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The Genetic Polymorphism of CYP2C8 in a Korean Population and Identification of Null Allelic Variant

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Background: The human cytochrome P450 (CYP) 2C8 is a major hepatic P450, constituting about 7% of total microsomal CYP content in the liver and is responsible for the metabolism of a wide range of drugs such as paclitaxel, cerivastatin, amiodarone and rosiglitazone. In the present study, the genotype profile of CYP2C8 was analyzed in a Korean population. Frequency in multi-ethnic population and in vivo functionality of novel null allelic CYP2C8 variant were evaluated.

Methods: Whole blood samples from 50 unrelated Korean subjects were genotyped for 3kb of 5' upstream region, all exon-intron boundaries, exons, and UTR regions of CYP2C8 gene by direct sequencing. Genotyping of CYP2C8 has been addressed only for null allelic variant, CYP2C8*M using pyrosequencing in the 447 Koreans, 93 African?CAmericans, 100 Caucasians, 348 Chineses and 100 Vietnameses. Then, in-vivo single PK study of CYP2C8 probe, rosiglitazone (4 mg), was conducted in 7 healthy subjects with CYP2C8*1/*1 and 2 with CY2C8*1/*M.

Results: We identified a novel null allelic variant(CYP2C8*M) in Koreans, Chinese and Vietnamese, but not founded in Caucasian and African-american population enrolled in this study. The allelic frequency of this novel SNP was 0.3% in 447 Koreans. After single oral dose of rosiglitazone, subjects with heterozygous mutation of CYP2C8*M seemed likely to be higher plasma concentration of rosiglitazone than those with wild genotype. The AUC of rosiglitazone in 2 subjects with CYP2C8*M (2,334 and 2,350 ng*hr/ml) showed higher value than that in those with CYP2C8*1/*1 (N=7, 1,414±311 ng*hr/ml).

Conclusion: The null allelic variant, CYP2C8*M, was identified in Asian races, but its frequency was rare (≤0.5%). Subjects with heterozygous mutation of CYP2C8*M showed the higher oral bioavailability of rosiglitazone than those with wild genotype. The subject with CYP2C8*M/*M mutant genotype would be expected to demonstrate the marked defective catalyzing activity of CYP2C8 substrates and might lead to clinically relevant results after taking those. * CYP2C8*M is designated as CYP2C8*11 by CYP nomenclature committee. SNP information will be released after publication.