일반연제 6

Effect of Novel CYP2J2 on the Pharmarcokinetics of Ebastine, a CYP2J2 Substrate

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Ebastine, a nonsedative H_1-receptor antagonist, is almost completely metabolized to the dealkylated metabolite (Des-BP) and carebastine, an active metabolite via hydroxylated ebastine (M-OH) by a first-pass effect. The conversion of M-OH to carebastine and the generation of Des-BP are known to be catalyzed by CYP3A4, whereas the oxidation of ebastine to M-OH is mainly mediated by CYP2J2. This study was designed to investigate the effect of the novel missense mutation of CYP2J2 (Gly312Arg) recently found in our laboratory on the pharmacokinetics of ebastine in healthy subjects. After a single oral administration of 20 mg ebastine in 5 wilds and 5 variants with hetero type mutation of CYP2J2, blood and urine samples were serially collected, and ebastine as well as three metabolites were simultaneously measured by LC/MS/MS. All subjects represented wild type in CYP3A4 genotyping. While there were no differences in the time courses of plasma carebastine concentration between two groups, AUC_{24hr} of ebastine in mutant group (16.0±7.0 ng*h/ml) seemed to be higher than that in wild (9.8±2.3 ng*h/ml, P=0.095). M-OH and Des-BP in plasma were rarely detected in both groups. The accumulated amount of Des-BP excreted in urine for 24 hrs in mutants (191±58 ng) was significantly increased in comparison with that in wilds (100±46 ng, P=0.026), but no changes in the other metabolites and ebastine. One could not observe any change in the generation of M-OH or carebastine in mutant group. It was probably due to that the major metabolic pathway of ebastine is the dealkylation to Des-BP by CYP3A4, and that the heterozygous mutation of CYP2J2 has a weak effect on the ebastine hydroxylation. However, the increases of ebastine and Des-BP in mutant group might be attributed to the inhibition of the oxidative metabolic pathway of ebastine by CYP2J2 variation. Our results suggest that Gly312Arg variation of CYP2J2 may decrease the hydroxylation of ebastine.