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GENETIC POLYMORPHISM OF CYTOCHROME P450 2B6 IN A KOREAN POPULATION. S. Lee, PhD, S. Kim, MS, H. Jeong, MS, J. Shon, MD, Y. Yoon, MD, PhD, J. Shin, MD, PhD, Inje University, Busan, Republic of Korea.

CYP2B6 gene shows genetic polymorphisms with interethnic variations, but no reports have been addressed in Korean population. Allelic distribution of CYP2B6*4, *5, *6, *7, and *9 was evaluated in a Korean population. Genotype was determined by PCR-RFLP analysis of three loci (G516T, A785G, and C1459T) in 86 healthy Korean subjects. There were no subjects with either CYP2B6*5 or *7, both of which include a C1459T mutation. Of 86 subjects, 37, 12, 8, 2, 1, and 2 subjects had genotypes of CYP2B6*1/*1, *1/*4, *1/*9, *4/*6, *6/*9, and *6/*6, respectively. And 24 subjects were found to have either CYP2B6*1/*6 or *4/*9 genotypes. Due to the absence of information on gametic phase, allelic frequencies of CYP2B6*4 (A785G), *6 (A785G, G516T), and *9 (G516T) could not be determined directly from PCR-RFLP method. Haplotype frequencies of CYP2B6*4, *6 and *9 were expected by Expectation-Maximization algorithm. The allelic frequencies of CYP2B6*4, *6 and *9 were 8.7%, 17.5%, and 5.8%, respectively. Allelic frequencies of CYP2B6*4 and *6 in Korean are similar to those of Japanese but different from those of Caucasians (Chi-square test, $p<0.1$). Further, CYP2B6*5, which is known to decrease CYP2B6 activity in vivo and found in Caucasians with high frequency (10.9%), was rarely found in Korean (0%) and Japanese (1.1%). Our results suggest that in the context of genetic polymorphism of CYP2B6 Korean population is similar to Japanese but significantly different from Caucasians.

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THE MUTANT A ALLELE FUNCTION IN EXON 21 G2677T/A OF HUMAN MDR1 GENE. S. Yi, K. Hong, MD, H. Lim, MD, J. Chung, MD, D. Oh, OMD, J. Kim, MD, H. Chung, J. Cho, PhD, I. Jang, MD, PhD, S. Shin, MD, PhD, Seoul National University College of Medicine, Seoul, Republic of Korea.

There are still contradictory reports on the relationship between the MDR1 genotype and disposition of the PGP substrates. The allele frequency for the mutant A allele of the exon 21 G2677T/A (Ala 893Ser/Thr) is about 20% in Asian groups but the frequencies are negligible in the Caucasian and African populations. We hypothesized that as yet unknown A allele function was the one of reasons of contradictory results. This study was performed to clarify the effects of the major MDR1 gene polymorphisms including a mutant A allele in exon 21 on the fexofenadine pharmacokinetics. A single oral dose of 180 mg fexofenadine HCl was administered in 33 healthy Korean male volunteers, who were divided into 6 groups on the basis of the MDR1 haplotype for G2677T/A and C3435T polymorphism. A significant relationship was observed between genotypes and AUCs ($p<0.05$). 2677AA/3435CC subject group ($n=3$) showed significant lower AUC(0-24) values than those of other 5 groups (2677/3435: GG/CC, GT/CT, TT/TT, GA/CC, TA/CT). Homozygous 3435TT subjects had significant higher AUC(0-24) and Cmax values than CC subjects who were stratified for genotypes at position 3435 [AUC(0-24) 5934 +/- 2064 ng*hr/mL vs 3998 +/- 1241 ng*hr/mL, Cmax 958 +/- 408 ng/mL vs 673 +/- 242 ng/mL; mean +/- SD]. It was thought that the A allele variant in exon 21 had more powerful efflux function of PGP than wild type or T allele variant.

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EFFECT OF THE SEX-RELATED MDR1 GENE POLYMORPHISMS ON FEXOFENADINE DISPOSITION. H. Chung, S. Yi, K. Hong, MD, H. Lim, MD, J. Chung, MD, D. Oh, OMD, J. Kim, MD, J. Cho, PhD, I. Jang, MD, PhD, S. Shin, MD, PhD, Seoul National University, Seoul, Republic of Korea.

There have been contradictory reports about the influence of MDR1 polymorphisms on P-glycoprotein (PGP) expression and function. We could speculate that sex-related MDR1 expression difference was the one of reasons of contradictory results. This study was performed to evaluate the MDR1 genotype frequency in the Korean population and impact of genotypes and sex differences on the disposition of the PGP substrate. A total of 232 healthy unrelated Korean volunteers were genotyped for the MDR1 exon 12 1236C>T, exon 21 2677G>T/A and exon 26 3435C>T polymorphism. A single oral dose of 180 mg fexofenadine HCl was administered to 31 healthy subjects, comprised of 9 subjects with 2677GG/3435CC (5 male, 4 female), 12 subjects with 2677GT/3435CT (6 male, 6 female), and 10 subjects with 2677TT/3435TT (6 male, 4 female). Four major haplotypes of C-A-C, C-G-C, T-G-C and T-T-T constitute 88.8% of all haplotypes in Korean subjects. Fexofenadine dispositions were not significantly different between gender groups in matched genotype. However, a significant difference in AUC(0-24) were observed in male groups (2677GG/3435CC vs 2677GT/3435CT vs 2677TT/3435TT: 4017 +/- 1137 vs 5786 +/- 976 vs 5934 +/- 2064 ng*hr/mL; $P=.038$) but not in female groups. We did not identify influence of MDR1 genotype matched sex difference on fexofenadine disposition.

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GENETIC POLYMORPHISM OF CYP2C9 IN A VIETNAMESE POPULATION. K. Kim, BS, Y. Sunwoo, MD, J. Ryu, MD, S. Lee, Y. Yoon, MD, PhD, I. Cha, MD, PhD, J. Shin, MD, PhD, Inje University, Busan, Republic of Korea.

CYP2C9 is the major cytochrome P450 2C enzyme in human liver and contributes to the metabolism of a number of drugs. This enzyme shows genetic polymorphism with high inter-ethnic variations, but no report has been addressed to the genetic polymorphism in Vietnamese population. Among 12 known allelic variations, CYP2C9*2 (Arg144Cys) and CYP2C9*3(Ile359Leu) genotypes have been most characterized due to its clinical relevance to cause enzymatic defects. Genetic polymorphism of these two alleles was determined in 157 Vietnamese subjects by PCR-RFLP method and compared with those of other ethnics. CYP2C9*2 allele was not detected in Vietnamese, which was consistent with the previous results suggesting no occurrence of CYP2C9*2 allele in East Asians including Korean, Japanese, and Chinese. This frequency is highly different from those of Caucasians (10-13%) and American (8%). Out of 157 Vietnamese subjects, 7 subjects were heterozygous for CYP2C9*3 allele, which gave allelic frequency of 2.23%. In the context of the allelic frequency of CYP2C9*3, Vietnamese is not different from African-American (0.5%) and East Asians including Korean (1.1%), Japanese (2.1%) and Chinese (1.7-2.6%), but significantly different from American (6%) and Caucasians (8-10%) (Chi-square test, $p<0.05$). Our results indicate that genetic polymorphism of CYP2C9 in Vietnamese population is similar to those of East Asians, but significantly different from those of American and Caucasians.