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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 [³H]digoxin were examined using LLC-PK₁ and LLC-GA5-COL150 cells, a porcine kidney epithelial LLC-PK₁ cell line transformed with *MDR1* cDNA from man which results in overexpression of P-glycoprotein on the apical membrane. Basal-to-apical transport of [³H]digoxin in LLC-GA5-COL150 cells was higher than in LLC-PK₁ cells; apical-to-basal transport was markedly lower in LLC-PK₁ cells and even lower in LLC-GA5-COL150 cells. This is consistent with the possibility that [³H]digoxin is transported by P-glycoprotein. Co-administration of nicardipine or itraconazole markedly inhibited the basal-to-apical transport of [³H]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 [³H]digoxin after apical application in LLC-GA5-COL150 cells was 2-3 times less than in LLC-PK₁ cells, and was increased by the addition of nicardipine or itraconazole, consistent with their inhibitory

effects on transcellular transport. Following basal application of [³H]digoxin, its intracellular accumulation in LLC-GA5-COL150 cells was, unexpectedly, comparable with that in LLC-PK₁ cells, and was hardly affected by the addition of nifedipine or itraconazole. In conclusion, it has been shown that nifedipine and itraconazole inhibited transport of digoxin, which is presumably mediated by P-glycoprotein. This explains their effects observed in clinical use.