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Benidipine is Mainly Metabolized by CYP3A in Vitro, but, Benidipine Disposition is not Influenced by CYP3A5 Genetic Polymorphism

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Objectives: This study was to elucidate the metabolism of benidipine and its enantiomers using human liver microsomes and to characterize the cytochrome P450 (CYP) enzymes responsible for the metabolism of benidipine in vitro. In addition, we evaluated the influence of CYP3A5 genotype on the disposition of benidipine and its metabolite in healthy subjects.

Methods: To identify CYP isoforms that catalyze the biotransformation of benidipine and its enantiomers, the incubation studies were conducted using human liver microsomesand recombinant CYP isoforms. To evaluate whether genetic polymorphisms of CYP3A5 influence the disposition of benidipine, a single oral dose of 8 mg benidipine was administered to 19 healthy mail subjects pre-genotyped for CYP3A5. The plasma concentrations of benidipine and its metabolite were monitored for up to 8 hours, and the pharmacokinetic parameters were estimated by noncompartmental analysis.

Results: Human liver microsomal incubation of benidipine in the presence ofNADPH resulted in the formation of two metabolites, N-desbenzyl- and dehydro-benidipine. The intrinsic clearance (Clint) of the formation of N-desbenzyl- and dehydro-benidipine metabolites from (-)-isomer were similar to those from the (+)-isomer. Correlation analysis in the 15 human liver microsomes showed that benidipine metabolism is correlated with CYP3A activity. The P450-isoform selective inhibition study in liver microsomes and the incubation study of cDNA-expressed enzymes also demonstrated that the N-debenzylation and dehydrogenation of benidipine are mainly mediated by CYP3A4 and CYP3A5. In in vivo clinical trials, the Cmax values of benidipine for subjects with the wild type, CYP3A5*1/*3, and CYP3A5*3/*3 genotypes were 4.82 3.62, 4.54 1.39, and 4.95 2.22 ng/ml, and the AUC0$\sim\infty$values of benidipine for the three genotype groups were 6.18 3.85, 8.01 4.11, and 9.91 4.27 ngh/ml, respectively. There was no significant difference in the pharmacokinetics of benidipine among the CYP3A5 genotype groups.

Conclusions: These findings suggest that CYP3A4 and CYP3A5 isoforms are major enzymes contributing to the disposition of benidipine. However, genetic polymorphism of CYP3A5 appears to have no significant effect on the disposition of benidipine in vivo. Further studies are remained to evaluate the clinical relevance of the genetic variants of CYP3A5.