137

Herpes Simplex virus in the mouse: zosteriform lesions with adoptive transfer of immune cells: a model which mimics human recurrent disease.

Aftab. R. Awan, Johan Harmenberg & Hugh. J. Field.

Centre for Veterinary Sciences, University of Cambridge, Madingley Road, Cambridge,CB3 OES. UK.

Existing murine models for cutaneous herpes simplex virus type 1 (HSV-1) infection may have limited relevance to recurrent disease in man, since the infection is often primary rather than reactivated and infection occurs in the absence of an established immune response. In order to obtain a reproducible model to study the effects of topical antiviral therapy on recurrent disease we have developed a mouse model which employs zosteriform spread of HSV-1 in the presence of adoptive transfer of immune cells (ATI) to produce lesions which more closely resemble human recrudescences. Mice were infected with HSV-1 by scarification at the lateroventral line of the neck; two days later, the mice received ATI from the cervical lymph nodes of syngeneic mice that had been infected in the ear pinna with the same strain of virus seven days earlier. Virus was cleared more quickly from the infected tissues in mice given ATI in comparison with mice similarly inoculated without ATI, however the intensity and duration of the inflammation was greater. The model was then used to test the effects of a topical formulation of foscarnet. The results presented demonstrate that the ATI model can provide useful data concerning the efficacy of topical antiviral chemotherapy in man.

138

Further Investigation into the Recurrence of Infectious Virus in the Nervous System of Mice Infected with HSV-1 on Cessation of Valaciclovir Therapy.

A.M. THACKRAY & H.J. FIELD, Cambridge University, U.K.

Previously we have reported the contrasting effects of famciclovir and valaciclovir in murine infection models for HSV-1 and HSV-2. A striking result was the reproducible recurrence of infectious virus in the nervous system of mice following cessation of valaciclovir therapy given for 5 or 10 days while no such recurrence was observed on cessation of famciclovir therapy (JID:73,291,1996 & AAC:40, 846-851). We had previously noted a recurrence of virus replication in mice treated intraperitoneally with aciclovir (AAC:15,554,1979). We therefore compared aciclovir with its prodrug valaciclovir in the murine infection model. Mice were inoculated with HSV-1 into the skin of the ear pinna. Valaciclovir was administered orally (50mg/kg b.i.d) from day 1-5 post infection. Further groups of mice were treated with aciclovir i.p. (50 mg/kg b.i.d.) or aciclovir *ad. lib.*in the drinking water (approx. 160 mg/kg/day). The clinical signs were noted and mortality, weight-gain, and inflammation in the ear were measured daily. Virus replication in the skin of the ear and in brain stem and trigeminal ganglion was also monitored daily from day 1 to 14 post infection. Aciclovir i.p. was the most and valaciclovir the least effective of the three regimens. When treatment was terminated on day 5; recurrence of infectious virus was observed in brain stem on day 8 in mice that had been treated with aciclovir in drinking water and on day 9 in mice that had been given valaciclovir. Recurrence in trigeminal ganglia was seen on day 8 but only in mice that had been given valaciclovir. No recurrences of infectious virus were recorded in the skin of the ear. These results confirm that, in contrast to famciclovir, neither oral aciclovir nor valaciclovir therapy prevents virus recurrence in this infection model, a factor that may limit their antiviral efficacy in man.

139

Evaluation of the antiviral activity of an organomatallic compound in the guinea pig model of genital herpes. N Boume* and LR Stanberry, Children's Hospital Research Foundation, Cincinnati, OH.

Cobalt-containing compounds have been reported to have in *vitro* and *in vivo* anti-herpesvirus activity (Vogt et al, Antivir Res 17(Suppl 1): 114, 1992). We evaluated the antiviral activity of CTC96, an organometallic compound (Redox, Greenvale, NY) in the guinea pig model of genital herpes. In two dose-ranging experiments, female guinea pigs were treated with topical/intravaginal CTC96 twice daily for 10 days beginning 12 hours after intravaginal HSV-2 challenge. At the highest concentrations the drug appeared to have a modest effect on virus replication in the genital tract. However, 50% of animals treated with 2% CTC96 and 38% of guinea pigs receiving 1% CTC96 developed no symptoms of primary genital herpes compared to the control groups where all animals developed vesiculoulcerative genital skin disease. Interestingly, while treatment with 0.1% failed to impact primary infection, the animals experienced fewer recurrences than the placebo treated controls. This surprising finding suggests that this cobalt-containing compound might interfere with the establishment of latent infection. Further studies of the mechanism of actions of this class of novel compounds appear warranted.

140

Effect of Prophylactic and Therapeutic Administration of Topical 9-[2-(phosphonomethoxy)ethyl]guanine (PMEG) in Genital Herpes Simplex Virus (HSV) Infections of Guinea Pigs. J. Palmer, E. Harden, C. Hartline, and E.R. Kern. Univ. of Alabama School of Med., Birmingham, Ala., USA

We have reported previously that Cidofovir (CDV, HPMPC) is very effective in the treatment of genital herpes infection of guinea pigs, including Acyclovir resistant isolates. Additionally, a single dose given 2-6 hrs prior to HSV-2 inoculation prevented completely any evidence of infection. The purpose of the current studies was to evaluate another phosphonatenucleotide,9-[2-(phosphonomethoxy)ethyl]guanine (PMEG), for its ability to prevent or treat experimental genital herpes. In tissue culture cells, PMEG is highly active against both ACV sensitive and resistant isolates. In a genital herpes infection in guinea pigs, concentrations as low as 0.01% applied topically once daily for 5 days beginning 24h after infection significantly reduced vaginal and lesion virus replication and lesion severity. A single treatment given 24hrs after infection was also effective although less so than multiple treatments. Similar efficacy was obtained in animals infected with either of two ACV-resistant isolates. A single dose of 0.1% PMEG given 24h prior to infection was also highly effective in reducing infection rates, vaginal viral replication, and lesion development. Topical PMEG was more toxic than CDV at equivalent doses, however, lower concentrations of PMEG could be utilized without toxicity. These results indicate that PMEG is highly effective when administered topically in a model of genital herpes and may have a role for treatment of genital infections of humans.