kim, Ji-Hong Shon, and Jae-Gook Shin

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

The inhibitory potentials of TCAs (imipramine, desipramine, amitriptyline, and nortriptyline) on phenytoin *p*-hydroxylation and probe metabolic pathways of each CYP isoforms were evaluated from incubation studies of human liver microsomes and cDNA-expressed cytochrome P450s *in vitro* in order to understand the mechanism of drug interaction between TCAs and phenytoin, a substrate of CYP2C9 and CYP2C19. Imipramine and amitriptyline strongly inhibited PHT *p*-hydroxylation as a competitive manner with the estimated *Ki* of 6.5 ± 2.6 μM and 2.2 ± 0.2 μM, respectively. The inhibitory effects of desipramine and nortriptyline were weaker than those of their parent drugs (up to $11 \sim 19$ % of control at highest concentration). All TCAs strongly inhibited CYP2D6-catalyzed dextromethorphan *O*-demethylation (*Ki* = $8 \sim 30$ μM). Imipramine and amitriptyline slightly inhibited CYP2C9-catalyzed tolbutamide 4-methylhydroxylation and CYP2C19-catalyzed S-mephenytoin 4-hydroxylation (< 25 %), but all TCAs showed no inhibition on CYP1A2- and CYP3A4-catalyzed reactions. TCAs inhibited the formation of p-hydroxyphenytoin in cDNA-expressed CYP2C9. In conclusion, TCAs appear to be remarkable inhibitors of CYP2D6 and CYP2C9, and to increase the serum concentration of PHT co-administered through the inhibition of CYP2C9-catalyzed phenytoin *p*-hydroxylation.