INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES (NEDO MICRODOSE-PJ) 2010-4 - EFFECT OF CURCUMIN ON THE INTESTINAL ABSORPTION OF SULFASALAZINE

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[Purpose] We previously reported that BCRP/ABCG2 limits the systemic exposure of sulfasalazine given orally in the small intestine. The present study examined the effect of curcumin, a BCRP inhibitor, on the disposition of sulfasalazine in healthy male volunteers. [Methods] Eight volunteers were given oral microdose (100μg) and therapeutic dose of (2g) of sulfasalazine with or without curcumin (2g) in a crossover fashion. Plasma concentrations of sulfasalazine and curcumin were quantified with LC/MS/MS. OATP2B1-mediated uptake of sulfasalazine was determined in OATP2B1 cRNA injected oocytes. [Results and Discussion] Curcumin significantly enhanced Cmax and the systemic exposure of sulfasalazine (AUC0-24), 2.0 and 1.3, and 3.7 and 3.2-fold at microdose and therapeutic dose, respectively. Plasma concentrations of sulfasalazine showed non-linearity. The dose normalized plasma concentrations of sulfasalazine at microdose level were 7.4-fold higher than those at the therapeutic dose level. OATP2B1-cRNA injected oocytes showed higher uptake of sulfasalazine compared with control oocytes. Mucosal-to-serosal transport of sulfasalazine was saturable in mice only when Bcrp was impaired. [Conclusions] Curcumin can be used in vivo inhibitor of BCRP. Saturation of OATP2B1-mediated uptake can be underlying mechanism in addition to saturation of dissolution.

INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES (NEDO MICRODOSE-PJ) 2010-5 - ROLE OF OATP2B1 IN THE INTESTINAL ABSORPTION OF BETA-BLOCKERS

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[Purpose] Recent clinical studies have revealed that the plasma concentration of several kinds of beta-blockers was decreased by the coadministration of grapefruit juice (GFJ), which was thought to be caused by the inhibition of uptake transporters in the small intestine. OATP (organic anion transporting polypeptide) 2B1 is one of the candidate transporters because it was reported to be expressed on the apical side of small intestine. In this study, to clarify the role of OATP2B1 in the intestinal absorption of beta-blockers, in vitro experiments and clinical pharmacogenetic study were performed. [Methods] Transcellular transport of compounds was investigated with normal and MDR1-knockdown Caco-2 cells to suggest their active uptake transport mechanisms. Uptake of compounds via OATP2B1 was examined by using OATP2B1-expressing Xenopus oocytes and HEK293 cells. In the clinical study, we examined the effect of SLC02B1 and T on the pharmacokinetics of celiprolol. [Results and Discussion] In the normal Caco-2 cells, basal-to-apical transport of fexofenadine and acebutolol was significantly larger than transport to the opposite direction, whereas their apical-to-basal transport was larger in the MDR1-knockdown Caco-2 cells. This implies the involvement of both MDR1 and an uptake transporter in their transport in Caco-2 cells. Significant uptake of fexofenadine, celiprolol and acebutolol and its inhibition by 1mM naringin were observed in OATP2B1-expressing oocytes. In the clinical study, the plasma AUC of celiprolol was significantly lower in subjects with SLCO2B1 and T, which results in the decreased transport function, compared with homozygotes of wild type alleles. Coadministration of grapefruit juice drastically decreased the plasma AUC of celiprolol and the effect of 1457C>T on the pharmacokinetics of celiprolol was disappeared. [Conclusions] These results suggested the possible role of OATP2B1 in the intestinal absorption of fexofenadine, celiprolol and acebutolol.