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The Anti-influenza Virus Activity of a Novel Neuraminidase (Sialidase) Inhibitor 4-Guanidino Neu5Ac2en

D.M. Ryan, J. Ticehurst, M.H. Dempsey, Glaxo Group Research Ltd, Chemotherapy Department, Greenford Road, Greenford, Middlesex UB6 0HE, UK

Neuraminidase is primarily responsible for promoting release of progeny virus from infected cells. Experiments reported here demonstrate the potent antiviral activity of a novel neuraminidase (sialidase) inhibitor 4-guanidino Neu5Ac2en, in comparison with Amantadine and Ribavirin, in experimental RTI (respiratory tract infections) induced with Influenza A and B viruses in mice and ferrets. We have reported (von Itzstein *et al* 1993) the potent antiviral activity of intranasally administered 4-guanidino Neu5Ac2en in reducing respiratory tract virus titres in mice and ferrets infected with Influenza A virus. In new studies reported here we show that it is similarly active against Influenza B virus by this route. Subsequent studies showed that 4-guanidino Neu5Ac2en is considerably less active against Influenza viruses A and B when given by the intraperitoneal route or oral route. 4-guanidino Neu5Ac2en is metabolically stable and its potent efficacy by the intranasal route, relative to Amantadine and Ribavirin, was explicable in terms of *in vitro* activity, bioavailability and pharmacokinetic properties. In efficacy experiments with Influenza A virus in ferrets, 4-guanidino Neu5Ac2en was active at doses as low as 0.05 mg/kg/dose in reducing nasal wash virus titres and pyrexia and was at least 100 times more effective than Ribavirin; Amantadine was poorly tolerated at doses required for effective efficacy. In subsequent experiments in ferrets 4-guanidino Neu5Ac2en showed only a slight loss in activity when treatments were delayed until 24 hours after infection.

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***In Vitro* Anti-Myxovirus Activity of Polyoxometalates.** S. Shigeta,[1*] S. Mori,[1] M. Hosoya,[1] M. Baba,[1] R.F. Schinazi,[2] A.M. Khenkin,[3] & C.L. Hill.[3] Department of Microbiology, Fukushima Medical College, Fukushima, 960-12, Japan,[1] Veterans Affairs Medical Center and Laboratory of Biochemical Pharmacology, Department of Pediatrics[2] and Chemistry[3], Emory University, Atlanta, GA, 30033, USA.

Polyoxometalates (POM) have been shown to inhibit the replication of retro-, toga-, paramyxo-, and herpesviruses. The primary mechanism of anti-HIV action of POMs seems to be inhibition of binding of virus to cells and inhibition of syncytium formation. Since myxoviruses are known to spread cell-to-cell *via* fusion of infected and uninfected cells, we examined the antiviral activity of 25 polyoxometalates for anti-ortho- and -paramyxoviruses activity by the MTT method *in vitro*. Among the compounds examined, 23 showed selective antiviral effect against FluV-A, 10 showed activity against RSV, 5 showed activity against measles virus, and 1 (each) compound showed activity against PFluV-2, PFluV-3, and mumps virus. The Keggin sandwich compound, $K_{10}Fe_4(H_2O)_2(PW_9O_{34})_2 \cdot nH_2O$ (HS-058), had an EC_{50} value of 1.6, 21.8, 8.6, 3.1, and 0.8 μM against FluV-A, FluV-B, RSV-A, RSV-B, and measles virus, respectively, but was not inhibitory against PFluV-2, PFluV-3, and mumps virus. Its IC_{50} (cytotoxicity) in MDCK, HEp-2, HMV-2 cells was 200, 200, and 50 μM. When HS-058 was added at different times after RSV infection, it inhibited virus binding to cells. However, at higher concentration, it also inhibited the later stages of virus replication.