151

Varicella Encephalitis After Prolonged Steroid Treatment of Varicella Uveitis in a Nonhuman Primate. M. D. Conway[1], A. N. Dueland[2], K. Srock[2], K. F. Soike[3], L. G. Ungerleider[4], D. H. Gilen[2] and G. A. Peyman[1]. [1]LSU School of Medicine, New Orleans, LA 70112; [2]University of Colorado School of Medicine, Denver, CO 80262; [3]Tulane Primate Center, Covington, LA 70433; [4]NIH, Bethesda, MD 20892.

Simian varicella virus (SVV) infection of primates is the counterpart of human varicella zoster virus infection. A 6 yr-old male African green monkey, inoculated intratracheally with 1.4 x 10^5 pfu of SVV, was treated with an antiviral nucleoside, 400 mg/kg/day, p.o., 2 - 12 days post-inoculation (PI). No rash, viremia or antibody developed. Three months PI, SVV was inoculated subretinally, in the right eye (OD). Within 2 weeks retinal edema, perivasculitis and uveitis developed. This uveitis persisted despite dexamethasone therapy, 1.0-1.4 mg/kg/day. I.M., from 6 weeks to 5 months PI. The left eye was normal. One week following cessation of steroid therapy, the animal appeared blind, and had no response to food or visually threatening stimuli. A T2-weighted MRI brain scan showed non-enhancing mirror-image convexity parasagittal parietal and occipital hyperintensities. The right hemisphere showed extensive damage in association visual cortex, but not in primary visual cortex. At necropsy, the right eye showed extensive uveitis with inflammation and SVV antigen. Mild necrosis, inflammation, intranuclear inclusions and SVV antigen were also seen in frontal, parietal and occipital cortex, more so on the right. The pathological and virological findings in brain are characteristic of varicella encephalitis, most likely caused by spread of SVV from the eye during prolonged steroid treatment. This dissemination of varicella to the brain during systemic steroid treatment may impact therapeutic decisions in humans who are treated with oral steroids for non-specific posterior uveitis amd may serve as an animal model of CNS dissemination of ocular viral disease.

152

Single and Combination Intravenous Therapy using USNUS-08 and DHPG during HCMV Chorioretinal Disease in the Rabbit. EC Dunkel[1], H Devlin[1], Q Zhu[1], D Pavan-Langston[1] and HA Blough[2], [1]Schepens Eye Research Institute, Deptof Ophthalmol, HMS, Boston, MA and [2]US Bioscience, West Conshohocken, PA, U. S. A.

N-phosphonacetyl-L-aspartate (PALA), a potent inhibitor of pyrimidine biosynthesis, was shown to inhibit both wild type and a DHPG resistant strain of cytomegalovirus (HCMV). In vitro there was a 2-3 log decrease in viral infectivity over 5 days. This drug, code named USNUS-08 was evaluated alone or in combination with DHPG in the rabbit model. HCMV (AD169; 10^6 pfu) was used to establish HCMV disease in rabbits. Beginning on day 1 PI and continuing for 10 days, rabbits received either USNUS-08, 50 or 25 mg/kg; DHPG, 10, 7.5 or 5 mg/kg/day or placebo alone; or combination USNUS-08 + DHPG intravenous therapy. Animals were evaluated daily, and HCMV recovery on days 2-6 PI. HCMV disease in placebo treated eyes developed to moderate levels; HCMV was recovered on days 2-6 PI (10^3-10^4 pfu). USNUS-08 (50 or 25 mg/kg) alone was moderately effective in reducing HCMV disease; HCMV was recovered on days 2-5 PI (10^3 pfu), and DHPG (10mg/kg) alone was effective; HCMV was recovered on day 2-4 PI (10^2-10^3 pfu). Combinational therapy was highly effective in reducing HCMV disease in USNUS-08 + DHPG intravenous groups receiving 50+10 or 50+7.5 mg/kg; HCMV was recovered on day 2-4 PI (10^2-10^3 pfu) in these groups. The 50 or 25 + 10 or 7.5 mg/kg combinations were superior to DHPG therapy alone. Combinational USNUS + DHPG (50+5 and 25+10) was minimally better than DHPG therapy alone; HCMVwas recovered on days 2-4 PI (10^2-10^3pfu). Histology showed focal to geographic retinal and choroidal pathology corresponding to intravenous therapy (Combinational therapy groups versus DHPG therapy alone had minimal pathology). High-dose PALA plus low-dose DHPG demonstrated an additive effect in reducing HCMV disease progression as evidenced by a decrease in HCMV titer, fewer number HCMV recovery days and in decreased ocular pathology. This compound should have efficacy in the treatment of human CMV retinitis.