183

Inhibition of Respiratory Syncytial Virus Replication *in vitro* by N-butyldeoxynojirimycin (NB-DNJ/SC-48334). S. P. Tucker, T R. Stiebel Jr., and M. L. Bryant. *Infectious Disease Research, Searle Research and Development, St. Louis, Missouri, U.S.A.*

The effects of the glucosidase inhibitor SC-48334 on the replication of respiratory syncytial virus (RS virus) in vitro, were determined. SC-48334 was found to significantly inhibit viral cytopathogenicity and a marked reduction in the size and number of syncytia was observed in SC-48334 treated cultures. A 50% effective concentration of approximately 20 μM was determined using a cell viability based assay. Apparent complete inhibition of viral cytopathogenicity was observed in the presence of 200 μM SC-48334. Treatment of mock infected cultures at identical concentrations resulted in no significant cytotoxicity. The inhibitory effect of SC-48334 may be mediated via a mechanism restricted to infected cells and is not a consequence of, for example, down-regulation of viral receptors since cytopathogenicity was not inhibited in cells that were treated with a single addition of SC-48334 and then incubated in the absence of SC-48334 during infection. No effect on protein synthesis was evident since the synthesis of viral proteins appeared unaltered by SC-48334 at concentrations up to 1.0 mM. However, the electrophoretic mobility of the viral fusion glycoprotein was altered in SC-48334 treated cultures in a dose dependant manner, suggesting a glycosylation-specific effect. Initial results also indicate that treatment of infected cells with SC-48334 resulted in a reduction in the titer of infectious virus released. The effects of SC-48334 on viral glycoprotein processing and the significance of this observation in the context of antiviral efficacy will be discussed.

184

Anti-Influenza Virus Activity of 4-Guanidino-2,4-Dideoxy-2,3-Dehydro-*N*-Acetylneuraminic Acid In Vitro. F Hayden, B Rollins, and L Madren. University of Virginia, Charlottesville, VA, USA.

The anti-influenza activity of the neuraminidase inhibitor 4-guanidino-Neu5Ac2en (4-G-NAc) was determined in Madin-Darby canine kidney (MDCK) cells by ELISA and in explants of human respiratory epithelium by yield reduction assay. In MDCK cells, 50% inhibitory concentrations (EC_{50}) averaged 0.5 μg/ml for influenza A/Virginia/88(H3N2) and 0.04 μg/ml for A/Texas/91 (H1N1). In human adenoid explants, concentrations causing at least 1.0 $\log_{10}$ decrease in yield (EC_{90}) at 48 h were <0.01 μg/ml for influenza A(H1N1) and A(H3N2) viruses and 0.25 μg/ml for B/Hong Kong/72. 4-G-NAc 100 μg/ml did not inhibit outgrowth of human adenoid epithelium at 6 d, whereas ribavirin 10 or 100 μg/ml reduced outgrowth by >50%. In MDCK cells, sequential passage of an influenza A(H3N2) virus 8 times in 4-G-NAc 32 μg/ml yielded virus which had susceptibility similar to virus passaged without drug. 4-G-NAc showed additive antiviral activity in MDCK cells when combined with rimantadine, ribavirin, or 2'-deoxy-2'-fluoroguanosine, without evidence of cellular cytotoxicity. 4-G-NAc is a potent inhibitor of clinical isolates of influenza A and B viruses in human respiratory epithelium and shows little propensity to resistance emergence during short-term passage. These features make 4-G-NAc a very promising candidate for clinical study.