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Cyclocreatine (1-carboxymethyl-2-iminoimidazolidine) Inhibits HCMV at or Near the Stage of DNA Replication.

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The expression of creatine kinase (CK) is induced in cells infected by human cytomegalovirus (HCMV). CK reversibly generates ATP from creatine phosphate (CrP), and plays an important role in cellular energy homeostasis. The induction of CK by DNA viruses implicates a role for the CK/CrP system in efficient viral replication. We have observed that an analog of creatine, cyclocreatine (CCr), exhibits antiviral activity against herpesviruses *in vitro* and *in vivo*. CCr does not act as a virucidal agent when exposed to HCMV directly, and prior exposure to CCr does not protect MRC-5 cells from infection by HCMV. Studies examining the effect of CCr on viral attachment, penetration and uncoating showed no significant differences between CCr-treated and untreated cells. The results from time-of-addition experiments demonstrated that CCr has maximal activity when added at 0 and 5 hr post-infection. A slight decrease in activity was observed when CCr was added 24 hr post-infection, and antiviral activity decreased by 3 logs when CCr was added at 48 hr post-infection. The effect of CCr on HCMV DNA synthesis was measured and it was found that CCr inhibits the replication of HCMV DNA in a dose-dependent manner. The ED_{50} was similar to the concentration that inhibits plaque formation by 50%. Preliminary experiments to examine the effect of CCr on viral protein synthesis suggest that immediate early and early protein synthesis was not affected, but late protein synthesis was inhibited. These results suggest that inhibition by CCr occurs at or before viral DNA replication. Studies to further define the mechanism of action of CCr are ongoing.

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Phase I Trial of a New Anti-cytomegalovirus Agent, (S)-1[3-hydroxy-2-(phosphonyl-methoxy)propyl]cytosine (HPMPC), in HIV-infected Volunteers. M Wachsman, BG Petty, HS Jaffe, K Cundy, P Fisher, and PS Lietman. The Johns Hopkins University School of Medicine, Baltimore, MD, and Gilead Sciences, Inc., Foster City, CA, USA.

We report a double-blind, placebo-controlled Phase I study of the safety, tolerance, pharmacokinetics, and bioavailability of (S)-1[3-hydroxy-2-(phosphonylmethoxy) propyl] cytosine (HPMPC) in HIV-infected patients. Five patients were randomized to receive drug and two to receive placebo per dosing tier. The drug or placebo was given by intravenous (IV) and oral routes at doses of 1, 3, and 10 mg/kg. Subjects at 1 and 3 mg/kg also received a dose subcutaneously (SQ). The order of the route of administration was randomized with a two-week washout period between doses. Pharmacokinetic profiles were determined for each route. For those subjects already taking zidovudine (AZT) for their HIV infection, the area under the concentration-time curve (AUC) for AZT was determined the day before and the day of each dose of HPMPC. HPMPC had a non-linear decay of logs of concentrations following IV dosing. Using non-compartmental analysis, the AUC was proportional to dose for IV dosing. The volume of distribution was 525 ± 168 ml/kg at 3 mg/kg and 465 ± 99 ml/kg at 10 mg/kg. Clearance was 156 ± 18 ml/hr/kg at 3 mg/kg and 147 ± 27 ml/hr/kg at 10 mg/kg by non-compartmental analysis for IV dosing. Oral dosing demonstrated poor bioavailability (estimated at < 5.3% compared to IV by comparison of AUC's in identical subjects). SQ dosing, while having good bioavailability (97.8 % ± 5.9%), was limited by local pain, the development of modest subcutaneous nodules at the injection site (presumably fibrosis), and the volume needed for drug administration. At the 10 mg/kg dose, nephrotoxicity, manifested as 4+ proteinuria and elevation of serum creatinine to 2.6 mg/dl, was seen in 1 of 5 patients. This patient had the highest AUC for both IV and oral dosings in our study. In this patient, proteinuria was accompanied by glucosuria, reduced serum uric acid, and alkaline urine (Fanconi syndrome) and the nephrotoxicity was only partially reversible over 10 months. The AUC for zidovudine was not consistently changed by the presence of concomitant HPMPC.