INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES (NEDO MICRODOSE-PJ) 2010 (10) - MICRODOSING PHARMACOKINETIC AND PHARMACOGENOMIC STUDIES OF TELMISARTAN

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[Purpose] Microdosing (MD) in humans offers a number of benefits to the drug development process. Telmisartan (TA) is taken up into the liver predominantly via OATP1B3 and subsequently undergoes glucuronidation by UGTs. It has been reported that TA showed nonlinear pharmacokinetics (PK) within the range of therapeutic dose in humans. The aims of this study are: 1) to evaluate the contribution of polymorphisms in drug transporter and metabolizing enzyme genes to the PK of TA in MD and therapeutic dose (TD) conditions; 2) to compare PK profiles of TA between the two dose conditions. [Methods] After a 100μg of TA (as a solution) was administered to SLCO1B3 genotyping matched 33 healthy volunteers, each subject received 80 mg of TA. Plasma concentrations of TA and its glucuronide were measured by LC/MS/MS. In addition to the DMET analysis, we identified SNPs or haplotypes in SLCO1B3, ABCC2, and UGTs genes. [Results and Discussion] Some SNPs in the UGTs markedly affected plasma AUC and oral clearance (CL/F) of TA in both dose conditions, while PK profiles of TA were different after MD and TD. [Conclusions] UGTs dominate the PK of TA, and careful interpretations are necessary to describe differences in PK between the two dose conditions.

INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDY (NEDO MicroDose-PJ) 2010 (11) - INVESTIGATION OF THE EFFECT OF GENETIC POLYMORPHISM OF CYP2C9 ON THE PHARMACOKINETICS OF ORALLY-ADMINISTERED MICRODOSE OF [14C]-TOLBUTAMIDE IN HEALTHY VOLUNTEERS

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[Purpose] To evaluate the impact of genetic polymorphism of CYP2C9 on the pharmacokinetics of orally-administered tolbutamide (TB), we performed microdosing clinical study of [¹⁴C]-TB with AMS. [Methods] Microdose of [¹⁴C]-TB (100μg/172 nCi/body) was orally administered to six healthy volunteers in two groups blindly allocated based on diplotype of CYP2C9 (diplotype A and B; each n=3). Blood, urine and feces were collected at designated time up to 24 h, 48 h and 72 h, respectively. The samples were fractionated by HPLC and the radioactivity of the parent TB, hydroxyTB (HTB) and carboxyTB (CTB) was measured by AMS. [Results and Discussion] Plasma concentration of the total radioactivity in B group (t½: 13.6 hr, AUC(0-∞): 231 ng eq./hr/g) was decreased slower than that in A group (t½: 8.6 hr, AUC(0-∞): 147 ng eq./hr/g), while Tmax (1hr) and Cmax (14ng/mL) were not significantly changed. Renal excretion of the total radioactivity in group B was a little bit more rapid than that in A group and the ratio of the amount of metabolites (HTB and CTB) to that of TB in the urine was significantly higher in group A compared to group B. According to these results, subjects with group B showed lower metabolic activity than group A, which is consistent to the pre-screened diplotype of CYP2C9 in each group (*1/*1 in group A, *1/*3 in group B). Therefore, this kind of microdosing study can be a powerful tool to quantitatively evaluate the metabolic activity of CYP2C9.