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EFFECTS OF CYP3A5 GENOTYPE ON NIFEDIPINE PHARMACOKINETICS WITH DIFFERENT DRUG ABSORPTION SITE

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CYP3A5 is polymorphically expressed in liver. The main reason for the variable expression has been attributed to a SNP, g.6986A>G, in intron 3 (known as the CYP3A5*3 allele), which causes missplicing. People with at least one CYP3A5*1 allele express large amounts of CYP3A5. Subjects without CYP3A5 expression was supposed to have higher plasma concentration and lower clearance. However, data are controversial when effects of CYP3A5 genotype on drug disposition were examined. In a multiple-dose Adalat OROS® study, we found a significantly higher nifedipine plasma concentration in CYP3A5*3/*3 male subjects. The difference was not found in females. We postulated that there is a compensational expression of intestinal CYP3A4 in CYP3A5-negative female subjects. Our laboratory previously reported no difference in midazolam pharmacokinetics in CYP3A5-negative and CYP3A5-positive male subjects. We further postulated that male has a CYP3A4 up-regulation in the upper part of intestine for CYP3A5-negative subjects. Midazolam can be absorbed in the jejunum, so it may be metabolized by CYP3A4 induced in upper part of intestine. On the other hand, Adalat OROS® is mainly absorbed in the ileum, so the nifedipine concentration is therefore higher in CYP3A5-negative male subjects. To confirm this hypothesis, we plan to recruit 80 healthy male volunteers. One group (n=40) is given a single-dose of Adalat®, and the other group (n=40) is given a single-dose of Adalat OROS®. Each group contains 20 CYP3A5-positive subjects and 20 CYP3A5-negative subjects. Blood samples are collected to analyze the AUC of nifedipine. The aim is to study the effect of CYP3A5 genotype on nifedipine pharmacokinetics with different dosage forms and the mechanism of how CYP3A5 polymorphisms affect drug disposition.

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EFFECTS OF P-GLYCOPROTEIN POLYMORPHISM ON PHENYTOIN PHARMACOKINETICS

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P-glycoprotein is the encoded product of the human MDR1 (ABCB1) gene that expresses major in the epithelial cells of the gastrointestinal tract, liver, and capillaries of the brain and it acts as a barrier to the uptake of xenobiotics. A number of single-nucleotide polymorphisms (SNPs) in MDR1 have been identified and the most important two SNPs are C3435T in exon 26 and G2677T in exon 21 of the MDR1 gene. A number of studies have shown that plasma level of many drugs belong to P-gp substrates are associated with that two SNPs. However, the reported effects of MDR1 SNPs have been inconsistent and even conflicting. Phenytoin, an antiepileptic drug, is substrate of P-gp. Persistent low levels of phenytoin in plasma and P-gp brain overexpression in several refractory epilepsy (RE) patients were reported. P-gp express in intestine may affect bioavailability of phenytoin. Our objective is to investigate that two SNPs C3435T in exon 26 and G2677T in exon 21 of the MDR1 gene may affect pharmacokinetics of phenytoin. Firstly we determine the SNPs of P-gp and select two genotypes including GC/GC and TT/TT (exon21-26/ exon21-26) by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and check them by direct sequencing. Two groups of the volunteers are both given oral and intravenous phenytoin. Concentration of phenytoin in plasma at different times are analyzed with HPLC and the data express as AUC (area under curve) and other pharmacokinetic parameters. Two SNPs of P-gp may affect pharmacokinetics of phenytoin and this study will help to understand the inter-individual difference in pharmacokinetics of phenytoin.