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The Safety, Pharmacokinetics, and Anti-CMV activity of weekly HPMPC in HIV positive patients excreting CMV. WL DREW[1], JP LALEZARI[1], E GLUTZER[1]; JC MARTIN[2], PE FISHER[2], HS JAFFE[2]. 1. Mount Zion Medical Center of UCSF, San Francisco, CA, U.S.A., and 2. Gilead Sciences, Inc., Foster City, CA, U.S.A.

(S)-1-[3-Hydroxy-2-(phosphonylmethoxy)propyl] cytosine (HPMPC) is a nucleotide analog with potent in vitro and in vivo activity against CMV. Phosphorylation of HPMPC to its' active intracellular metabolite is independent of virus infection and associated with prolonged antiviral effect. We conducted a phase I/II study of weekly intravenous HPMPC in HIV infected patients with asymptomatic shedding of CMV in urine and semen. Five patients were enrolled at each of four dose levels (0.5, 1.0, 3.0, and 10.0 mg/kg) and treated for four weeks. Nephrotoxicity was observed in 2 of 5 patients at the 3.0 mg/kg level after 6 and 14 doses respectively, and was dose limiting after 2 doses at the 10 mg/kg level. Reduction of CMV titer in semen and/or conversion to urine culture negative was observed at both the 3.0 and 10.0 mg/kg dose levels. These reductions were observed by viral titration via plaque assay as well as a branched chain DNA assay. Nine additional patients then received HPMPC at 5.0 mg/kg on a weekly or every other week schedule with concomitant administration of probenecid, an inhibitor of organic anion transport which protects against HPMPC nephrotoxicity in animal models. Preliminary results indicate a HPMPC-probenecid dose dependent interaction. The combination of concomitant probenecid and every other week dosing intervals appears to substantially reduce the nephrotoxic effects of HPMPC, while retaining anti CMV effect.

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Comparative Activity of Selected Antiviral Compounds on *In Vitro* Replication of Varicella Zoster Virus Clinical Strains

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Fifteen freshly isolated varicella zoster virus (VZV) strains were evaluated, in parallel with the reference strains expressing specific thymidine kinase (TK) (Oka, YS) or deficient for viral TK (07-1 and YS-R), *in vitro* in a plaque assay for their susceptibility to a broad range of antiviral substances including acyclovir, BVDU, BVaraU, ganciclovir, FIAC, ara-T, ara-C, ara-A, foscarnet, phosphonoacetic acid, the acyclic nucleoside phosphonates HPMPC, HPMPA, cyclic HPMPC, 3-deaza-HPMPA, PMEA and PMEDAP, and the N7-isomeric acyclic nucleoside analogue 2242. For 13 out of the 15 clinical isolates the order of decreasing activity against VZV was BVaraU > BVDU > ara-C ≈ ara-T ≈ HPMPA ≈ cyclic HPMPA ≈ 3-deaza-HPMPA ≈ 2242 ≈ FIAC > acyclovir ≈ ganciclovir ≈ HPMPC ≈ cyclic HPMPC > PMEA ≈ PMEDAP ≈ foscarnet ≈ phosphonoacetic acid ≈ ara-A. The two strains (isolated from the cerebrospinal fluid of an AIDS patient) that were shown to have a truncated TK, were clearly resistant to all the compounds that need the viral TK for their phosphorylation, while the sensitivity to the acyclic nucleoside phosphonates, foscarnet, phosphonoacetic acid and ara-A remained unchanged. A slight (5-fold) increase was noted in the IC_{50} of compound 2242 for the TK-based drug-resistant VZV strains as compared to the sensitive VZV strains. Also, ganciclovir and FIAC showed a marked decrease in activity against these two strains, but not as pronounced as for the other TK-dependent drugs. From our results, it appears that the acyclic nucleoside phosphonates should be considered for the treatment of TK-based drug-resistant VZV infections.