Pharm. Pharmacol. Commun., 6, 167-171, 2000.

Nicardipine and Itraconazole Inhibited Transcellular Transport of Digoxin.

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The inhibitory effects of nicardipine, nifedipine and itraconazole on P-glycoprotein-mediated transport of [^{3}H]digoxin were examined using LLC-PK$_1$ and LLC-GA5-COL150 cells, a porcine kidney epithelial LLC-PK$_1$ cell line transformed with *MDR1* cDNA from man which results in overexpression of P-glycoprotein on the apical membrane. Basal-to-apical transport of [^{3}H] digoxin in LLC-GA5-COL150 cells was higher than in LLC-PK$_1$ cells; apica l-to-basal transport was markedly lower in LLC-PK$_1$ cells and even lower in LLC-GA5-COL150 cells. This is consistent with the possibility that [^{3}H]d igoxin is transported by P-glycoprotein. Co-administration of nicardipine or it raconazole markedly inhibited the basal-to-apical transport of [^{3}H]digoxin in LLC-GA5-COL150 cells, and apical-to-basal transport also increased. The effect of nifedipine was less marked than that of nicardipine or itraconazole. Intracellular accumulation of [^{3}H]digoxin after apical application in LLC-GA5-COL150 cells was 2-3 times less than in LLC-PK$_1$ cells, and was increased by the addition of nicardipine or itraconazole, consistent with their inhibitory

effects on transcellular transport. Following basal application of [^{3}H]digoxin, its intracellular accumulation in LLC-GA5-COL150 cells was, unexpectedly, comparable with that in LLC-PK$_1$ cells, and was hardly affected by the addition of nicardipine or itraconazole. In conclusion, it has been shown that nicardipine and itraconazole inhibited transport of digoxin, which is presumably mediated by P-glycoprotein. This explains their effects observed in clinical use.