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IN VITRO INHIBITION BY TRICYCLIC ANTIDEPRESSANTS OF PHENYTOIN *p*-HYDROXYLATION: MECHANISTIC APPROACHJi-Young Park, Min-Jung Kim, Ji-Hong Shon, and Jae-Gook Shin

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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 K_i of $6.5 \pm 2.6 \mu\text{M}$ and $2.2 \pm 0.2 \mu\text{M}$, respectively. The inhibitory effects of desipramine and nortriptyline were weaker than those of their parent drugs (up to 11~19 % of control at highest concentration). All TCAs strongly inhibited CYP2D6-catalyzed dextromethorphan *O*-demethylation ($K_i = 8 \sim 30 \mu\text{M}$). 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.