Pharmacogenetic Relevance of Metabolic Disposition of Imipramine in Oriental Subjects

Department of Pharmacology, College of Medicine, Gyeongsang National University : **Dong-Ryul Sohn, Ki Churl Chang**
Department of Pharmacology, College of Medicine, Inje University : **Jae-Gook Shin**
Department of Psychiatry, College of Medicine, Inje University : **Young-Hun Kim**

We studied the metabolic disposition of imipramine by measuring imipramine and its metabolites in plasma and urine simultaneously after a single oral dose of 25mg of imipramine hydrochloride administered to 16 healthy(thirteen Korean and 3 Japanese) volunteers. Four of the subjects were poor metabolizers(PMs) of metoprolol but extensive metabolizers(EMs) of *S*-mephenytoin(PM_{ML}/EM_{MP}), five subjects were EMs of metoprolol but PMs of *S*-mephenytoin(EM_{ML}/PM_{MP}), and seven subjects were EMs of both metoprolol and *S*-mephenytoin. The mean (± S.D.) oral clearances of imipramine were smaller in the PM_{ML}/EM_{MP} group and the EM_{ML}/PM_{MP} group than in the EM_{ML}/EM_{MP} group, although a statistical difference($p<0.05$) was found only in the EM_{ML}/PM_{MP} *vs.* the EM_{ML}/EM_{MP} group. The mean area under the plasma concentration-time curve(AUC) of desipramine was 9 times greater($p<0.01$) in PM_{ML}/EM_{MP} group, whereas the mean value was 0.8 times smaller($p<0.05$) in the EM_{ML}/PM_{MP} group than in the EM_{ML}/EM_{MP} group. The $\log_{10}$ metoprolol/α-hydroxymetoprolol ratio correlated positively with the AUC of desipramine($p<0.01$) and with the AUC ratio of desipramine/imipramine($p<0.05$) but negatively with the AUC ratio of 2-hydroxyimipramine/imipramine($p<0.05$). Log_{10} percent 4'-hydroxymephenytoin excreted in 8-hr urine correlated positively with the AUC of desipramine($p<0.01$) and with the AUC ratio of desipramine/imipramine($p<0.01$). The urinary excretions of imipramine and its metabolites also reflected the data derived from plasma samples in the three different phenotype-paired panels.

The results suggest that the 2-hydroxylation and the *N*-demethylation of imipramine metabolism are under a pharmacogenetic control of debrisoquin- and *S*-mephenytoin-type oxidation, respectively, in Oriental subjects.