EFFECT OF P-GLYCOPROTEIN ON ORAL DRUG ABSORPTION -QUANTITATIVE EVALUATION OF IN VIVO INTESTINAL PERMEABILITY OF P-GLYCOPROTEIN SUBSTRATE DRUGS-

Yoshiyuki Shirasaka1, Yoshie Masaoka1, Makoto Kataoka1, Shinji Sakuma1, Toshiyasu Sakane2, Yuichi Sugiyama3, and Shinji Yamashita

1Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan, 2School of Pharmacy, Shujitsu University, 1-6-1, Nishigawara, Okayama 703-8516, Japan and 3Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

The purpose of this study is to develop a kinetic model that can predict quantitatively the effect of P-glycoprotein (P-gp) on the in vivo intestinal absorption of its substrate drugs from in vitro study. Apical to basal absorptive permeability of typical P-gp substrate drugs, quinidine, verapamil, vinblastine and digoxin, were measured in several cell monolayers having different levels of P-gp expression, normal, P-gp-induced, P-gp-highly induced and MDR1-knockdown Caco-2 cells and MDR1-MDCKII cells. In all cell monolayers, absorptive permeability of these drugs increased with increasing their concentration, showing the sigmoid type-relation to the apical drug concentration. These results were kinetically analyzed to obtain $K_{m(app)}$ and $V_{max}$ for P-gp-mediated transport. Assuming that drug concentration at the vicinity of the P-gp binding-site is proportional to the apical concentration, $K_{m(app)}$ could be regarded as an apparent affinity of the drug to P-gp which is defined based on the apical drug concentration. These fundamental parameters were compared with P-gp expression levels in used cells quantified by real time quantitative PCR and Western Blotting. Both $K_{m(app)}$ and $V_{max}$ showed the proportionality relation to the expression level of P-gp. Then, P-gp expression levels in rat small intestine (jejunum and ileum) were incorporated in this relation to simulate the concentration-dependent permeability of drugs in rat small intestine. It was confirmed that simulated permeability in rat jejunum and ileum corresponded well with that obtained by in situ single-pass perfusion experiment. This study clearly demonstrated the possibility to estimate the permeability of P-gp substrate drugs in human intestine from the expression level of P-gp, thus the possibility to predict the oral absorption of those drugs.

PREDICTION OF INTESTINAL ENZYME MEDIATED DRUG-DRUG INTERACTION AND NONLINEAR INTESTINAL FIRST-PASS METABOLISM

Tatsuhiko Tachibana1, Motohiro Kato1, Tomoko Watanabe2, Tetsuya Mitsui1 and Yuichi Sugiyama2
1Chugai Pharmaceutical Co., Ltd., 1-135 Komakado, Gotemba, Shizuoka 412-8513 and 2Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

CYP3A4 mediates hepatic and intestinal first-pass metabolism of many oral drugs. Prediction methods for intestinal enzyme mediated drug-drug interactions (DDIs) or nonlinear first-pass intestinal extraction (metabolism) have not yet been established because of the difficulty in estimating intestinal volume. The purpose of this study is to predict a safe dose that does not lead to DDIs or nonlinear pharmacokinetics mediated by intestinal enzymes. For prediction of intestinal DDIs, the ratio of the inhibitor concentration (I) in the intestine and the inhibition constant (Ki) was used. For simplicity, we named the ratio of the inhibitor dose to Ki (dose/Ki) the “DDI number”. The DDI number value (in [L]) is an index for DDIs because the inhibitor dose is the product of (I) and the volume of the intestinal fluid (Vg) which is independent of drugs. We collected reported data from DDI studies of substrates that exhibit intestinal first-pass metabolism and the Ki of inhibitors and calculated the DDI numbers. In cases DDI numbers below 2.76 L, there were no reports of an obvious interaction. In cases of a DDI number above 10 L, most inhibitors showed an obvious interaction. Mechanism based inhibitors (MBIs) with a low DDI number tended to cause a greater interaction than non-MBIs. For prediction of nonlinear intestinal availability, we used the ratio of the substrate dose to Km, similar to the DDI number. In cases of a dose/Km value above 10 L, midazolam and nicardipine showed nonlinear pharmacokinetics. In conclusion, the DDI number is useful in classifying inhibitors according to risk of interaction and dose/Km is useful in predicting nonlinear pharmacokinetics mediated by intestinal first-pass metabolism.