INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES
(NEDO MICRODOSE-PJ) 2010 (8)-A DRUG-DUPLICATE INTERACTION STUDY BETWEEN METFORMIN AND A
POTENT MATE INHIBITOR, PYRIMETHAMINE
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[Purpose] In vivo inhibitors selective for the target transporter are useful to investigate the importance
of the transporter in drug disposition. We have found in a mice study that pyrimethamine (PYR), a potent
MATE inhibitor, significantly reduced the efflux of metformin into the bile and urine. Furthermore, PYR could
completely inhibit the uptake of metformin by the brush border membrane from human kidney in the presence
of outward H+ gradient, showing the key role of MATE1 and/or MATE2-K in H+/organic cation exchange in
the kidney. The present study examined the effect of PYR on the renal elimination of metformin in healthy
volunteers. [Methods] Healthy male volunteers were given a microdose (100 μg) of metformin orally with or
without preadministration of PYR (50 mg, po) in a crossover fashion. Plasma concentrations and the amount
of metformin excreted into the urine were quantified with LC/MS/MS. [Results and Discussion] PYR treatment
caused a slight delay in the elimination of metformin from the systemic circulation. The renal clearance, and
intrinsic clearance for the tubular secretion of metformin were reduced by 27 and 35% in the PYR-treated
group, respectively. [Conclusions] PYR is useful to assess the contribution of MATE proteins to the disposition

Innovative Strategies for drug development using microdosing clinical studies (NEDO MicroDose-PJ) 2010 (9)- The
importance of OATPs and UGTs in the non-linear PK of telmisartan in rats
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[Purpose] Telmisartan is an angiotensin II receptor antagonist for the treatment of hypertension. Telmisartan
is metabolized to telmisartan acylglucuronide (tel-glu) by UDP-glucuronosyltransferases (UGTs) in the
hepatocytes and enterocytes. Our previous reports have suggested that organic anion transporting polypeptide
(OATP) 1B3 is predominantly involved in the hepatic uptake of telmisartan and tel-glu in humans (Ishiguro
N. et al., DMD, 34 1109 (2006) and DMD, 36, 796 (2008)). Its non-linear pharmacokinetics (PK) was observed
in the range of clinical dose and also observed in rats at the similar dose range. In this study, we clarified the
relative importance of OATPs and UGTs in the non-linear PK of telmisartan in rats. [Methods] Low (1mg/kg)
and high (30mg/kg) dose of telmisartan was administered to Wistar rats and Gunn rats (genetically defect in
the expression of UGT1 family) by intravenous (i.v.), intraportal vein (i.p.v.) and intraduodenal (i.d.) infusion.
[Results and Discussion] Non-linear PK of telmisartan was observed after i.p.v. and i.d. administration. And
the clearance after i.d. administration was largely decreased in Gunn rats compared with Wistar rats. The
intestinal availability (Fg) was 0.27 in rats, which was smaller than that in humans (0.71-1.0). [Conclusions] We
demonstrated that non-linear PK of telmisartan was mainly caused by the saturation of intestinal UGTs in rats.
However, this cannot be applied to the case in humans probably because of the lower intestinal UGT activities.
In human, the saturation of hepatic clearance can be the major cause of its non-linear PK.