Biol. Pharm. Bull., **22 (12)**, 1355-1359, 1999

Cellular Pharmacokinetic Aspects of Reversal Effects of Itraconazole on P-Glycoprotein- Mediated Resistance Anticancer Drugs.

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The reversal effect of itraconazole on P-glycoprotein (P-gp)-mediated resistance of vinblastine, daunorubicin and doxorubicin was analyzed from a cellular pharmacokinetic point of view, namely by [^{3}H]azidopine photoaffinity labeling, intracellular accumulation and transcellular transport experiments. The LLC-GA5-COL150 cells, which expressed human P-gp selectively on the apical membrane due to transfection of *MDR1* cDNA into the porcine kidney epithelial cells (LLC-PK$_1$ cells), was used here, since this cell line constructs the monolayer with tight junction, being able to characterize the cellular pharmacokinetics. In LLC-GA5-COL150 cells, itraconazole caused a reversal from resistance as shown by a growth inhibition assay. [^{3}H]azidopine photoaffinity labeling demonstrated that itraconazole, vinblastine, daunorubicin and doxorubicin showed higher binding ability for P-gp compared with digoxin, suggesting the following results were *via* P-gp. The intracellular accumulation of [^{3}H]vinblastine, [^{3}H]daunorubicin and [^{14}C]doxorubicin after their application on the basal and apical sides was increased by itraconazole. These changes were similar to the dose modifying factors determined by the growth inhibition assay. However, their basal-to-apical transport was hardly affected by itraconazole, and this was explained by the fact that itraconazole inhibited P-gp, and subsequently increased their intracellular concentration and then the non‐P-gp mediated transport from the intracellular space to apical side. The apical-to-basal transport of [^{3}H]vinblastine, [^{3}H]daunorubicin and [^{14}C]doxorubicin was increased by itraco-

nazole, and this was reasonably explained by the inhibition of P-gp, and partly also by the increase of their intracellular concentration *via* the inhibition of P-gp.