INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES (NEDO MicroDose-PJ) 2010 (6) – KINETIC ANALYSIS ON DOSE-DEPENDENT ORAL ABSORPTION OF THREE CA-ANTAGONIST DRUGS –

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[Purpose] In the 24th annual meeting of JSSX, we have reported the result of Microdose clinical study (MD study) in which three Ca-antagonist drugs were administered orally and intravenously to healthy volunteers as a cassette. Among three drugs, only nifedipine showed the comparable BA with that in the therapeutic dose study, while BA of nicardipine and diltiazem became significantly lower in MD study. The present study was performed to elucidate the reason of linear or nonlinear BA of those drugs by measuring their metabolic stability and membrane permeability in vitro.

[Method] Human intestinal and liver microsomes were obtained from XenoTech and were used to assess the metabolic stability of three drugs. Caco-2 cell and MDCK-MDR1 cell monolayers were used to investigate the transport of these drugs by P-glycoprotein (P-gp).

[Result and Discussion] In the metabolic stability study using human intestinal microsomes, nicardipine was most unstable and the rank order of Km value was nicardipine < diltiazem << nifedipine. In addition, nicardipine and diltiazem, but not nifedipine, were revealed to be transported by P-gp, suggesting the involvement of P-gp mediated transport in the nonlinear absorption of these drugs as well as the intestinal first-pass metabolism. Based on in vitro parameters for metabolism and transport, BA of these drugs in both MD and therapeutic dose were simulated to quantify the contribution of CYP3A and P-gp to their dose-dependent absorption.

INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES (NEDO MicroDose-PJ) 2010 (7) – MAJOR CONTRIBUTION OF OATP TRANSPORTERS TO THE HEPATIC CLEARANCE OF ATORVASTATIN CLARIFIED BY CASSETTE MICRODOSE STUDY

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[Purpose] It is widely accepted that atorvastatin is first taken up into hepatocytes by OATPs and subsequently metabolized by CYP3A4. Our cassette microdose drug-interaction study was intended to clarify the relative importance of OATPs and CYP3A4 in the hepatic elimination of atorvastatin. For this purpose, atorvastatin was co-administered with probe substrates of both OATPs (pravastatin) and CYP3A4 (midazolam).

[Methods] We performed an open-label, three-period clinical study. Eight healthy male volunteers are originally recruited and received a cocktail of microdose of atorvastatin, pravastatin and midazolam (33 μg each) at baseline, with single p.o. dose of 600mg rifampicin (OATPs inhibitor), and with i.v. dose of 200 mg itraconazole (CYP3A4 inhibitor). Plasma and urine samples were collected and drug concentrations were quantified with LC/MS/MS.

[Results and Discussion] Rifampicin greatly increased the AUC of atorvastatin and pravastatin, while itraconazole had an effect only on that of midazolam.

[Conclusions] Our cassette microdose study clearly demonstrated the dominant contribution of the hepatic uptake process via OATPs to the hepatic clearance of atorvastatin.

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