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In Vivo Potentiation Of Acyclovir By Methoxypolyethyleneglycol-Thymidine Phosphorylase. G. W. Koszalka*, D. Lobe, M. W. Stonefield, J. Vanhooke, R. Ferone, K. Waters, and M. N. Ellis, Burroughs Wellcome Co., Research Triangle Park, NC 27709, U.S.A.

Thymidine in culture media affects acyclovir (ACV) -mediated inhibition of herpes simplex virus type 1 (HSV-1). Pretreatment of media with purified *E. coli* thymidine phosphorylase (TPase) lowered the ACV IC_{90} for HSV-1 from 6 μM to 0.5 μM. *E. coli* TPase was reacted with methoxypolyethyleneglycol-succinimidyl succinate (MPEG; mol. wt. 5000) and the product, MPEG-TPase, was examined for its ability to lower plasma thymidine levels in mice. Reaction conditions were established to maximize the amount of MPEG bound to the enzyme while minimizing the loss of catalytic activity. The pH profiles for thymidine cleavage by the modified enzyme (MPEG-TPase) and the native enzyme were identical. Although the K_m value for thymidine was unchanged (400μM), the V_{max} for the MPEG-TPase was 9-fold lower than the V_{max} for the native enzyme (26 vs. 240 μmol/min/mg). Mice treated with 2500 units/kg of MPEG-TPase had reduced thymidine levels that persisted for up to five days. The *in vivo* anti-HSV-1 activity of ACV was potentiated by the co-administration of MPEG-TPase. Mice injected with 2500 units/Kg of MPEG-TPase 72 hours after intranasal infection with HSV-1 and given ACV in the drinking water (0.4 mg/ml; *ad libitum*) exhibited an increase in survival relative to animals receiving ACV alone or ACV in combination with unmodified TPase. MPEG-TPase was antigenic to mice; both IgG and IgM antibodies were produced. These data suggest that depressing thymidine levels *in vivo* may prove useful in enhancing the activity of thymidine-sensitive chemotherapeutic agents.

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Topical HPMPC Is The First Effective Broad-Spectrum Antiviral To Inhibit Both HSV-1 and Adenovirus in the NZ Rabbit Eye Models. Y.J. Gordon, E.A. Romanowski, & T. Araullo-Cruz, The Eye & Ear Institute of Pittsburgh, Pittsburgh, PA, USA.

Historically, no antiviral agent has been demonstrated to be effective against HSV-1 and adenovirus (AD) in the same animal model. Compared to the control group in the NZ Rabbit eye model, topical 0.2% HPMPC promoted healing of HSV-1 epithelial keratitis [Keratitis score (Day 7): 0.05 vs 2.63, P <.0001], reduced HSV-1 viral titers (Day 7) [6.0×10^0 vs 1.4×10^4, P <.0002], and shortened duration of HSV-1 shedding [5.6 vs 7.8 days, P< 001]. In the same model, 0.2% HPMPC was also effective in reducing adenoviral type 5 eye titers (Day 7) [2.6×10^1 vs 1.1×10^4 control, P< .0001], duration of viral shedding [5.1 vs 12.7 days control, P< .0001], and percent AD5-positive eyes [35/80 (45%) vs 73/80 (91%) control, P< .000001]. A new concept of a broad-spectrum topical antiviral agent effective against both HSV-1 and adenovirus was demonstrated for the first time in an ocular animal model.