【Grant-in-Aid for Scientific Research(S)】

Biological Sciences (Medicine, dentistry, and pharmacy I)

Title of Project : Development of quantitative prediction methods for alteration in pharmacokinetics caused by interindividual variability in transporter function and transporter-mediated drug-drug interaction

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Research Area : Pharmacokinetics and drug metabolism

Keyword : Transporter, Drug-drug interaction, Polymorphism, PBPK modeling

【Purpose and Background of the Research】

Transporters are expressed in liver, kidney, intestine and blood-brain barrier and known to mediate transports of various drugs and endogenous molecules. It has been reported that transporter functions are altered by polymorphisms, hepatic/renal disorders and drug-drug-interactions (DDI) in human, which may affect pharmacokinetics (PK) and main/adverse effects of clinically-used drugs. The purpose of this study is to establish methods for the quantitative prediction of PK variation and alteration based on mechanisms.

【Research Methods】

In order to accomplish our purpose, we should perform 5 studies: (1) Developing transporter-specific probes (substrates) and inhibitors which are useful for the evaluation of transporter functions in human. (2) Constructing methods for the quantitative prediction of transporter polymorphism effects on PK (Fig. 1). (3) Analyzing alteration in transporter functions in patients with hepatic/renal disorders, and constructing prediction methods for PK alteration. (4) Establishing quantitative prediction methods of DDI based on PBPK modeling and simulation (Fig. 2), performing several clinical studies. (5) Developing PET/SPECT probes which are useful for real-time and non-invasive analyses of drug distribution. Predicting effects at the target organs and toxicity more precisely using transporter probes.

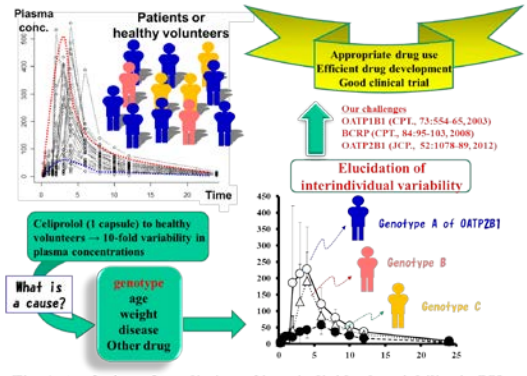

Fig. 1 Analysis and prediction of interindividual variability in PK

【Expected Research Achievements and Scientific Significance】

Our achievements will contribute to understanding variations in PK parameters and DDI mechanisms in drug development, and also contribute to improving efficacy and safety of clinical drug uses.

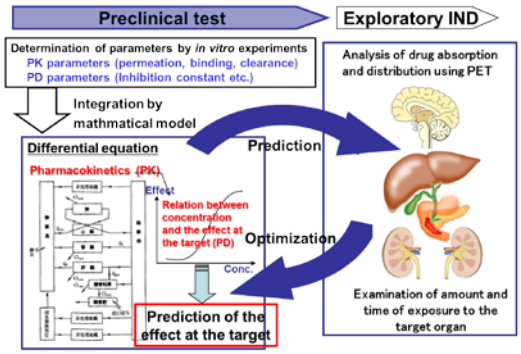

Fig. 2 Prediction of PK and drug effects based on PBPK modeling and simulation

【Publications Relevant to the Project】

Ito S, Sugiyama Y et al. Competitive inhibition of the luminal efflux by multidrug and toxin extrusions, but not basolateral uptake by organic cation transporter 2, is the likely mechanism underlying the pharmacokinetic drug-drug interactions caused by cimetidine in the kidney. J Pharmacol Exp Ther 340:393-403, 2012.

Maeda K, Sugiyama Y et al. Identification of the rate-determining process in the hepatic clearance of atorvastatin in a clinical cassette microdosing study. Clin Pharmacol Ther 90:575-581, 2011.

Kusuhara H, Maeda K and Sugiyama Y. Impact of drug transporters in the pharmacological and adverse reactions of drugs. In New Horizons in Predictive Toxicology. Current Status and Application, ed. AlanG.E. Wilson, pp 563-588, RSC Publishing, 2012.

【Term of Project】 FY2012-2016

【Budget Allocation】 148,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.riken.jp/r-world/research/lab/ippm/index.html