Micellar electrokinetic chromatographic analysis for in vitro accumulation of anthracyclines enhanced by inhibitors of cell membrane transporter-proteins in cancer cells

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BSTRACT

Cell membrane transporter-proteins have been partly implicated in lowering the accumulation of drugs in cancer cells, leading to multidrug resistance (MDR). Two cancer cell lines, A549 and RDES, were continuously exposed to subclinical concentration (250 nM) of anthracyclines and micellar electrokinetic chromatography was used to investigate their *in vitro* accumulation after treatment with inhibitors of membrane transporter-proteins. The four anthracylines [doxorubicin (DOX), epirubicin (EPI), daunorubicin (DNR), and idarubicin (IDA)] were separated within a short analysis time of less than 15 min in borate buffer (80 mM, pH 9.22) containing sodium taurodeoxycholate (35 mM), 2-hydroxypropyl-γ-cyclodextrin (3.5% wt/v), and sodium dodecylsulfate (20 mM). Laser-induced fluorescence was used for detection of the anthracyclines. Three inhibitors, verapamil, cyclosporine A and probenecid, were examined by adding each inhibitor independently or two inhibitors simultaneously to the culture medium. It was found that independent use of each inhibitor leads to more efficient accumulation than combined use of verapamil and probenecid. In addition, the results show that effect of inhibitors on the accumulation of anthracyclines depended on type of cell: in RDES, inhibitors enhanced accumulation of all four anthracyclines, while in A549, inhibitors showed different accumulation behavior for each anthracycline. Generally higher accumulation of anthracyclines was observed in RDES cells than A549, as evidenced by dead cells (7–16%) after 24 h of continuous exposure to subclinical concentration.