INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES – (3) PREDICTION OF NONLINEAR PHARMACOKINETICS OF MDR1 SUBSTRATES IN HUMANS FROM NONCLINICAL DATA

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[Purpose] Clinical studies were performed to clarify whether nonlinear pharmacokinetics of drugs in humans can be predicted by nonclinical data. In the clinical study, verapamil and quinidine, good substrates of MDR1, were selected as test drugs and the pharmacokinetic parameters were compared between their microdose and therapeutic dose. The increase in the bioavailability due to the saturation of MDR1 in small intestine observed in this clinical study was also predicted based on the Km values and estimated drug concentration in the small intestine. [Methods] Studies were done in 2 separate open-label 4-stepwise dose-titration designs including 8 healthy male subjects for verapamil and quinidine. Doses for verapamil were 100 µg, 3, 16 and 80 mg and doses for quinidine were 100 µg, 1, 10 and 100 mg. For the prediction, the drug concentrations in small intestine were estimated by dividing the actual dose by the lower limit of apparent intestinal volume (3L) proposed by Tachibana et al. (Xenobiotica, 39, 430-43 (2009)). [Results and Discussion] By increasing the dose from microdose to therapeutic dose, the bioavailabilities of quinidine and verapamil were altered from 0.197 to 0.504 and from 0.049 to 0.113, respectively. By using a simple mathematical model with estimated intestinal concentration, the apparent Km values determined by fitting of clinical data were close to the in vitro Km values for MDR1. The saturation of intestinal CYP3A4 also contributes to their nonlinearity and the similar type of prediction is now on going. [Conclusions] Nonlinear pharmacokinetics of drugs can be explained by nonclinical data. Microdose clinical trials are a promising choice, even in cases with some concerns for nonlinear pharmacokinetics.

INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES(4) –ASSESSMENT OF ORAL BIOAVAILABILITY OF DRUGS BY CASSETTE IV AND PO DOSING

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[Purpose] Purposes of this project are 1) to investigate the possibility of Miclodosing (MD) clinical study to accelerate the development of oral drug products 2) to develop a rationale method to assess the oral absorbability of drugs by MD study and 3) to simulate the human BA of drugs based on the in vitro and in vivo (MD) studies. [Methods] In this study, three Ca-antagonists (nifedipine, nicardipine and diltiazem) were chosen as model drugs. These drugs are reported to undergo the extensive first-pass metabolism and P-gp mediated transport that makes it difficult to predict the oral BA from the preclinical animal study. In the protocol of MD study, cassette IV and PO dosing of three drugs were employed to develop a rationale method to select the best candidate for oral products efficiently. [Results and Discussion] Since a clinical study with cassette IV and PO dosing has not been reported yet, the method for cassette dosing was carefully searched before the clinical study. For IV administration, protocol was designed to inject the solution of each drug at 1-2 min intervals by using a tube with 3-way bulb to prevent a precipitation or degradation of drugs by mixing IV solutions of three drugs before administration. In vitro experiment revealed that 100% of dose can be injected by flushing the tub with 5-10 ml saline. In the presentation, results of MD clinical study will be reported with the in vitro prediction of human BA of these drugs.