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Antiviral Activity of Selected Nucleoside Analogues against Human Herpes Virus Type 6

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Human Herpes Virus type 6 (HHV-6) was originally isolated from peripheral blood lymphocytes of patients with immunocompromising disorders and has been proposed to be a cofactor in the progression of acquired immune deficiency syndrome (AIDS). We now report on the *in vitro* susceptibility of HHV-6 to a broad range of antiviral compounds, including several acyclic nucleoside phosphonates, as well as acyclovir (ACV), ganciclovir (GCV), brivudin (BVDU), idoxuridine (IDU) and foscarnet (PFA). Inhibition of HHV-6-induced cytopathicity in human T-lymphocyte HSB-2 cells (i.e., appearance of enlarged, refractile cells) was determined as parameter of the antiviral activity of the compounds. Moreover, we have developed a sensitive, specific and reliable flow cytometric technique to assess the inhibitory effect of the antiviral agents on HHV-6-specified antigen expression in the infected cell cultures. PFA, (*S*)-HPMPA, (*S*)-HPMPC, (*S*)-3-deaza-HPMPA, (*S*)-3-deaza-cHPMPA, (*S*)-cHPMPC, (*S*)-HPMPG, (*R*)-HPMPG, (*S*)-cHPMPG and PMEDAP effected the highest inhibition of HHV-6 replication with 50% inhibitory concentration (IC_{50}) values, as determined by the flow cytometric method, ranging between 1 and 4 μg/ml. PMEA and (*S*)-HPMPDAP had an IC_{50} of 8-12 μg/ml, followed by (*S*)-cHPMPA (IC_{50}: ~ 20 μg/ml). The IC_{50} of ACV was 70 μg/ml, whereas (*S*)-FPMPA, (*R*)-PMPDAP, (*S*)-8-deaza-HPMPDAP, (*R*)-cHPMPG, BVDU, BVaraU, carbocyclic oxetanocin A, carbocyclic oxetanocin G, FIAC and GCV showed no anti-HHV-6 activity at subtoxic concentrations. A close correlation was found between the inhibitory concentrations of the test compounds against HHV-6-induced cytopathicity as determined microscopically and their inhibitory concentrations against HHV-6-induced antigen expression as evaluated in the indirect immunofluorescence/flow cytometric method. The anti-HHV-6 activity of the acyclic nucleoside phosphonates paralleled their activity against other herpesviruses (i.e., herpes simplex virus type 1 and 2, and human cytomegalovirus). Since HIV-1 and HHV-6 are thought to be able to coinfect lymphocytes, the fact that compounds such as PMEA and PMEDAP are active against both viruses may have important clinical applications. We are now planning to examine the effects of these compounds on dual HIV-1/HHV-6 infection.

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Antiviral activity of compounds against human herpesvirus 6

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Human herpesvirus 6 (HHV-6) is a causative agent of exanthem subitum in infants and is latent in several organs thereafter. HHV-6 often reactivates in immunosuppressed patients with such as AIDS, bone marrow and kidney transplantation and it is supposed to be the cause of pneumonia and marrow failure. In the present study, the in vitro antiviral activity of nucleoside analogues to HHV-6 was evaluated in MTT assay by using MT-4 cells and HST strain (variant B). Among the compound, BVDU, IDU inhibited the viral replication at 4μM by 40 - 50 % and foscarnet, DHPG,ACV, AraA were also effective at 4μM by 30 - 40%. HHV-6 is proved to be deficient in viral thymidine kinase (TK) gene. In our experiment, it is not clear why BVDU and ACV were inhibitory against HHV-6 and how they were phosphorylated in the infected cells. In HCMV which defects viral TK, UL97 open reading frame was found to encode a protein that phosphorylates DHPG. HHV-6 has 30 - 50% amino acid homology with HCMV in the several genes and has the homologue of HCMV UL97. It has been also reported that HHV-6 is sensitive to DHPG and ACV. These results support the possibility that UL97 homologue of HHV-6 may be responsible for the phosphorylation of TK-dependent nucleoside analogues in infected cells. In addition the MTT assay that we used was found to be easy and reliable for screening anti-HHV-6 compounds.