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CYP2C19 AND CYP2C9 GENO-AND PHENOTYPES IN HEALTHY SWEDISH AND KOREAN SUBJECTS

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Abstract

Cytochrome P450s (CYPs) are responsible for approximately 75% of the phase I-dependent drug metabolism. Several important polymorphisms in these enzymes are known to affect the individual drug response. CYP2C19 and CYP2C9 are both polymorphic enzymes and are responsible for the metabolism of many therapeutically used drugs, e.g. anticoagulants, antidepressants and antiulcer drugs. This thesis focuses on comparing genotypes and phenotypes in healthy Swedish and Korean subjects. A higher incidence of poor metabolizers (PMs) was found in the enzyme CYP2C19 in Koreans (14%) compared to Swedes (4 %). The frequency of the CYP2C19*2 allele was 16 % and 28 % in Swedes and Koreans, respectively. The Asian specific *3 allele was present in 11% of Korean alleles. The frequency of the CYP2C19*17 allele was very low in Koreans (0.3%) compared to Swedes (20%) and this allele caused an increased enzyme activity in the Swedish subjects. Among subjects homozygous for CYP2C19*1, Koreans displayed significantly lower CYP2C19 enzyme activity than Swedes ($p < 0.000001$). In Koreans a pronounced gender difference was apparent and females ($n=24$) had significantly lower metabolic ratio (MR) of omeprazole and its metabolite hydroxyomeprazole than males ($n=30$; $p < 0.0001$). Such a gender difference was not seen among Swedes. Controlling for the effect of genotype and sex, Koreans display lower CYP2C19 activity than Swedes. Swedish females who used oral contraceptives (OC) had higher MR (lower activity) than non users (NOC) ($p < 0.00001$). No effects of smoking were observed. A higher MR of losartan was found in Swedes compared to Koreans. The allele frequency of CYP2C9 *2 was 10% in the Swedes and due to its infrequent occurrence not determined in Koreans. The frequency of the allele CYP2C9*3 was higher in Swedes (10%) compared to Koreans (6%). Swedish females user of OC had a higher MR than NOC in the genotype group *1/*1 ($p=0.001$). Only one Korean woman was user of OC. The woman in the case report in this thesis required treatment with high doses of phenytoin. When fluconazole, a potent inhibitor of CYP2C9 was added to the treatment regimen, the patient developed adverse drug reactions. The losartan MR was < 0.13 for this patient which is lower than any of the 190 healthy Swedish subjects used for comparison. The patient is thus an UM (ultrarapid metabolizer) of the CYP2C9 substrates phenytoin and losartan. Ultra-rapid metabolism of drugs may have a genetic, epigenetic or environmental basis that can explain the clinically observed differences in the metabolism of drugs.

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