3-A-9-1

INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES
(1)--ETHICS AND HUMAN SUBJECTS PROTECTION IN THE PROJECT OF MULTIPLEX STUDIES
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[Purpose] To develop the system of managing multiplex clinical studies in the “Research Project for Establishment of Evolutional Drug Development with the Use of Microdose Clinical Trial”, to assure quality of the studies and human subjects protection. [Methods] A Clinical Research Management Team has been established and practical management, discussion meetings, and document development work have been conducted as part of the research project. [Results and Discussion] The following items were identified as the essential elements in the management system of multiplex studies: (1) visiting and quality check of the clinical sites and of the product manufacturing sites; (2) organizing several bodies for radiological protection of human subjects; (3) systematic literature search and inquiry for safety issues and error recovery procedures; (4) systematic documentation and SOP (standard operating procedure)/guidance development; and (5) Ethics Committees submission support. Some of these procedures seem to provide some hints to redesign clinical drug development in Japan. [Conclusions] The clinical research management system we have developed would be useful especially for conducting new types of studies such as microdosing clinical studies and molecular imaging PET studies. [Acknowledgement] This and the following 5 studies are sponsored by the New Energy and Industrial Technology Development Organization (NEDO).

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INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES – (2)
PREDICTION OF THE CHANGE IN THE PHARMACOKINETICS OF DRUGS BY GENETIC POLYMORPHISMS IN TRANSPORTERS AND TRANSPORTER-MEDIATED DRUG INTERACTIONS FROM IN VITRO STUDIES AND MICRODOSING CLINICAL STUDIES
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[Purpose] Recently the importance of transporters in the detoxification of drugs has been increasingly recognized by several in vitro and clinical studies on the genetic polymorphisms in drug transporters and transporter-mediated drug-drug interactions (DDIs). However, the evidences of the quantitative prediction of time profiles in the tissue and plasma concentrations of transporter substrate drugs from in vitro data with modeling and simulation have not been accumulated so far. Thus, in the present study, we validated our strategies to predict the pharmacokinetics (PK) of some drugs from in vitro data and mathematical modeling. We also tried to show the significance of microdosing clinical studies for this kind of prediction. [Method] Atorvastatin (a bi-substrate of CYP3A4 and OATPs) and telmisartan (a bi-substrate of UGTs and OATP1B3) are chosen as a model compound for the PK prediction. In the clinical study, microdose of atorvastatin, midazolam (probe for CYP3A4) and pravastatin (probe for OATP1B1) is coadministered with rifampicin (inhibitor for OATPs) and itraconazole (inhibitor for CYP3A4) to healthy volunteers. For telmisartan, the effect of genetic polymorphisms of OATP1B3 on its PK parameters is observed. Some in vitro and animal studies to obtain the intrinsic parameters for the PK modeling are also performed. [Results and Discussion] The saturable uptake of atorvastatin was observed in rat and human hepatocytes and the in vivo hepatic intrinsic clearances of four kinds of statins were well correlated with their uptake intrinsic clearances rather than metabolic enzymes, suggesting that the rate-limiting step for the clearance of these statins is uptake process mediated by OATPs. Regarding the telmisartan, non-linear PK was observed when changing its dose in rats and its clearance after i.d. dose was largely decreased by the function defect of UGT1s in Gunn rats, suggesting that non-linearity of its PK was mainly caused by the saturation of intestinal UGTs, though species difference in the PK of telmisartan in humans and rats.