Efflux transporter: Role of P-glycoprotein (P-gp) on intestinal absorption and species differences of its substrate recognition

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In drug discovery stage, it is very important to assess an in vivo impact of new chemical entries (NCEs) as soon as possible. However, there is little information available for evaluating the influence of P-gp-mediated efflux on the intestinal absorption of NCEs. In this symposium, we investigated the intestinal absorption characteristics of various model compounds having diverse physicochemical properties after their oral administration to mdr1a/1b knockout (KO) or wild-type (WT) mice using portal-systemic blood concentration difference (P-S) method. Eight compounds were selected as model drugs, and were orally administered to mice at a dose of 0.3-20 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 obtained from portal and systemic plasma concentration of compounds, their apparent availability of intestinal absorption (F_aF_g) was obtained. Comparing F_aF_g and other kinetic parameters in WT and KO mice, contribution of P-gp on the intestinal absorption of model compounds is able to be estimated. Caffeine and propranolol, non-P-gp substrates, showed similar absorption properties in both WT and KO mice, and were found to be well absorbed from the intestine. F_aF_g values of paclitaxel and fexofenadine in KO mice were significantly higher than those in WT mice. Furthermore, human F_aF_g values of various drugs calculated from literatures showed a good correlation with F_aF_g values in WT mice obtained from this study. Taken together, these results indicate that the P-S difference method is appropriate to evaluate the human F_aF_g value after oral administration of NCEs.