Metabolism of Ebastine in Healthy Subjects with CYP2J2 Heterozygous Mutation

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Ebastine is a potent and selective H_1-receptor antagonist characterized by a lack of sedative effects and adverse cardiovascular effects. Ebastine is well absorbed but undergoes an extensive first-pass metabolism in the small intestine and in the liver to the dealkylated metabolite (desalkylebastine) and carebastine, an active metabolite via hydroxylated ebastine (hydroxyebastine) by CYP enzymes. The generation of desalkylebastine is known to be catalyzed by CYP3A4, whereas the oxidation of ebastine to hydroxyebastine is mainly mediated by CYP2J2, and hydroxyebastine is further oxidized to pharmacologically active carebastine by both CYP2J2 and CYP3A4. Therefore, CYP2J2 may play an important role in the biotransformation of ebastine to its active metabolite, carebastine. CYP2J2 is genetically polymorphic, and six genetic variants (CYP2J2*2, *3, *4, *5, *6 and *7) have been reported in Caucasians.

In our previous study, two novel genetic polymorphisms (Gly312Arg in exon6 and Pro351Leu in exon7) were newly identified. According to our recent in-vitro study using a baculoviral expression system, Gly312Arg variant caused an almost complete loss of catalytic activity toward astemizole and ebastine compared with wild-type. On the other hand, the other variant, Pro351Leu, did not affect the enzyme activity [1]. Therefore, this study was designed to investigate the metabolism and disposition profiles of ebastine in Korean healthy subjects with the novel genetic variant of Gly312Arg in CYP2J2.

After a single oral administration of 20 mg ebastine in 5 subjects with wild type and 5 ones with mutation, blood and urine samples were serially collected, and ebastine as well as its three metabolites were simultaneously measured by LC/MS/MS [2].

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) tended to be higher than that in wild (9.8 ± 2.3 ng h/ml, P=0.095). Hydroxyebastine and desalkylebastine in plasma were rarely detected in both groups. The accumulated amount of desalkylebastine excreted in urine for 24hrs in mutants (191 ± 58 ng) was significantly greater than that in wilds (100 ± 46 ng, P=0.026),

but no changes in the other metabolites and ebastine. The increases of plasma ebastine and urinary desalkylebastine in subject with Gly312Arg variation in CYP2J2 might be attributed to the inhibition of the oxidative metabolic pathway of ebastine. However, the plasma and urinary concentration profiles of carebastine were not significantly different in the subjects with the variation, suggesting that clinical consequence may not be significant. Regarding transportation of the drugs, one could rule out the influence of P-glycoprotein, because P-glycoprotein is not involved in the transportation of those at the dose clinically used [3].

In conclusion, the novel heterozygous mutation of Gly312Arg in CYP2J2 did not represent the significant enzyme activity loss concerning the metabolism of ebastine in vivo. Further study in subjects with the homozygous variation is still needed.

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[2] Kang W, et al., Simultaneous determination of ebastine and its three metabolites in plasma using liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci, 2004;813:75-80.

[3] Imamura Y, et al., Transport chraracteristics of ebastine and its metabolites across human intestinal epithelial Caco-2 cell monolayers. Biol Chem Bull, 2001;24:930-934.