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Differential Effects of OATP1B1 Genetic Polymorphism on the Pharmacokinetics of Pravastatin and Pitavastatin

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Aims: Genetic variants of the organic anion transporting polypeptide 1B1 (OATP1B1) gene, in particular OATP1B1*15/*15 genotype, have been associated with changes in the pharmacokinetics of statins in humans. Pravastain is a hydrophilic substrate of OATP1B1 with low affinity (i.e., the Km value: 85.7 micM) and pitavastatin is a lipophilic substrate with high affinity (i.e., the Km value: 3.0 micM). This study is to investigate the issue whether lipophilicity and in vitro transporter activity of two substrates contribute to the effect of OAPT1B1 polymorphism on the pharmacokinetics of pravastatin and pitavastatin.

Methods: Eleven healthy male subjects (6 with OATP1B1*1a/*1a and 5 with *15/*15) were divided into 2 groups on the basis of the genetic polymorphism of OATP1B1. In a cross-over study, each subject took a single dose of 40 mg pravastatin and 2 mg pitavastatin with a 2 wks washout. Blood samples were collected up to 48 hr.

Results: The AUC of pravastatin and pitavastatin was 1.99~fold ($p<0.01$) and 2.62~fold ($p<0.001$), respectively, greater in subjects with *15/*15 than in those with *1a/*1a. The mean Cmax of pravastatin and pitavastatin was 2.12~fold ($p<0.01$) and 3.12~fold ($p<0.001$), respectively, greater in subjects with *15/*15 than in those with *1a/*1a. The t1/2, of pravastatin was not significantly different between subjects with different OATP1B1 genotypes ($p=0.45$) whereas the t1/2, of pitavastatin was 1.64~fold increased in subjects with *15/*15 than in those with *1a/*1a ($p<0.05$).

Conclusion: These results suggest that the fold changes in pharmacokinetic parameters of pitavastatin in subjects with OATP1B1*15/*15 compared to OATP1B1*1a/*1a were larger that those of pravastatin. Considering the lipophilicity and higher affinity to the OATP1B1 transporter of pitavastatin, physicochemical properties and in vitro transporter activity may contribute the different effect of OAPT1B1 polymorphism on the pharmacokinetics of pravastatin and pitavastatin.

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