INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES (NEDO MICRODOSE-PJ) 2010-(14)- PREDICTION OF CATIONIC DRUG DISPOSITION IN THE HUMAN BRAIN
Chunyong Wu, Hiroyuki Kusuhara, and Yuichi Sugiyama
Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[Purpose] Microdose Project has challenged to prediction of pharmacological action in the brain based on microdose clinical study to expand its usability in the drug development. The unbound concentration of drugs in the brain is closely related to the pharmacological action in the brain. Once the systemic exposure of test compound is determined by microdose study, in vitro/in silico estimation of the parameters governing the disposition in the brain, and interaction with target molecule provides the occupancy at the therapeutic doses. The present study predicted the occupancy of D2 receptor and 5-HTT by olanzapine and fluvoxamine, respectively. [Methods] According to the multi-compartmental theory, we performed PK-PD modeling for olanzapine and fluvoxamine using the plasma concentration-time profiles and occupancy. The uptake of olanzapine and fluvoxamine was examined in hCMEC/D3 cells, an immortalized cell line of human brain capillary endothelial cells. [Results and Discussion] Modeling and simulation where only passive diffusion was taken into consideration underestimated the occupancy in human brain by olanzapine and fluvoxamine at therapeutic dose. The uptake of olanzapine by hCMEC/D3 cells was a temperature- and concentration-dependent, and inhibited by quinidine (100 μM) and probenecid (10 mM). Fluvoxamine also exhibited a temperature-dependent uptake. Furthermore, the uptake of olanzapine and fluvoxamine by D3 cells was decreased by pretreatment with 25 μM FCCP, a protonophore. [Conclusions] The present study suggests that transporter-mediated uptake across the BBB enhances the pharmacological action of olanzapine and fluvoxamine in the brain.

INNOVATIVE STRATEGIES FOR DRUG DEVELOPMENT USING MICRODOSING CLINICAL STUDIES (NEDO MICRODOSE-PJ) 2010-(15)-PREDICTION OF CNS EFFECT OF HISTAMINE H1 ANTAGONIST BASED ON THE SYSTEMIC EXPOSURE AND IN VITRO EXPERIMENTS
Kayoko Kanamitsu, Hiroyuki Kusuhara, Kazuhiko Yama, Yuichi Sugiyama
1Graduate School of Pharmaceutical Science, The University of Tokyo, Tokyo, Japan, 2School of Medicine, Tohoku University, Miyagi, Japan.

[Purpose] Microdose Project has challenged to prediction of adverse reaction in the brain based on microdose clinical study to expand its usability in the drug development. Once the systemic exposure of test compound is determined by microdose study, in vitro/in silico estimation of the parameters for the disposition in the brain, and interaction with target protein provides the occupancy at the therapeutic doses. In the present study, we predicted the occupancy of brain H1 receptor (RO) by diphenhydramine and ketotifen, which is associated with their sedative effect. [Methods] Plasma concentrations and unbound fractions were cited from previous reports. Unbound fractions in the brain were determined using mouse brain homogenate by the equilibrium dialysis method. Dissociation rate constant (k_{on}) was estimated from the reported Ki values and average association constant (k_{off}) of H1 receptor antagonists. Permeability across the blood-brain barrier was estimated in silico. Unbound brain concentrations and RO were simulated. [Results and Discussion] There is a good agreement between predicted and actual RO by diphenhydramine at different time point (2.5 hr at 30mg po, and 12 hr at 50mg po), whereas RO by ketotifen underestimated the actual value at 3.5 hr (1 mg, po). [Conclusions] In vitro/in silico estimation of the pharmacokinetic/pharmacodynamic parameters could predict the RO by diphenhydramine at the therapeutic dose. However, further studies are necessary to improve the predictability for ketotifen. Overestimation of Ki and/or uptake transport at the BBB is possible underlying mechanism. [References] a Liu X et al, DMD 32: 132-9, 2004. b Tashiro M et al. Br J Clin Pharmacol 65: 811-21, 2008.