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Influence of the Size of the Virus Inoculum on the Efficacy of Acyclovir (ACV) and Implications for the Treatment of Herpes Simplex Labialis. M.B.McKeough and S.L.Spruance, University of Utah, Salt Lake City, Utah, USA.

Herpes labialis has been the subject of more than 50 trials of antiviral chemotherapy over 25 years of investigation, yet there are no FDA-approved treatments for this disease in the United States. Because of the rapid evolution of episodes (*Oral Surg Oral Med Oral Path* 1984;58:667-671) and the dense inervation of the lips (*Clin Res* 1983;31:50a), we have hypothesized that the virus inoculum from neurons (multiplicity of infection, moi, virions/cell) may be large. To evaluate the effect of moi on the efficacy of ACV, mink lung cell monolayers in 6-well 35 mm plates were infected with herpes simplex virus type 1 at nine different moi's ranging from .0001 to 10, incubated for 2 hours, washed and then treated with 0, 4, 20 or 200 μM ACV in a liquid medium overlay. Drug efficacy was measured by visual assessment of the percent cytopathic effect (CPE) in the monolayer. Moi had a marked effect on drug efficacy. At an moi of .0001, all three concentrations of ACV were effective in preventing CPE while control cultures were completely destroyed after 60 hours. At an moi of .001, only 20 and 200 μM ACV were protective, and at an moi of .01, only the highest level of ACV was efficacious. At moi's $\geq$.1, ACV was ineffective at any concentration. While the exact moi encountered in human epithelium can only be a matter of speculation, these results argue that exploration of higher drug doses are a logical way to attempt to improve clinical efficacy.

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Antiviral Activity of Phosphinic Cyclocreatine (2-iminoimidazolidine-1-Methyl Phosphinic Acid) Against HCMV and HSV-1.

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Human cytomegalovirus (HCMV) induces the expression of the cellular enzyme creatine kinase (CK), which is involved in rapid regeneration of ATP at sites of cellular work. The induction of CK upon infection with HCMV suggests an important function for the enzyme and its substrates, creatine and creatine phosphate, in viral replication processes. Cyclocreatine (CCr), an analog of creatine, exhibits antiviral activity against herpesviruses *in vitro* and *in vivo*. In this study, phosphinic cyclocreatine (PhCCr), another analog of creatine that has improved solubility relative to CCr, was tested against HCMV and HSV-1 *in vitro*. PhCCr inhibited HSV-1 and HCMV plaque formation in a dose dependent manner (ED_{50} = 6 mM and 3 mM, respectively). Similarly, a decrease in HCMV DNA synthesis was observed (ED_{50} = 3 mM). In the antiviral susceptibility analysis, PhCCr exhibited the same potency against three ganciclovir and two foscarnet-resistant HCMV strains. The antiviral activity observed was below cytotoxic doses, as monitored by XTT assay and growth curve analysis (IC_{50} >100 mM). Susceptibility of clinical isolates of HCMV to this novel compound, and studies aimed at evaluating the combinatorial effects of PhCCr with ganciclovir are currently ongoing.