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Treatment of Opportunistic Cytomegalovirus and Herpes Simplex Virus Infections in Murine AIDS (MAIDS). J.D. Gangemi, L. De Castro, A. Ghaffar, E.P. Mayer, *E. De Clercq, **P.E. Vogt, and **E.R. Kern. Univ. of South Carolina Sch. of Med., Columbia, SC, 29208, USA; *Rega Inst. Med. Res., Katholieke Universiteit Leuven, Belgium; **Univ. of Alabama Sch. of Med., Birmingham, AL, 35294, USA.

Two nucleoside analogs, 9-(2-Phosphonylmethoxyethyl) adenine (PMEA), (S)-1-(3-Hydroxy-2-Phosphonylmethoxy-propyl) cytosine, (HPMPC), and a recombinant human interferon alpha hybrid (rhuIFN-α B/D) which is active in murine cells, were evaluated in immunocompromised mice infected with murine cytomegalovirus (MCMV) or herpes simplex virus type 1 (HSV-1). Immunosuppression was induced in C57BL/6 mice with the LP-BM5 retrovirus complex resulting in splenomegaly, lymphadenopathy and suppression of B and T cell responses 100 days post infection. Intraperitoneal inoculation of these mice with MCMV or HSV-1 resulted in enhanced virus replication (3-5 $\log_{10}$ pfu/gm tissue) in lung, liver and spleen, compared to normal control mice and death occurred in 7-12 days. Treatment of HSV-1 infections with PMEA (100 or 10 mg/kg, i.p.) or rhuIFN-α B/D (10^6 units per mouse) on day 0,2,4,6, & 8, protected more than 50% of infected mice and prolonged survival time of those that died. In mice superinfected with MCMV, treatment with rhuIFN-α B/D (10^6 units/mouse S.C.) had no protective effect. In contrast, HPMPC or ganciclovir (DHPG) treatment effectively reduced mortality and increased the mean survival time. Of the two, HPMPC appeared to be more effective. These results indicate that LP-BM5 immunosuppressed mice superinfected with HSV or MCMV provides a model for evaluating antivirals against these opportunistic infections.

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(S)-[3-Hydroxy-2-(phosphonylmethoxy)propyl]cytosine (HPMPC): Studies on Intracellular Metabolism and the Effect of Infrequent Dosing on Antiviral Efficacy. J.J. Bronson, H-T. Ho, H. De Boeck, K.L. Woods, I. Ghazzouli, H. Yang, L.J. Klunk, J.W Russell, V.J. Whiterock, R. Datema, J.C. Martin and M.J.M. Hitchcock. Bristol-Myers Squibb Co., Wallingford, CT 06492.

HPMPC is an acyclic nucleotide analogue which has good antiherpesvirus activity in vitro, and has been found to exert a potent antiviral effect in vivo against herpes simplex viruses (HSV) and murine cytomegalovirus (MCMV). Intracellular metabolism studies using radiolabelled compound have shown that HPMPC is activated to mono- and diphosphorylated derivatives (HPMPCp and HPMPCpp), as well as a third metabolite which has been tentatively identified as a phosphate choline adduct (HPMPCp-choline) by analogy with the metabolism of ddC and ara-C. Upon removal of drug from the medium, these metabolites decayed with half-lives of 6, 17, and 48 h for HPMPCp, HPMPCpp, and HPMPCp-choline, respectively. These results suggested that dosing of HPMPC could be done on an infrequent basis since a prolonged antiviral effect would be possible due to persistence of the activated species in cells. An HSV 2 infection model in mice was used to explore the effectiveness of different treatment schedules. Initial experiments showed that a single intraperitoneal dose of 50 mg/kg of HPMPC given 3 h post-infection was as effective as the same total dose given BID for five days (5 mg/kg/dose times 10 doses). A dose of 5 mg/kg of HPMPC also resulted in significant reduction in mortality using either treatment schedule. Further experiments have shown that the single dose regimen is effective even when treatment is delayed until 96 h post-infection. Pharmacokinetic studies in rats (single iv dose of 5 mg/kg of HPMPC) showed a long elimination half-life (9 h), providing further evidence for the persistence of HPMPC.