CYP3A5, GENDER, AND INTESTINAL ENZYME EXPRESSION AFFECT PHARMACOKINETICS OF NIFEDIPINE
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[Purpose]…CYP3A5 is polymorphically expressed in human liver and small intestine. One with at least 1 CYP3A5*1 allele express a higher amount of CYP3A5 and are supposed to have lower plasma drug concentration and a higher clearance. Literature data are controversial on effects of CYP3A5 genotype on drug disposition. We postulated a CYP3A4 up-regulation in the small intestine for CYP3A5-negative subjects. To investigate the possible CYP3A4 up-regulation, we studied the effect of CYP3A5 genotype on nifedipine pharmacokinetics with different dosage forms.

[Methods]…The immediate-released nifedipine is absorbed in the upper intestinal tract and extended-release nifedipine is absorbed the lower part. To each gender, subjects were given a single-dose of Adalat® (immediate-released nifedipine), or a single-dose of Coracten® (extended-released nifedipine). Each group contains 12 CYP3A5*1/*3 subjects and 12 CYP3A5*3/*3 subjects. Blood samples were collected to analyze the pharmacokinetics of nifedipine.

[Results and Discussion]…We found that CYP3A5 genotype has no effects on nifedipine pharmacokinetics of males in the Coracten® study. In the Adalat® study, CYP3A5*3/*3 subjects exhibited lower peak concentrations than CYP3A5*1/*3 subjects. In female subjects, we found that CYP3A5 genotype has significant effects on nifedipine pharmacokinetics in the Coracten® study, but not in the Adalat study.

[Conclusions]…The studies support the hypothesis of intestinal up-regulation of CYP3A4. However, males and females are up-regulated differently. The data suggest that there is a up-regulation of CYP3A4 in the upper region of intestinal tract in males and in the lower region of intestinal tract in females.