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# CHARACTERICS OF OXIDATION PHARMACOGENETICS IN ORIENTAL POPULATIONS AND ITS CLINICAL IMPLICATIONS

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Hepatic drug oxidation is a major source of interindividual variations in drug pharmacokinetics and its therapeutic response. Among genetically determined oxidation polymorphisms of drugs, the most studied oxidation is the debrisoquine (D)−type or mephenytoin(MEPH)−type oxidation. However, informations on these oxidation pharmacogenetics have come mainly from Caucasian populations. Therefore, P450−IID6−and P450IIC9−mediated oxidation polymorphisms were examined using metoprolol(M) and MEPH, respectively, in 3 native Oriental populations according to the reported phenotyping criteria by use of the urinary metabolic ratios(MRs). The incidence of poor metabolizers (PMs)was : 0.7% in 295 Japanese, 0.5% in 218 Koreans, and 0% in 107 Chinese for M : 22% in 200 Japanese, 11% in 206 Koreans, and 17% in 98 Chinese for MEPH. There were no statistically significant differences in these frequencies among the 3 Oriental groups. However, the respective mean (±SD) MRs of M (0.87±0.90 and 0.85±1.14) in Japanese and Korean extensive metabolizers(EMs) were significantly ($p<0.001$) less than that in Chinese EMs(2.81±2.35), and the probit data of Chinese EMs were shifted to the right compared with those for Japanese and Korean EMs.

The results indicate that 1) the Oriental populations studied have a lower frequency of PMs of the D−type oxidation and a greater frequency of PMs of MEPH type oxidation compared with the respective frequencies(3−10% and 3−6%) reported from Caucasian populations and 2) oxidation capacities mediated P450IID6 and C9 appear to differ between the EMs within similar ethnic groups residing in the same geographic region, although the frequencies of the PM phenotype are similar. I wish to discuss these findings in the light of clinical implications and drug development in Oriental populations. In addition, I present diazepam demethylation and hydroxylation in 12 Japanese human liver microsomes that were phenotyped for MEPH. Moreover, I present our recent data on diazepam kinetics in the extensive and poor hydroxylators of mephenytoin recruited from a Korean population. An interglobal pharmacogenetic study would help settle several aspects of the unresolved interethnic differences in clinical pharmacoepidemiological problems.