ASSESSMENT OF INTESTINAL ABSORPTION PROPERTIY OF P-GLYCOPROTEIN SUBSTRATES: IN VIVO ESTIMATION USING PORTAL-SYSTEMIC BLOOD CONCENTRATION DIFFERENCE METHOD

Ikuo Nomura, Kenji Kusumoto, Iichiro Kawahara, Naoki Okada, Akira Yamamoto and Takuya Fujita
Department of Biochemical Pharmacology, Kyoto Pharmaceutical University, Kyoto 607-8414, Japan

It has been generally accepted that p-glycoprotein (P-gp) mediated efflux affects the pharmacokinetics especially for oral absorption and brain distribution. Because P-gp is expressed in Caco-2 cells, the efflux ratio calculated from secretory/absorptive permeability is considered to be an indicator of potential for P-gp. When we encounter the new chemical entities showing high efflux ratio in the drug discovery process, it is important to assess an in vivo impact as early as possible. However, little information is available which explains P-gp transport to possible in vivo effect quantitatively. In the present study, we investigated the intestinal transport characteristics for various model compounds having diverse physicochemical properties using portal-systemic blood concentration difference method. Various test compounds, such as verapamil, propranolol, caffeine, and rhodamine-123, were administered orally to ddY mice at a dose of 10 mg/kg. After administration, portal and systemic blood were simultaneously collected from portal vein and vena cava, respectively, at desired time points. After calculating the AUC values (AUC_{pv} and AUC_{sys}) obtained from portal and systemic plasma concentrations of compounds, apparent availability (F_{aFg}) for intestinal absorption of test compound was estimated by following equation: 

\[ F_{aFg} = \frac{Q_{pv} \times R_b \times (AUC_{pv} - AUC_{sys})}{dose} \]

Where \( Q_{pv} \) is blood flow rate in portal vein, \( R_b \) is partition ratio of drugs between plasma and blood. Comparing \( F_{aFg} \) values in the absence or presence of a P-gp inhibitor cyclosporine, contribution of P-gp on intestinal absorption of test compounds is able to be estimated. In this meeting, we will discuss the contribution of P-gp on drug transport across the intestine and the correlation between the present study and in vitro Caco-2 permeation study.