EFFECT OF OATP1B1 (OATP-C/OATP2)*1b ON THE PHARMACOKINETICS OF PRAVASTATIN, VALSARTAN AND TEMOCAPRIL IN HEALTHY JAPANESE VOLUNTEERS

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Hepatic uptake is the first step in the biliary excretion of several compounds. This process often becomes the rate-determining step in the hepatic clearance, so alteration in uptake function may affect the pharmacokinetics and subsequent pharmacological/toxicological effects. OATP1B1 (OATP2/OATP-C) is thought to be responsible for the hepatic uptake of organic anions in humans because of its exclusive expression on the basolateral membrane of human liver and its broad substrate specificity. Recently, a number of SNPs in the SLCO1B1 gene have been identified and some of them may affect the transport activity of mutated OATP1B1. In particular, Asn130Asp (A388G) and Val174Ala (T521C) are commonly observed and their frequencies exhibit ethnic differences. Previous clinical studies have also shown that SNPs in OATP1B1 affect the pharmacokinetics of pravastatin. We have already reported that subjects with the OATP1B1*15 (Asn130Asp and Val174Ala) allele had an increased plasma AUC of pravastatin compared with those with OATP1B1*1b (Asn130Asp) allele1). Our in vitro kinetic analyses revealed that the *15 mutant has a lower intrinsic \( V_{\text{max}} \) value compared with wild type (*1a)2). On the other hand, Mwinyi et al. have reported that OATP1B1*1b causes an increase in the total clearance of pravastatin in white male subjects3). However, they only compared the pharmacokinetics of pravastatin in *1a/*1a carriers with that in (*1a/*1b + *1b/*1b) carriers and did not classify the subjects systematically by genotype. Moreover, we have no evidence that this effect is also present in the Japanese population. The purpose of our study was to clarify the effect of OATP1B1*1b on the pharmacokinetics of three clinically important anionic drugs, pravastatin (HMG-CoA reductase inhibitor), valsartan (Angiotensin II receptor antagonist) and temocapril (ACE inhibitor). Our in vivo transport studies using the expression system of OATP1B1 confirmed that pravastatin, valsartan and temocapril (an active metabolite of temocapril) are substrates of OATP1B1.

A total of 23 healthy Japanese volunteers were enrolled in a 3-group crossover study. Among the 23 volunteers, 5, 6, 7 and 5 people were found to be *1a/*1a, *1a/*15, *1b/*1b, and *1b/*15 carriers, respectively. Each volunteer received a single oral dose of 10mg of pravastatin sodium (Mevalotin; Sankyo Co.,Ltd.), 40mg of valsartan (Diovan, Novartis Pharma AG) or 2mg of temocapril hydrochloride (Acecol, Sankyo Co.,Ltd.). Blood samples were collected before and at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 24 hours after administration and urine samples were collected for 24 hours. The plasma AUC (0-24 hr) of pravastatin, valsartan and temocaprilat was 56.9 ± 24.6, 9600 ± 4340, 402 ± 80 (ng*hr/mL; mean ± SD), respectively. The plasma AUC of pravastatin in *1b/*1b carriers was about 65% that in *1a/*1a carriers, while the AUC in *1b/*15 carriers was about 55% that in *1a/*15 carriers. These results suggest that the plasma AUC of pravastatin in OATP1B1*1a carriers is significantly greater than that in OATP1B1*1b carriers, which is consistent with the previous report. In the case of valsartan, we observed the same pattern as pravastatin, although the difference was not statistically significant. Interestingly, the plasma AUC of valsartan in each subject was significantly correlated with that of pravastatin (Fig. 1), suggesting that the clearance mechanism of pravastatin and valsartan may be common at least in part. On the other hand, the plasma AUC of temocaprilat was not affected at all by the genotype of SLCO1B1 gene. The renal clearance remained unchanged among each genotype for all drugs. This result suggests that OATP1B1*1b is one of the determinant factors governing the interindividual variability in the pharmacokinetics of pravastatin and possibly valsartan. To clarify the reason why the relative impact of the effect of SNPs in the SLCO1B1 gene on the plasma AUC of each drug was different, we investigated the contribution of OATP1B1 to the overall hepatic uptake of each drug using a previously published method4) and investigated whether mutations in OATP1B1 affected the transport activity of each drug.