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Effective Inhibition of Equine Herpesvirus-1 In Vivo by Phosphonylmethoxyalkyl Derivatives of Adenine.

Field, H.J., De La Fuente, R. & Awan A.R. Department of Clinical Veterinary Medicine, University of Cambridge, UK.

Mice were infected with EHV-1 by intranasal inoculation. Clinical signs were produced and virus replication was precisely located in the olfactory mucosa and the mucosal linings of the lower respiratory tract. Active virus replication in ciliated mucosal cells was confirmed by electron microscopy and virus replication in these tissues monitored by titration. Viraemia resembling that in the natural host occurred reproducibly during the acute phase of the infection. The number of infected leukocytes was determined by infectious centre assay. The model was used to study several different antiviral regimens. Among these hydroxyphosphonyl-methoxypropyl adenine (HPMPA) was found to be extremely effective. Clinical signs were ameliorated, virus titres in the tissues were reduced by several log10 and the number of infected leukocytes quickly reduced to undetectable levels. The virological findings were supported by a careful histological study of the target tissues in animals receiving chemotherapy. The production of a series of mutants strains which had acquired resistance to the HPMPA proved the virus specific mode of action of this antiviral compound.

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Evaluation of Infrequent Dosing Regimens with (S)-1-[(3-hydroxy-2-(phosphonylmethyoxy)propyl]cytosine (HPMPC) in Simian Varicella Infection in Monkeys. K.F. Soike, J.-L. Huang, J.-E. Zhang, M.J.M. Hitchcock and J.C. Martin. Delta Regional Primate Research Center, Covington, LA and Bristol-Myers Squibb, Wallingford, CT.

(S)-1-[(3-Hydroxy-2-phosphonylmethoxy)propyl]cytosine (HPMPC is a member of a new class of nucleotide analogues that have antiviral efficacy against some DNA viruses. In vitro studies against simian varicella virus infection in Vero cells have demonstrated the ED_{50} to lie between the acyclic nucleosides and bromovinyluracil or the fluorinated pyrimidinenucleoside analogues. In vivo studies where African green monkeys were infected with simian varicella virus showed intravenous doses of 5 mg/kg/day given as divided doses twice daily for 10 days beginning 48 hours after virus inoculation prevented rash development and significantly reduced viremia. An i.v. dose of 1 mg/kg/day similarly administered had a minimal antiviral effect. Simian varicella virus infected monkeys receiving a total HPMPC dose of 50 mg/kg given i.v., as either (1) 5 mg/kg/day for 10 days beginning on day 2, or (2) 10 mg/kg at 2, 4, 6, 8, and 10 days post-infection or (3) 25 mg/kg on day 2 and day 6 showed each of the three treatments to be efficacious. Antiviral activity was also assessed following a single 50 mg/kg dose of HPMPC where treatment was given either 2 days, 4 days or 6 days after virus inoculation. No obvious toxicity was observed clinically or by hematology or clinical chemistry tests taken during the course of any of these treatment regimens.
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