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Comparative Efficacy of Acyclovir (ACV) and (*S*)-1-(3-Hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) in the Treatment of Cutaneous HSV-1 and HSV-2 Lesions in Athymic-Nude Mice

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We recently isolated from an AIDS patient, while under acyclovir therapy for persisting HSV-2 lesions, an acyclovir-resistant (ACV^r) HSV-2 strain (designated HS-44). Following topical treatment with HPMPC, the lesions regressed. From the lesions that relapsed after HPMPC treatment had been stopped, ACV-sensitive HSV-2 (designated HS-47) was isolated. Also, from a bone-marrow transplant recipient we isolated an HSV-1 strain (Hu-10) that was resistant to both ACV and foscarnet. Later, after the lesions had healed following HPMPC treatment, the HSV-1 strain (Hu-3) isolated from the relapsing lesions appeared to be ACV-sensitive (ACV^s). The ACV^s HSV strains (HS-47, Hu-3) and ACV^r HSV strains (HS-44, Hu-10) were inoculated intracutaneously in athymic-nude mice, which were then treated topically with ACV (5% in DMSO) for 5 days (four times daily) or with HPMPC (1% or 0.25% in DMSO) for 3 days (once daily) starting on the day of viral infection. Mortality (for HS-44, HS-47 and Hu-3) and morbidity (for Hu-10) were recorded for a period of 2 months.

Strain	Morbidity/Mortality[a]			
	Control	ACV (5%)	HPMPC (0.25%)	HPMPC (1%)
HS-44	12 (2/2)	15 (4/4)	22 (4/4)	40 (1/4)
HS-47	7 (2/2)	13 (4/4)	12 (1/4)	- (0/4)
Hu-10	13 (3/3)	8 (4/4)	36 (1/4)	- (0/4)
Hu-3	7 (3/3)	17 (4/4)	13 (2/3)	- (0/4)

[a]Results are expressed as mean day of death (HS-47, HS-44, Hu-3) or mean day of lesion appearance (Hu-10). Indicated in parentheses are the number of dead mice/the total number of mice per group.

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Inhibitory Effects of (*S*)-9-(3-Hydroxy-2-phosphonylmethoxypropyl)adenine and (*S*)-1-(3-Hydroxy-2-phosphonylmethoxypropyl)cytosine on Murine Adenovirus Replication *in vitro* and *in vivo*

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Severe (or even lethal) manifestations of adenovirus infections can occur in immunocompromised patients. No efficient chemotherapy against adenovirus infections is currently available. We have investigated the inhibitory effects of (*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA) and (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) on murine adenovirus replication *in vitro* and *in vivo*. Both HPMPA and HPMPC demonstrated a selective antiviral effect in murine fibroblast C3H/3T3 cells infected with murine adenovirus, their EC_{50} (concentration required to inhibit viral cytopathicity by 50%) being 0.005 and 0.04 µg/ml, respectively. These concentrations were at least 500-fold lower than the concentrations causing cytotoxicity. HPMPA and HPMPC also exerted a marked antiviral efficacy in suckling mice that had been inoculated intraperitoneally with murine adenovirus. When administered subcutaneously on day 0 (the day of infection), day 2, and day 5, HPMPA and HPMPC, at a dose of 2, 5 or 10 mg/kg, significantly increased the survival of the adenovirus-infected mice, the mean day of death (MDD) being ~ 9 (HPMPA) or ~ 8 (HPMPC), as compared to 6 for the (virus-infected, untreated) control group. Other dosage and treatment regimens are being investigated. We are also evaluating the antiviral efficacy of HPMPA and HPMPC in SCID (severe combined immune deficiency) mice infected with murine adenovirus.