inclusion (Henderson-Patterson inclusion bodies or Molluscum bodies) was observed. When raft cultures were incubated for a shorter period of time, few infected cells were predominantly observed in the upper layers of the raft cultures. Several clinical isolates of MCV have been successfully passaged in monolayer cultures of PHKs. Furthermore, the presence of MCV could be confirmed following electron microscopy analysis both in 2D and 3D cultures. Cells contained the characteristic mature, intracellular brick-shaped virions associated with other poxvirus infections. In conclusion, MCV isolates induced a characteristic cytopathic effect on normal human keratinocytes grown as monolayer or in a differentiated epithelium allowing the study of MCV replication and development of antivirals.

doi:10.1016/j.antiviral.2008.01.051

38

In Vitro and *In Vivo* Efficacy of a Pyrimidine Nucleoside Analog Against Vaccinia and Cowpox Viruses

Debra Quenelle [1,*], Mark Prichard [1], Kathy Keith [1], Deborah Collins [1], Terri Rice [1], John Secrist [2], Kamal Tiwari [2], Joseph Maddry [2], Earl Kern [1]

[1] The University of Alabama, School of Medicine, Birmingham, USA; [2] Southern Research Institute, Birmingham, USA

A novel nucleoside analog, SRI 21950, a 4′-thionucleoside, was synthesized and evaluated for activity against vaccinia (VV) and cowpox viruses (CV). In cell culture, SRI 21950 was effective at concentrations less than 1.0 μM against wild-type VV and CV. In addition, it retained its antiviral activity against cidofovir-resistant and ST-246-resistant strains. A thymidine kinase negative strain of VV exhibited reduced susceptibility to the drug suggesting that it may be specifically activated by this enzyme. In vitro cytotoxicity was measured by neutral red uptake and CellTiter-Glo® cell viability assays and indicated a cell cytotoxic (CC_{50}) value of greater than 100 μM for this compound using either method. To determine if this compound had activity in vivo, mice were lethally infected intranasally with either VV or CV. In the initial experiments, SRI 21950 was administered i.p. twice daily at 5, 15 or 50 mg/kg beginning 24 h post-VV infection and continued for 5 days. Treatment with SRI 21950 completely protected VV-infected mice from mortality at all doses ($P < 0.001$). In a second experiment, SRI 21950 was administered i.p. twice daily at 1.5, 5 or 15 mg/kg beginning 24 h after infection with CV and continued for 5 days and again treatment resulted in complete protection from mortality at all doses ($P < 0.001$). To determine if SRI 21950 had activity when administered orally, the compound was given by oral gavage twice daily at 5, 15 and 50 mg/kg. Again, a significant reduction in mortality at all doses ($P < 0.001$) was observed. Additional studies using lower doses of SRI 21950 initiated several days after CV or VV infection are in progress to help determine the potential of this compound, however, the results to date indicate that SRI 21950 has promise for treatment of adverse reactions to smallpox vaccinations, monkeypox or smallpox disease.

doi:10.1016/j.antiviral.2008.01.052

39

Effect of Treatment with the Cidofovir Analogue HDP-CDV in Guinea Pig Models of Cytomegalovirus Infection

Fernando Bravo [1,*], Rhonda Cardin [1], Karl Hostetler [2], David Bernstein [1]

[1] Cincinnati Children's Hospital Medical Center, University of Cincinnati, Division of Infectious Diseases, Cincinnati, USA; [2] Division of Infectious Diseases, University of California, San Diego, La Jolla, USA

Congenital cytomegalovirus (CMV) infection can be life-threatening and often results in significant sequelae including neurosensorial hearing loss. Currently available anti-CMV antivirals are effective, but their use is limited due to the lack of an effective oral formulation and the significant side effects associated with therapy. We evaluated hexadecyloxypropyl-CDV (HDP-CDV), an orally active ether lipid ester analogue of cidofovir in guinea pig models of congenital CMV infection. Pregnant Hartley guinea pigs were inoculated SQ with 1×10^5 pfu GPCMV during the late second/early third trimester of gestation. HDP-CDV (20 mg/kg, $N = 5$) or placebo ($N = 4$) was administered PO at 24 h post-infection (p.i.) and 7 days p.i. to pregnant animals. Pup survival was increased in the drug treated group (15/16, 93.8%) compared to placebo (10/18, 62.5%, $P = 0.02$). The viral load, examined by real-time PCR, in tissues harvested from pups sacrificed within 7 days of birth was significantly ($P < 0.05$) lower in the spleen (1.7 ± 0.7 $\log_{10}$ copies/μg DNA) and the liver (1.9 ± 0.8 $\log_{10}$ copies/μg DNA) of drug treated pups compared to the controls (2.5 ± 1.1 $\log_{10}$ copies/μg DNA and 2.9 ± 1.5 for the spleen and liver, respectively). Further evaluation of treatment on viral replication was performed in a guinea pig model in which viable newborn strain 2 guinea pigs were inoculated IP with GPCMV (1×10^6 pfu) within 48 h of life. Pups then received either HDP-CDV (4.0 mg/kg PO, $N = 12$) or placebo ($N = 11$), beginning 24 h p.i. and continued for 10 days. All pups were sacrificed on day 10 p.i. and the tissues were harvested for evaluation of the viral load by real-time PCR. The viral load in the spleen, liver, lung and brain of drug treated animals was significantly ($P < 0.005$) lower (1.3–2.8 $\log_{10}$) when compared to controls. These results indicate that oral HDP-CDV is well tolerated and effective in limiting CMV infection in these models and may provide an oral alternative to other therapies.

doi:10.1016/j.antiviral.2008.01.053