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Effects of 12 Ca^{2+} antagonists on multidrug resistance, MDR1-mediated transport and MDR1 mRNA expression

Takara K[1], Sakaeda T[2], Tanigawara Y[3], Nishiguchi K[2], Ohmoto N[2], Horinouchi M[2], Komada F[4]（駒田　富佐夫）, Ohnishi N[1], Yokoyama T[1], Okumura K[2].

Department of Hospital Pharmacy, Faculty of Pharmaceutical Sciences, Kyoto Pharmaceutical University[1]. Department of Hospital Pharmacy, School of Medicine, Kobe University[2]. Department of Hospital Pharmacy, School of Medicine, Keio University[3]. Department of Drug Informatics, Faculty of Pharmaceutical Sciences, Josai University[4]

The effects of 12 Ca(2+) antagonists on MDR1 were examined by two independent models: the inhibitory effect on MDR1-mediated transport of [(3)H]digoxin using MDR1-overexpressing LLC-GA5-COL150 cell monolayers and the reversal effect on cytotoxicity of vinblastine or paclitaxel using MDR1-overexpressing Hvr100-6 cells. The inhibitory effects on [(3)H]digoxin transport were assessed as the 50% inhibitory concentration during 4 h exposure, and the values were the lowest for nicardipine (4.54 microM), manidipine (4.65 microM) and benidipine (4.96 microM), followed by bepridil (10.6 microM), barnidipine (12.6 microM), efonidipine (13.0 microM), verapamil (13.2 microM) and nilvadipine (18.0 microM). The reversal effect on cytotoxicity was assessed by the 50% growth inhibitory concentration after 3 days exposure, and the resistance to vinblastine or paclitaxel in Hvr100-6 cells was reversed by manidipine, verapamil, benidipine, barnidipine, and nicardipine, in that order. Bepridil, barnidipine, efonidipine, verapamil and nilvadipine showed similar inhibitory effects on [(3)H]digoxin transport, but barnidipine and verapamil showed a stronger effect in reversal of cytotoxicity. Real-time quantitative RT-PCR assay indicated a decrease in MDR1 mRNA expression by barnidipine and verapamil. It is concluded that Ca(2+) antagonists cannot only be direct inhibitors of MDR1 but that some may at the same time act as inhibitors of expression of MDR1 via down-regulation of MDR1 mRNA.