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Evaluation of Ganciclovir Against Human Adenovirus Type-5 Infection in Cell Culture and Cotton Rat Eyes. M. D. Trousdale, P. L. Goldschmidt† and R. Nóbrega, Doheny Eye Institute, Los Angeles, California and †Laboratoire de Virologie, Hôpital Broussais, Paris, France.

Adenoviruses (Ads) are ubiquitous in nature and cause many medical problems, including ocular and respiratory disease around the world. In the United States, Ads are the most common cause of acute viral infections of the eye for which there are no effective antiviral drugs. Until recently, pathogenesis studies and antiviral drug testing for Ad-induced ocular disease were not practical because no animal model was available. However, the new discovery of animal models for human Ad-induced ocular and respiratory infections has now made it possible to study the molecular mechanisms of pathogenesis and potent antiviral compounds for treatment. For these studies, we selected Ad5 wt300, a genetically defined virus that has been shown to cause both ocular and respiratory infections. Ganciclovir and Acyclovir were preliminarily tested for antiviral activity against Ad5 in A549 human lung carcinoma cells (ID_{50} of 47 and >600 μM, respectively). Forty cotton rats (Sigmodon hispidus) were inoculated bilaterally with 10^5 pfu/eye of Ad5 and then treated topically with either Ganciclovir (3, 1, or 0.3%) or placebo five times per day for 21 consecutive days. All inoculated eyes were virus culture positive on days 1 through 3 with increased infectivity titers regardless of treatment. Incidence and duration of virus shedding was reduced in eyes treated with 3% Ganciclovir. Anti-Ad5 ELISA sera antibody titers were less in animals treated with 3% Ganciclovir. Biomicroscopic examination of eyes during treatment did not reveal differences in the clinical appearance of eyes in the various treatment groups. In summary, beneficial results were observed in Ad-infected cell cultures and Ad-infected animals treated with Ganciclovir.

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A Single Large Dose of HPMPC is Highly Effective at Inhibiting HCMV when Administered in an *In Vitro* Drug Delivery System, MR Moore, FM Hamzeh, FE-H Lee, and PS Lietman, Division of Clinical Pharmacology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

(S)-1-(3-Hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) is a novel nucleotide analog and a potent inhibitor of HCMV replication in conventional *in vitro* studies. Preliminary data suggest that HPMPCpp (the presumed active metabolite) may have a long intracellular half-life (~ 17hrs). It has been hypothesized that a single large dose of HPMPC might effectively inhibit the growth of HCMV. We administered HPMPC to HCMV-infected (Towne strain) MRC-5 cells using a novel *in vitro* drug delivery system(DDS) in which inputs, concentrations, and rates of elimination can be manipulated in order to mimic human pharmacokinetics. This DDS allows the administration of HPMPC as either a bolus dose or as a continuous infusion in a tightly controlled and reproducible manner. When given as a continuous infusion, HPMPC produces an effect which is similar to that measured by conventional methods, i.e., ED_{50}=0.1μg/ml, ED_{90}=1.0μg/ml. When a 220μg bolus of HPMPC was administered to the DDS with a volume of distribution of 65ml and a half-life of 15hrs, a peak level of 3.4μg/ml was achieved, as well as an area under the drug concentration-time curve (AUC) of 61μg-hrs/ml and a time above the ED_{50} of 70hrs. Six days after dosing (more than three days after the drug level had fallen below the ED_{50}) intracellular viral DNA (measured by dot-blot hybridization) was only 8% of an untreated control. A higher dose(500μg) with an AUC of 138μg-hrs/ml produced no additional effect suggesting that a plateau on the dose-response curve had been reached by the 220μg dose. Lesser doses(100μg, 50μg) with correspondingly lesser AUCs(37 and 17μg-hrs/ml, respectively) were associated with lesser effects(61% and 100% of control values, respectively). We conclude that a single large dose of HPMPC can effectively inhibit HCMV viral DNA synthesis in this novel *in vitro* drug delivery system. This system provides an efficient approach to the determination of the importance of such pharmacokinetic parameters as peak levels, trough levels, AUCs, and times-above some critical level in anti-HCMV therapy. In addition, this system provides a convenient model for studying intracellular metabolism of HPMPC as a function of constantly changing extracellular concentrations.