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Potentiation by dipyridamole of dideoxynucleoside activity against HIV-1: differential effects on salvage of deoxy- and dideoxy-nucleosides as a possible mechanism. J. Szebeni, S.S. Patel, G.V. Betageri, L.M. Wahl* and J.N. Weinstein. National Cancer Institute and **National Institute of Dental Research, National Institutes of Health, Bethesda, MD, USA

Dipyridamole (DP), a widely used coronary vasodilator and antiplatelet agent, markedly potentiates the antiviral effects of azidothymidine (AZT) and dideoxycytidine (ddC) in human monocyte and lymphocyte lineage cells infected with HIV-1 (PNAS 86:3842, 1989). In an effort to clarify the mechanism of this effect, we studied the influence of DP on cellular salvage of dideoxynucleoside drugs in comparison with their deoxy- counterpart. We found in uninfected monocyte/macrophages and T-lymphocytes that DP has no influence on cellular uptake and phosphorylation of ^{3}H-AZT and ^{3}H-ddC, whereas it significantly inhibits cellular salvage of ^{3}H-deoxythymidine and ^{3}H-deoxycytidine. Consequently, the triphosphate forms of the latter ^{3}H-nucleosides were reduced by about 60% in the cells. Since the triphosphates of physiological nucleosides compete with dideoxy-nucleoside triphosphates for HIV reverse transcriptase, these results suggest that the potentiating effect of DP on the antiviral activity of AZT and ddC may be related, at least in part, to suppression of an antagonistic influence on the action of these dideoxynucleosides.

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FURTHER STUDIES ON THE HIV PROTEINASE INHIBITOR RO 31-8959

S. Galpin, J.Martin*, T.O'Connor, S.Redshaw*, N.Roberts* and D.Kinchington.
Department of Virology, Medical College of St. Bartholomew's Hospital, West Smithfield, London EC1A 7BE. * Roche Products UK Ltd., Welwyn Garden City, AL7 5AY, UK.

The peptide derivative, RO 31-8959 is a potent inhibitor of HIV proteinase and has marked antiviral activity with an EC50 of 2 x 10^{-9}M against HIV-1(RF) actutely infected C8166 cells, as measured by P24 in tissue culture. Using this system further studies show that increasing the MOI from 5-500 TCID50 or the cell culture period from 3 to 7 days does not significantly alter the EC50 values. To study the mechanism of action, the time of addition of the compound post infection was delayed for up to 48 hours and the results compared to those obtained with ddC and a TIBO derivative. It was found that addition could be postponed 18-20 hours to retain significant antiviral activity, whereas ddC and the TIBO derivative lost activity after 5-10 hours delayed addition. This is consistant with proteinase inhibitors acting later in the replication cycle than inhibitors of reverse transcriptase. In addition, RO 31-8959 showed strong antiviral effect in HIV-1 RF chronically infected H9 cells, with an EC50 of 0.3 uM, compared to ddC which showed no effect at 10 uM. This compound also gave EC50 values in the low to sub-nanamolar range against other strains of HIV-1, HIV-2 (ROD) and SIV Mac251.