133

Antiviral Activity of Cyclobutyl Guanine Against Herpes Virus Infections.

E.R. Kern, C. Hartline, B. Lidin, and P.E. Vogt. Department of Pediatrics, University of Alabama School of Medicine, Birmingham, Alabama 35294, USA

The nucleoside analog (±)-9-[(1β, 2α, 3β)-2, 3-bis (hydroxymethyl)-1-cyclobutyl] guanine (cyclobutyl guanine) was evaluated for in vitro and in vivo activity against members of the herpes virus group. In tissue culture cells, the following ED_{50} values were obtained: HSV-1=0.07 μg/ml; HSV-2=0.06 μg/ml; HCMV=3.6 μg/ml; MCMV=0.10 μg/ml; VZV=0.80 μg/ml; EBV=0.02 μg/ml. Against all the viruses tested, cyclobutyl guanine had activity that was equivalent or superior to Acyclovir (ACV) or Ganciclovir (DHPG). In these same cells, however, cyclobutyl guanine was also slightly more toxic than ACV or DHPG. In mice inoculated intranasally with HSV-1, i.p. treatment with 20 mg/kg of cyclobutyl guanine twice daily for seven days resulted in significant protection when begun 72 hours post infection. When mice were inoculated intranasally with HSV-2, the same treatment regimen conferred significant protection when initiated 96 hours after viral inoculation. If mice were inoculated i.p. with MCMV, similar treatment to that used above resulted in significant protection when therapy was initiated 48 hours after infection. In all the animal studies, cyclobutyl guanine gave at least equivalent results to those obtained with ACV or DHPG. These results indicate that cyclobutyl guanine has excellent activity against herpes virus infections in tissue culture and murine models and suggests that this drug may have potential for treatment of herpes virus infections in humans.

134

Effect of Treatment with HPMPC on Mortality and Pathogenesis of Experimental Herpes Simplex Virus Infections.

E.R. Kern and P.E. Vogt. Department of Pediatrics, University of Alabama School of Medicine, Birmingham, Alabama 35294, USA

The phosphonate nucleoside analogue (S)-1-(3-hydroxy-2-phosphonyl methoxypropyl) cytosine (HPMPC) has broad spectrum activity for members of the herpes virus group. Herpes simplex virus type 1 and type 2 (HSV-1, HSV-2) replication in tissue culture cells is inhibited by about 1.0 μg/ml, whereas acyclovir (ACV) has an ED_{50} of about 0.05-0.10 μg/ml. The purpose of this study was to compare the efficacy of HPMPC with ACV in HSV-1 and HSV-2 infections of mice. When mice were inoculated i.p. or intranasally (i.n.) with HSV-1, treatment with 5-20 mg/kg of HPMPC, twice daily, for 7 days resulted in significant protection when begun 72-96 hrs after infection. In the i.n. infection, therapy with HPMPC reduced considerably viral titers in blood, lung, spleen, olfactory lobe, cerebral cortex, cerebellum, diencephalon, and pons/medulla. In all tissues HPMPC treatment was at least equivalent to ACV and in some cases was superior. If mice were inoculated i.p. or i.n. with HSV-2, a similar effect on mortality to that described above was observed, however, HPMPC was generally more effective than ACV. Treatment of an i.n. HSV-2 infection also dramatically reduced viral replication in blood, lung, liver, spleen, kidney, and brain. Again, HPMPC was generally more effective than ACV. These studies indicate that HPMPC treatment is very effective against HSV-1 and HSV-2 infections of mice and suggest that this compound may have potential for treatment of herpes encephalitis and neonatal herpes in humans.