ORGANIC ANION TRANSPORTING POLYPEPTIDES (OATPS)-MEDIATED DRUG INTERACTION STUDY BETWEEN ROSUVASTATIN AND CYCLOSPORIN A IN CHIMERIC MICE WITH HUMANIZED LIVER

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Cyclosporin (CsA), known as OATP inhibitor, has reported to increase the AUC of rosuvastatin (RS), known as OATP substrate, by 7.1-fold in heart transplant recipients. PXB-mice®, chimeric animal models with humanized liver, are urokinase-type plasminogen activator/severe combined immunodeficiency (uPA/SCID) mice repopulated with 80% or more human hepatocyte. It has been reported that a lot of human transporters and metabolic enzymes are expressed in the liver of PXB-mice. We examined OATPs-mediated drug interaction between RS and CsA in PXB-mice, compared with SCID mice as control mice. The area under the blood concentration-time curve ($AUC_{0\text{-}4h}$) of intravenously administered RS was increased by 2.5 to 6.2-fold in PXB-mice, when pretreated with CsA, while it was increased by 4.6-fold in SCID mice pretreated with CsA. On the other hand, the $AUC_{0\text{-}4h}$ of orally administered RS was increased by 3.3 to 11-fold in PXB-mice, when pretreated with CsA, while was increased by 13-fold in SCID mice pretreated with CsA. The AUC increase in orally administered RS with CsA was slightly higher than that in intravenous administered RS. Liver-to-blood concentration ratios of RS were decreased by the pretreatment with CsA in both PXB- and SCID mice. Moreover, lactone form (human UDP-glucuronosyltransferase 1A metabolite) and N-desmethyl form (human cytochrome P450 2C metabolite), known as human metabolites of RS, were monitored. Lactone form was detected in liver of PXB-mice and N-desmethyl form was also detected in plasma and liver of PXB-mice, while these metabolites were hardly detected in SCID mice. It suggests that these metabolites might be human-specific or -abundant metabolites. Our results indicate that PXB-mice would be useful tools for predicting human OATP-mediated DDIs and human metabolites.