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Comparison of Efficacy and Toxicity of HPMPC and Cyclic HPMPC in Animal Models for Severe Herpesvirus Infections. E.R. Kern, J. Palmer, C. Hartline, and P.E. Vogt. University of Alabama School of Medicine, Birmingham, AL, U.S.A.

The phosphonyl nucleotide analogue (S)-1-[3-hydroxy-2-(phosphonyl-methoxy)propyl] cytosine (HPMPC) which is a potent inhibitor of herpesvirus replication has been reported to have dose-limiting nephrotoxicity in animals and man. The purpose of these studies was to compare the efficacy of HPMPC with a less toxic derivative, cyclic HPMPC (cHPMPC), in tissue culture and in mice inoculated with Herpes Simplex Virus Types 1 and 2 (HSV-1, HSV-2) or murine cytomegalovirus (MCMV). In human foreskin fibroblast cells, the EC_{50} values for HPMPC and cHPMPC were similar for all the herpesviruses tested including ACV and GCV-resistant mutants of HSV and CMV. In mice inoculated intranasally with HSV-1, treatment once daily with 5 mg/kg of either compound provided significant protection when begun 72h post infection. After inoculation with HSV-2, HPMPC appeared to have superior efficacy. When normal mice were inoculated i.p. with MCMV and treated either once daily or with a single dose of each compound beginning 48h after infection, 5-20 mg/kg provided similar levels of protection. Both compounds also reduced MCMV replication in target organs with HPMPC being slightly more effective. When immunocompromised (SCID) mice were inoculated i.p. with MCMV and treated twice weekly, HPMPC provided better protection than cHPMPC. Both compounds also reduced MCMV replication by 2-5 logs in all target organs tested. These results indicate that both HPMPC and cHPMPC are highly efficacious in animal models for severe HSV and CMV infections.

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Hydrocephalus Induction in Mice Infected with Herpes Simplex Virus Type 2 after Antiviral Treatment. X. Yao, and R. F. Schinazi.* Veterans Affairs Medical Center and Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory University School of Medicine, Decatur, Georgia 30033, USA.

Our group had previously reported that herpes simplex virus (HSV)-induced retinitis and cataracts could occur in mice surviving intracerebral infection after antiviral treatment, including treatment with 2'-fluoro-5-methylarabinosyluracil (FMAU). This study addresses the occurrence of hydrocephalus in FMAU-treated mice surviving infection with HSV-2 and provides a new mouse model for HSV-2-induced hydrocephalus. Groups of BALB/c mice were infected either intracerebrally (ic) or intraperitoneally (ip) with a lethal dose of prototype HSV-2 (strain G). FMAU was administered ip 2 days after virus inoculation to moderate the lethal effect of the virus at a non-toxic dose (10 mg/kg per day x 4 d). By day 21, 80% and 71.4% of the mice infected ic or ip, respectively, survived. The surviving animals were randomly subdivided into different groups and some were rechallenged ic or ip with a lethal or superlethal dose of homologous virus. The mice were sacrificed at 2 or 3 months after the initial virus infection. Neuropathological changes of the brains were assessed. Dilation of lateral and third ventricles was noted in the animals initially inoculated ic, especially in all the animals inoculated ic and rechallenged ic with a superlethal virus inoculum, but not in those inoculated ip. Microscopic examination of hydrocephalic brains also revealed evidence of viral meningoencephalitis. Evidence is provided that suggests that the induction of the hydrocephalus is related to an occlusion of the cerebral aqueduct. This model could have merits for assessing the prevalence of secondary effects of HSV-2 infections after antiviral treatment, for evaluating novel antiviral agents in their ability to prevent hydrocephalus, and to study the detailed pathogenesis of HSV-induced hydrocephalus in mice. This model is particularly relevant since HSV-induced cases of hydrocephalus have been reported to occur in humans.