[10:30 – 11:00]

Effect of *MDR1* Haplotypes on P-glycoprotein Substrates Disposition in Korean Subjects

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Introduction

Many factors, such as dietary intake, age, environmental conditions, and concurrent drug therapies, affect a person's response to medications [1-3]. Importantly, genetic makeup determines inherent pharmacokinetics, giving rise to interperson differences in drug absorption, distribution, metabolism, and excretion. Some of these differences can be explained by genetic variations in transport proteins (e.g., P-glycoprotein (P-gp) and organic anion transporting polypeptide, which affect drug absorption), in drug targets (e.g., β_2- adrenergic receptors, which affect drug response), and in the function of cytochrome (CYP) P450 or phase 2 drug-metabolizing enzymes (e.g., N-acetyltransferase 2 or thiopurine S-methyltransferase, which affect drug metabolism) [4]. The recent explosion of interest in the use of pharmacogenomics for new-drug development and individualized drug prescribing has been accompanied not only by a flood of new or improved technologies for the analysis of single-nucleotide polymorphisms (SNPs), but also by gene-based haplotype approaches that take into account the combination of SNP present in an allele.

Purposes

The purposes of this study were to analyze haplotype frequencies on *MDR1* (exon 12, 21 and 26) gene in Korean population and to investigate the genotypic and haplotypic relationship to phenotype of P-gp substrates such as risperidone, levosulpiride, and sparfloxacin in Koreans.

Methods

Genotyping and haplotype analysis

Four hundred and thirty Korean subjects were genotyped for *MDR1* gene by polymerase chain reaction-restriction fragment length polymorphism (PCR-PFLP) [5]. Allele and genotype frequencies for the SNPs were assessed for deviation from Hardy-Weinberg equilibrium using chi-square analysis. Linkage disequilibrium between the different pairs of SNPs was determined in terms of the classical statistic |D|. Haplotype frequencies were estimated based on the Expectation-Maximization (EM) algorithm [6]. Haplotype frequencies on *MDR1* genes were estimated using the population genetics data analysis program HapAnalyzer [7].

Subjects

Based on the genotype analysis, each subject with different genotypes who gave us informed consent recruited. The study protocol was approved by the Institutional Review Board (IRB) of Institute of Bioequivalence and Bridging Study, Chonnam National University (Gwangju, Korea). Each subject was physically normal and had no antecedent history of significant illness or hypersensitivity to any drugs.

Pharmacokinetic study

Each drug dose was given orally with 240 mL of water after an overnight fast. Blood samples were taken during the predetermined time after the dose. Serum concentrations of each drug were measured using HPLC method and the pharmacokinetic parameters were calculated.

Results

Genotyping and haplotype analysis

Of the 430 individuals analyzed, the allele frequencies of *MDR1* 1236T, 2677T, 2677A and 3435T were 56.86, 31.63, 3.49 and 36.51% in Korean population, respectively (Table 1).

Table 1. Allele and genotype frequencies in the *MDR1*.

Exon	Genotype frequency (%)			Allele frequency (%)			HWE *P*-value
12	CC	CT	TT	C	T		0.2325
C1236T	20.00	46.28	33.72	56.86	43.14		
21	GG	GT	TT	G	T	A	0.1284
G2677T	40.47	48.84	10.70	64.88	31.63.	3.49	
26	CC	CT	TT	C	T		0.0741
C3435T	38.37	50.23	11.40	63.49	36.51		

Haplotype analysis of *MDR1* gene, restricted to variants in exon 12, 21 and 26, revealed seven of twelve theoretically possible haplotypes. Three *MDR1* haplotypes (CGC, TTT and TGC) were observed with higher frequencies in Koreans (Fig. 1).

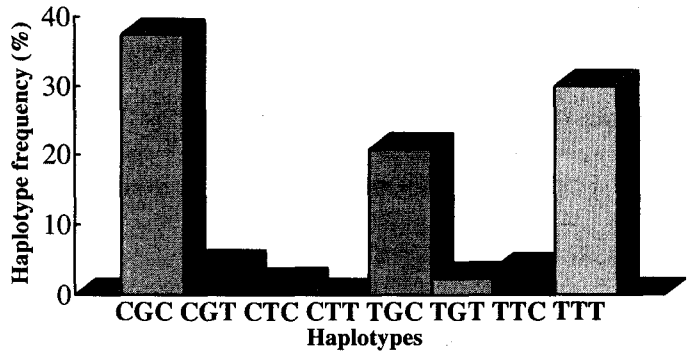

Fig. 1. *MDR1* haplotypes based on SNPs in exon 12, 21 and 26.

Pharmacokinetics of risperidone, levosulpiride and sparfloxacin in relation to MDR1

A correlation between the pharmacokinetic parameters of risperidone and levosulpiride and genotypes and/or haplotypes was observed (Fig. 2-5). However, in case of sparfloxacin, we could not find any correlation between such parameters of sparfloxacin and genotypes and/or haplotypes (Fig. 6-7).

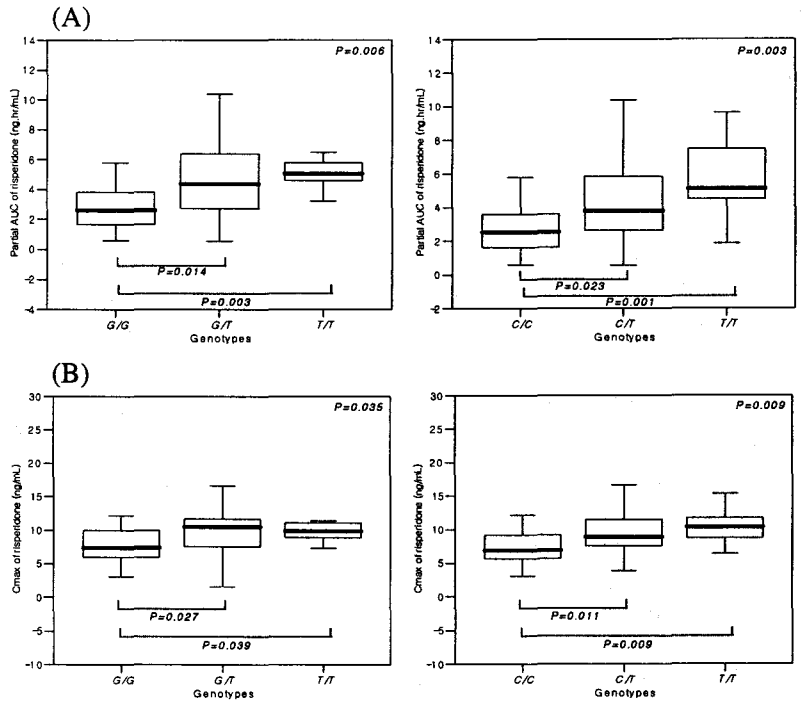

Fig. 2. Correlations of the *MDR1* SNP (G2677T and C3435T) with $AUC_{0\text{-}1h}$ (A) and C_{max} (B) of risperidone, in healthy male Korean subjects.

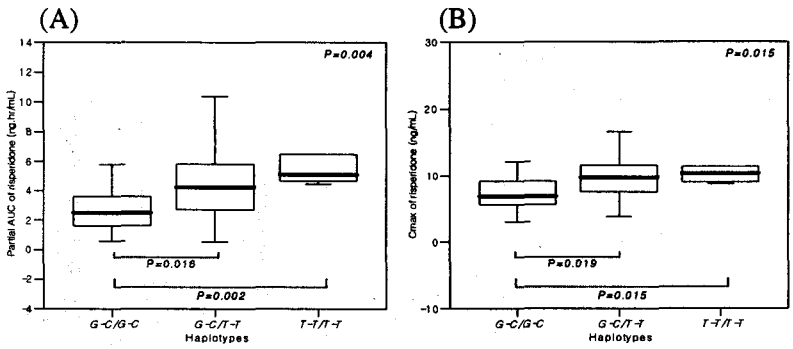

Fig. 3. Correlations of the *MDR1* haplotype with $AUC_{0\text{-}1h}$ (A) and C_{max} (B) of risperidone, in healthy male Korean subjects.

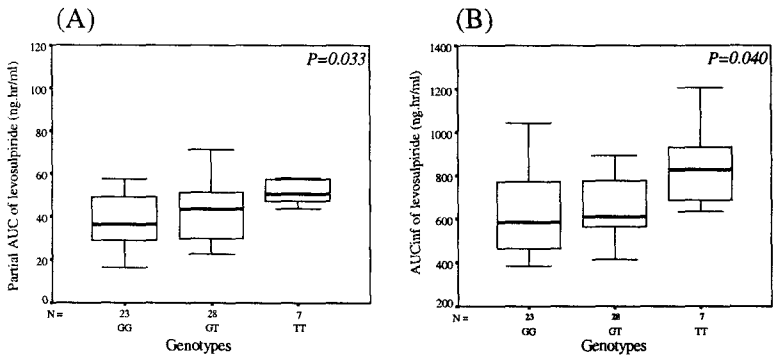

Fig. 4. Comparison of the partial AUC ($AUC_{0\text{-}2h}$) (A) and $AUC_{0\text{-}\infty}$ (B) of levosulpiride among the three different *MDR1* G2677T genotype groups.

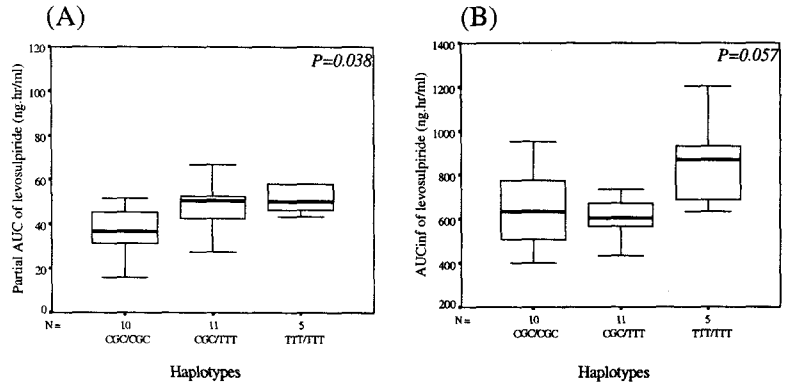

Fig. 5. Comparison of the partial AUC ($AUC_{0\text{-}2h}$) (A) and $AUC_{0\text{-}\infty}$ (B) of levosulpiride among the three different *MDR1* haplotype groups.

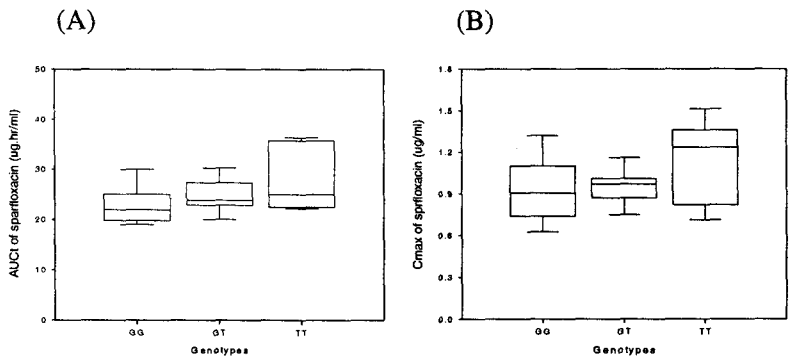

Fig. 6. Comparison of the AUC ($AUC_{0\text{-}72h}$) (A) and Cmax (B) of sparfloxacin among the three different *MDR1* genotype groups.

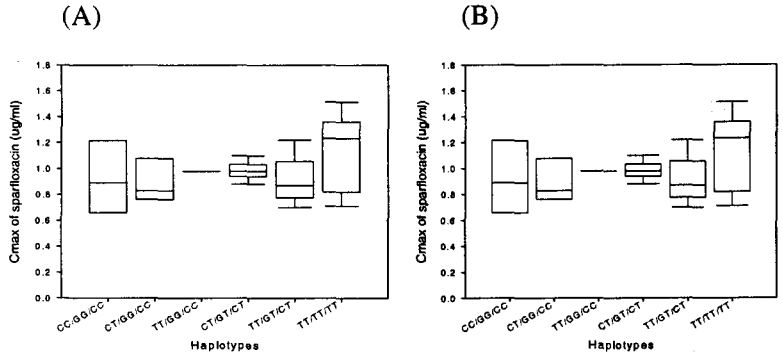

Fig. 7. Comparison of the AUC ($AUC_{0\text{-}72h}$) (A) and Cmax (B) of sparfloxacin among the different *MDR1* haplotype groups.

Conclusion

These results suggest that some genotype-phenotype and haplotype-phenotype correlations of risperidone and levosulpiride could reliably predict the drug disposition in different individuals.

References

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(7) http://www.ngri.re.kr/HapAnalyzer/right.html.