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Comparative anti-viral effects of Acyclovir and Penciclovir (Famciclovir).

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We have compared the anti-viral activity of Acyclovir (ACV) with Penciclovir (PCV) and Famciclovir (FCV) in several *in vitro* and *in vivo* experimental systems with the following results. In plaque and yield reduction assays ACV and PCV were shown to have approximately equivalent activity against three laboratory and ten clinical isolates of HSV-1. In contrast in the same assays ACV was shown to have superior activity to PCV against one laboratory and ten clinical isolates of HSV-2. PCV was found to have particularly poor activity against HSV-2 when yield reduction assays were performed using high in-put virus. For other herpes viruses whilst the *in vitro* activity of ACV and PCV against VZV was shown to be comparable, PCV was shown to have poor activity against EBV. In experiments designed to investigate the effect of short periods of exposure of compound on the anti viral effect of HSV we could not discriminate between the ACV and PCV. The profile of sensitivity between ACV resistant mutants showed that there is likely to be no significant advantage for PCV in treating resistant virus in the clinic. In the zosteriform model of HSV disease , ACV, PCV and FCV given twice daily by mouth in doses ranging from 5-50 mg/kg were found to give equivalent protection against HSV-1. However, against HSV-2 in the same model ACV was more effective than FCV, significantly preventing virus dissemination. In a study of single daily dosing against HSV-1. ACV, PCV and FCV were administered once daily by mouth at 50mg/kg and all were similarly effective: Our comparison of the anti viral activity of ACV and PCV have confirmed that for HSV-1 the compounds show similar anti viral activity. However, it is also clear that PCV is significantly less active than ACV against HSV-2. The lack of any significant activity against EBV would show that in the immune compromised, where EBV is of clinical significance, PCV may not have beneficial effect. Finally reports suggesting that the prolonged half-life of the active triphosphate form of PCV would afford superior activity *in vivo* were not substantiated in our model systems which we believe to be relevant to human disease.

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Sequence-specific Antiviral Activity of a Phosphorothioate Oligonucleotide Complementary to Immediate Early mRNA of Human Cytomegalovirus. *K.P. Anderson*, R.F. Azad*, and K. Tanaka°. *ISIS Pharmaceuticals, 2280 Faraday Ave., Carlsbad CA 92008 USA, and °Eisai Co., Ltd., Tsukuba Research Laboratories, Tsukuba-shi, Ibaraki 300-26 JAPAN*

Phosphorothioate oligonucleotides complementary to messenger RNA of the human cytomegalovirus (HCMV) DNA polymerase gene, or to RNA transcripts of the major immediate early region (IE1 and IE2) of HCMV were evaluated for antiviral activity in a 96-well immunoassay using primary human dermal fibroblasts as host cells. Oligonucleotides complementary to RNA of the IE2 region exhibited the most potent antiviral activity. One of these oligonucleotides, ISIS 2922, was chosen for further analysis. ISIS 2922 inhibited virus antigen expression by 50% at concentrations of 0.2 to 0.5 μM in the 96-well immunoassay and was approximately 30-fold more potent than ganciclovir. Plaque reduction assays and infectious virus yield assays yielded comparable relative activities. Greater than 90% inhibition of intracellular infectious virus yield was achieved using oligonucleotide concentrations as low as 0.3 μM. A control phosphorothioate oligonucleotide of the same length, but different nucleotide sequence exhibited less potent antiviral activity, with 90% inhibition of virus yield observed only at concentrations exceeding 3 μM. Cytotoxicity as measured by MTT or neutral red assays was not observed at concentrations ≤ 100 μM. The specificity and potency of ISIS 2922 suggests that it may be useful for the treatment of cytomegalovirus disease in humans.