Oral Session VI — Herpesvirus Infections II, Papillomavirus Infections

100

Enhanced Penetration of Acyclovir into Brain Tissue by RMP-7 in a Rat Model of Herpes Encephalitis. E.R. Kern, D. Bidanset, R. Rybak, J. Palmer, R. Bartus, L. Placidi, and J.-P. Sommadossi. Univ. of Alabama Sch. of Med., Birmingham, AL.; and Alkermes Inc., Cambridge, MA, USA

Herpes simplex virus (HSV) is the most common cause of sporadic fatal encephalitis in the U.S. and although therapy with Acyclovir (ACV) has markedly reduced morbidity and neurologic complications, treatment is not optimal. The amount of ACV that penetrates into brain tissue during therapy is quite low presumably due to limited uptake of drug through blood brain barrier. A bradykinin analogue, RMP-7, has been shown to increase the permeability of therapeutic agents across the barrier into the central nervous system. The purpose of our experiments was to determine if RMP-7 would enhance penetration and efficacy of ACV in a rat model of HSV encephalitis. Catheters were placed in jugular and femoral veins of uninfected or HSV-1 infected 175-200 g Fisher male rats. RMP-7 was infused at 6 μg/kg followed by a bolus of 50 μci of ^{14}C-ACV. After 20 minutes, blood, CSF, and brain samples were collected and assayed for total radioactivity. Uninfected animals that received RMP-7 had three times the ACV (4.1 vs 1.4 nmol/g) in brain tissue compared with those that received saline. Animals infected intranasally with HSV-1 and given RMP-7 and ^{14}C-ACV had ACV levels in brain that were two times greater than in saline treated rats (3.5 vs 1.7 nmol/g). These data indicate that RMP-7 enhances penetration of ACV into both uninfected and HSV-infected rat brain and suggests that clinical studies to determine if RMP-7 might enhance efficacy of ACV in HSV-1 encephalitis are warranted.

101

Combination of antiviral with anti-inflammatory preparations for the topical treatment for recurrent herpes simplex assessed using a zosteriform murine infection model.

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

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

A new zosteriform murine infection model will be described which employs the adoptive transfer of immune cells (ATI) to recipient infected mice to produce a disease that closely mimics human recurrent HSV. Mice were infected with HSV-1 by scarification at the lateroventral line of the neck; two days later, the mice received adoptive transfer of immune cells from HSV-1 infected syngeneic mice. Though virus was cleared quicker from the target tissues of virus replication in recipient mice, ATI resulted in a heightened inflammatory response, and delayed healing. This model was used to test the effects of topical formulations containing foscarnet combined with anti-inflammatory agents including non-steroidal and steroidal anti-inflammatory drugs. Virus clearance and clinical signs including ear thickness and zosteriform spread of lesions were studied. The presence of anti-inflammatory agents in the formulations extended the presence of infectious virus for up to 3 days but the reduction in ear thickness and other clinical signs was greater than that obtained with topical foscarnet or acyclovir alone. These results are discussed in relation to pain, inflammation and discomfort experienced by patients and a possible role for anti-inflammatory formulations in the treatment of HSV reactivation episodes in man.