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Interaction of Docetaxel (“Taxotere”) with Human P-Glycoprotein.

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The interaction of docetaxel (“Taxotere”) with P-glycoprotein (P-gp) was examined using porcine kidney epithelial LLC-PK_1 and LLC-GA5‐COL150 cells, overexpressing human P-gp selectively on the apical plasma membrane by transfection of human *MDR1* cDNA into the LLC-PK_1 cells. The basal-to-apical transport of [14C]docetaxel in LLC-GA5-COL150 cells significantly exceeded that in LLC-PK_1 cells, but the apical-to-basal transport was decreased in LLC-GA5-COL150 cells. The intracellular accumulation after its basal or apical application to LLC-GA5-COL150 cells was 4- to 20-fold lower than that of LLC-PK_1 cells. Multidrug resistance (MDR) modulators, i.e., cyclosporin A and SDZ PSC 833, inhibited the basal-to-apical transport and increased the apical-to-basal transport of [^{14}C]docetaxel in LLC-GA5-COL150 cells, but verapamil affected only apical-to-basal transport. The intracellular accumulation after basal or apical application to LLC-GA5-COL150 cells was also increased by these three MDR modulators. These observations demonstrated that docetaxel is a substrate for human P-gp, suggesting that docetaxel-drug interactions occur via P-gp. The inhibition of ［^{14}C］ docetaxel transport by the MDR modulators, as well as daunorubicin and vinblastine, was also found in LLC-PK_1 cells, which endogenously express P-gp at lower levels, and concentrations showing similar 1eve1s of inhibition were lower than those in the case of LLC-GA5-COL150 cells. These observations indicate that it is necessary to consider the pharmacokinetic and pharmacodynamic interactions of docetaxel via P-gp.