Cellular pharmacology of a liposomal preparation of N4-hexadecyl-1-beta-D-arabinofuranosylcytosine, a lipophilic derivative of 1-beta-D-arabinofuranosylcytosine

Daniel Horber, H. Schott & R. Schwendener

The in vitro deamination, cytotoxicity, cellular drug uptake, distribution and cellular pharmacology in HL-60 cells of N4-hexadecyl-1-beta-D-arabinofuranosylcytosine (NHAC), a lipophilic derivative of arabinofuranosylcytosine (ara-C), were studied. Compared with ara-C, NHAC in liposomal formulations was highly resistant to deamination, resulting in levels of formation of arabinofuranosyluracil 42 and ten times lower in plasma and liver microsomes respectively. The cytotoxicity of NHAC was independent of both the nucleoside transporter mechanism and the deoxycytidine (dCyd) kinase activity as demonstrated by co-incubating NHAC with dipyridamole and/or dCyd. In ara C-resistant HL-60 cells NHAC was still cytotoxic, requiring drug concentration only 1.6 times higher than sensitive cells. Uptake of NHAC was six times higher and was not inhibited by dipyridamole. The pharmacokinetics of NHAC revealed that its intracellular half-life is 4.8 times longer than that of ara-C. Ara-CTP formation and incorporation into DNA was up to 25-50 times lower than that of ara-C and contributed only marginally to the cytotoxic effects of NHAC. These results indicate that, because of the significantly increased stability, the transporter-independent uptake and the dCyd-kinase-independent cytotoxicity, NHAC might be active in ara-C-resistant cells.