RELATIONSHIPS BETWEEN EXCRETION CLEARANCES OF RHODAMINE 123 AND P-GLYCOPROTEIN (PGP) EXPRESSION INDUCED BY REPRESENTATIVE PGP INDUCERS

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P-glycoprotein (Pgp) locates in several tissues in the living body, and acts as an efflux pump for many drugs. In this study, to identify the usefulness of rhodamine123 (Rho123) administration as a marker for detecting the inducing effect of Pgp by drugs, the relationships between excretion clearances of Rho123 via Pgp and its expression under treatment with representative Pgp inducers, rifampicin (RFP), dexamethasone (DEX) and St John’s Wort were examined. Rats received RFP (10 mg/kg/d) for 4 days, DEX (50 mg/kg/d) for 4 days, or St John’s Wort (15 mg/kg/d) for 7 days orally. In all rats groups, the excretion clearances of Rho123 after intravenous administration (0.2 mg/kg) from the blood circulation to the intestinal lumen and/or to the bile increased significantly. In contrast, there was no notable change in the urinary excretion of Rho123 though rats received these inducers. Western blot analysis with a monoclonal antibody for Pgp (C219) evidenced that Pgp levels in the small intestine and liver in the inducer-treated rats increased as compared to the control. In addition, there were good correlations between fold-induction levels of Pgp in the liver or small intestine but not kidney and the excretion clearances. These observations suggest that the excretion clearances of Rho123 from blood circulation to the small intestine or to the bile after intravenous administration of Rho123 are useful indicators to assume the Pgp function in the presence of Pgp inducers. We applied this method to the pharmacokinetic study of ritonavir (RTV) during repeated administration to detect the alteration of Pgp function. The data on the RTV pharmacokinetics will be also presented.