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New Models of Murine Cytomegalovirus Infection in Immunocompromised Mice. D. F. Smee, J. Coombs, R. A. Burger, J. H. Huffman, K. M. Okleberry, J. D. Morrey, and R. W. Sidwell. Antiviral Program, Department of Animal, Dairy and Veterinary Sciences, Utah State University, Logan, Utah, U.S.A. 84322-5600.

We developed two mouse immunosuppression models of MCMV infection for evaluating antiviral agents. Immunosuppression was achieved by treatment of BALB/c mice with cyclophosphamide (CP, 100 mg/kg given at 3-4 day intervals) or by 21 days of infection with Friend leukemia virus (FLV). In the CP model, treatment with ganciclovir (12.5, 25 and 50 mg/kg/day starting 24 hours after virus challenge) for 5 or 10 days did not prevent mortality but delayed death 8-12 days after the last ganciclovir dose. This mimics the situation in AIDS patients where disease progresses after termination of antiviral therapy. Ganciclovir-treated, CP-immunosuppressed mice had increases in T-cell and B-cell blastogenic responses and reduced virus titers in organs and tissues on days 4 and 7 relative to the placebo group, indicating an antiviral effect at those time points. In the FLV/MCMV dual infection model, a 5-day course of ganciclovir therapy prevented death during the MCMV phase of the infection, but the mice went on to die of apparent FLV disease. As was observed in the CP model, ganciclovir treatments caused improvements in T-cell and B-cell blastogenic responses and reduced virus titers in organs and tissues on days 4 relative to the placebo group. Survivors of the MCMV phase of infection lived significantly longer than mice infected only with FLV, indicating that MCMV superinfection retarded FLV disease progression. Supporting this statement was the fact that FLV infectious centers in spleen cells were reduced in FLV/MCMV-infected mice relative to animals infected only with FLV.

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Efficacy of (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine [HPMPC] against intraperitoneal and intracerebral murine cytomegalovirus infections.

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The acyclic phosphonate nucleoside derivative (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) was evaluated for its inhibitory effect on murine cytomegalovirus (MCMV) infection in NMRI mice. Mice were infected either intraperitoneally (i.p.) ($10^5$ $CCID_{50}$) or intracerebrally (i.c.) ($5 \times 10^4$ $CCID_{50}$) and HPMPC was administered subcutaneously. At a dose of 1 mg/kg, HPMPC completely suppressed mortality if administered on day 0, 2 and 4 after i.p. MCMV infection. Also, a single dose of HPMPC at 100 mg/kg at either 0, 1, 2 or 3 days before i.p. MCMV infection offered significant protection against MCMV-induced mortality. In mice infected i.c. with MCMV, HPMPC administered at a dose of 5 mg/kg 2 hrs after the infection completely suppressed MCMV-induced mortality, without any obvious signs of toxicity for the host. When evaluated under the same experimental conditions, HPMPC was significantly more effective than DHPG (ganciclovir). HPMPC prevented mortality of mice infected i.c. with MCMV, when administered at a dose as low as 0.2 mg/kg/day for 5 consecutive days. Only at a dose of 25 mg/kg/day HPMPC caused a slight toxicity, as was apparent from a small retardation of animal growth. Similar levels of protection against mortality were achieved with DHPG at 25 mg/kg/day as with HPMPC at 0.2 mg/kg/day, but at this dose (25 mg/kg/day) DHPG significantly retarded animal growth.