Poster Session II — Herpesvirus, Respiratory Virus, Other Infections

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ANTIVIRAL ACTVITY OF A NOVEL COMPOUND P-4018 AGAINST DIFFERENT STRAINS OF HERPES SIMPLEX VIRUS IN VITRO AND IN VIVO

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A fatty acid derivative of ganciclovir (GCV), P-4018, has been evaluated for its inhibitory activity against laboratory and clinical strains of herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in human embryonic lung (HEL) cells. GCV, HPMPC (cidofovir), ACV (acyclovir), BVDU (brivudin) and PFA (foscarnet) were included as reference compounds. Viruses included wild-type, thymidine kinase-deficient (TK^-) and PFA-resistant (PFA^r) HSV strains. IC_{50} values for P-4018 were 5- to 50-fold lower than those observed for GCV, the IC_{50} value of P-4018 for the HSV-1 reference strain KOS being 0.00007 μM. Similar patterns of sensitivity/resistance to GCV and P-4018 were noted when TK^- and PFA^r strains were tested. Thus, GCV and P-4018 were not active against TK^- HSV-1 and HSV-2 strains, but they remained active against PFA^r strains. The antiviral effect of P-4018 was also evaluated in an *in vivo* model of intracerebral HSV-2 (196 strain) infection in NMRI mice. Animals were treated intraperitoneally with P-4018, GCV or placebo once daily for 10 days, starting the day of infection. Survival was registered till day 20 post infection. Compound P-4018 proved to be more active than GCV in this model. Thus, survivors were observed at a dose of 0.8 mg/kg/day for P-4018 as compared to 3 mg/kg/day for GCV. Fifty % of survival was achieved at a dose of 5 mg/kg/day and 12 mg/kg/day for P-4018 and GCV, respectively. P-4018 proved also active against HSV-2-infected mice when administered orally once daily for 10 days, starting the day of infection. Survivors were noted at 6 mg/kg/day for P-4018 and at 12.5 mg/kg/day for GCV, 50% survival being achieved at a dose of 25-50 mg/kg/day for both compounds.

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Influence of Replacement of Oxygen with Sulfur at the 4'-Position on the Antiherpesviral Activities of Arabinofuranosyl Purine and Uracil Nucleosides

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To search influence of substitution with sulfur atom at the 4'-position of arabinofuranosyl nucleosides on their antiherpesvirus activities, we synthesized 2'-fluoro-4'-thio and 4'-thio arabinofuranosyl nucleosides, and evaluated them for the antiherpesviral activities in comparison with non sulfur-substituted arabinofuranosyl nucleoside congeners. Among synthesized 4'-thio arabinosyl purine nucleosides, 2'-fluoro-4'-thio arabinosyl guanine and 2,6-diaminopurine showed particularly marked anti-HSV-1, HSV-2, VZV, and CMV activities (ED_{50} values in the plaque assay were 0.006, 0.05, 0.1, and 0.07 μg/ml, respectively), flowed by the 4'-thio congeners, though the latter showed more potent anti-CMV and anti-cell proliferative activities than the former. In contrast, arabinosyl guanine and diaminopurine had weak anti-herpesvirus activities, but they showed anti-cell proliferative activity equivalent to that of 2'-fluoro-4'-thio analogues. Antiviral activity of 4'-thio araA was almost equivalent to that of araA. Introducing the 4'-thio substitution into sorivudine (BV-araU) or 2'-fluoro BV-araU reduced anti-VZV and anti-HSV-1 activities of the mother compounds. The 4'-thio substitution in other 5-substituted arabinosyl and 2'-fluoro arabinosyl uracils little influenced antiviral activities, except that activities of 5-ethyluracil nucleosides against HSV-1 and HSV-2 increased. These 4'-thio and 2'-fluoro arabinosyl uracils were inactive against CMV, except that 2'-fluoro-4'-thio arabinosyl 5-methyluracil exhibited anti-CMV activity comparable to that of 2'-fluoro arabinosyl 5-methyluracil.