(S)-9-(3-Hydroxy-2-phosphonylmethoxypropyl)adenine (S-HPMPA): Antiviral Activity and Pharmacokinetics. M.J.M. Hitchcock, I. Ghazzouli, Y.H. Tsai, C.A. Bartelli, R.R. Webb, and J.C. Martin. Bristol-Myers Co., Wallingford, CT 06492

The anti-herpes activity of S-HPMPA was assessed. In vitro, the 50% inhibitory dose (ID_{50}) of S-HPMPA against (TK^+) herpes simplex viruses (HSV) type 1 & 2 was 13-25 μg/ml and 5 μg/ml against a (TK^-) herpes strain. The ID_{50} values of S-HPMPA against human CMV and VZV were 0.15 and 0.37 μg/ml, respectively. Cell growth of uninfected tissue cells was not inhibited at 100 μg/ml. In mice, S-HPMPA was found to provide significant protection from a lethal infection of HSV-1 and/or 2 when the drug was administered orally at 100 mg/kg/day. However, toxicity was observed with higher doses. In guinea pigs cutaneously infected with HSV type 1, topical treatment with a 5% ointment of S-HPMPA significantly reduced the severity of the disease. S-HPMPA levels in plasma and urine were quantitated by an HPLC assay after administration of 100 mg/kg either i.v, i.p. or p.o. Peak plasma concentrations of 196 and 117 μg/ml were achieved at 5 min for i.v. and i.p. dosing, respectively, and absorption phase half lives were about 12 min. Thereafter, elimination of the drug was much slower. Oral dosing produced low plasma concentrations (between 0.4 and 1.5 μg/ml) at all sample times measured. Comparison of urinary recoveries showed essentially complete (96%) bioavailability of the compound administered i.p. whereas it was only about 5% bioavailable by the oral route.

Effect of Ribavirin on Hepatitis A Virus Replication in Vitro. R.K. Chaudhary and A.P. Andonov. Laboratory of the National Viral Hepatitis Reference Centre, Viral Diagnostic Services Division, Bureau of Microbiology, Laboratory Centre for Disease Control, Health and Welfare Canada, Ottawa.

The effect of ribavirin on FRhk-4 (Fetal Rhesus Monkey Kidney) cells acutely or chronically infected with hepatitis A virus (HAV) was studied in vitro. The ribavirin treatment was started immediately after adsorption of the virus. Ribavirin at 50 ug/ml significantly reduced HAV yield and with 100 ug/ml the antigenic activity of the virus was undetectable by radioimmunoassay (RIA) in cells inoculated with 100 to 800 $TCID_{50}$. An increase in the inoculum from 800 to 1600 $TCID_{50}$ resulted in the production of a small amount of HAV (S/N 2.9). The effect of ribavirin was time dependent and required more than 96 hours of treatment to completely inhibit the virus. Ribavirin was somewhat less effective in treating cells persistently infected with HAV. HAV activity was significantly inhibited (82%) in persistently infected cells treated for 7 days with 100 ug/ml of ribavirin, however the inhibition was significantly less (60%) when cells were treated with 50 ug/ml. When the persistently infected cells were passaged and treated twice with the same dose of ribavirin the inhibitory effect was more pronounced. Ribavirin had some inhibitory effect on uninfected cells but did not produce any morphological changes.