177

Human Cytomegalovirus (HCMV) Strains Selected under Selective Pressure of Phosphonoformate (PFA) are Resistant for Both PFA and Phosphonylmethoxyethyl (PME) Derivatives *in vitro*

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HCMV has been well described as one of the major pathogens responsible for morbidity and mortality in immunocompromised patients. With the broad use of ganciclovir (GCV), particularly in patients with the acquired immune deficiency syndrome (AIDS), emergence of strains resistant to GCV has been noted. The drug of choice to treat such patients is foscarnet (PFA) since for almost all GCV-resistant (GCV^r) strains isolated, no cross-resistance to PFA was found. We report here the isolation of resistant HCMV strains under the pressure of PFA. The drug-resistant strains were obtained by serial passage of the reference HCMV AD169 strain in the presence of increasing concentrations of PFA in human embryonic lung (HEL) fibroblasts. After reaching the highest possible concentration of PFA (100 μg/ml), a last passage was done in drug-free medium and different clones were isolated by plaque purification. The PFA-resistant (PFA^r) strains showed an increase in the IC_{50} values for PFA and phosphonoacetic acid (PAA) of 7- to 10-fold, as compared to the reference strain AD169. The PFA^r strains were also resistant to the PME derivatives of adenine (PMEA) and 2,6-diaminopurine (PMEDAP) and acyclovir (ACV). No cross-resistance was noted with the 3-hydroxy-2-phosphonylmethoxypropyl (HPMP) derivatives of adenine (HPMPA) and cytosine (HPMPC), ganciclovir (GCV) and vidarabine (AraA). Also, resistant strains selected under the pressure of PMEDAP showed cross-resistance to PMEA, PFA, PAA and ACV, but they remained sensitive to the HPMP derivatives. In addition, HCMV strains selected under the pressure of HPMPC, HPMPA or GCV did not show cross-resistance with the PME derivatives, PFA, PAA and ACV. Our data provide further evidence for a common mechanism of anti-HCMV action of PFA, PAA and the PME derivatives that is different from the mechanism of action of the HPMP derivatives.

178

Effects of Desferrioxamine on Human Cytomegalovirus Replication and Expression of HLA Antigens and Adhesion Molecules in Human Vascular Endothelial Cells

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Desferrioxamine (DFO), commonly used in therapy as a chelator of ferric ion in disorders of iron overload, is a potent inhibitor of human cytomegalovirus (HCMV) replication in cultured fibroblast cells. Moreover, DFO has immunomodulatory activity both in vitro and in vivo. We studied DFO effects on HCMV replication in human vein endothelial cells and on the expression of several cell surface molecules which mediate interactions of the endothelium with other cell types in the immune system. The concentrations of DFO required for 50% reduction in the number of endothelial cells expressing HCMV-late antigen ranged for several HCMV strains from 5.2 to 8.8 µM. DFO concentrations ranging from 5 to 40 µM inhibited cellular DNA synthesis in a dose dependent manner without any significant effects on cell viability. DFO at 10 µM concentration suppressed expression of intercellular adhesion molecule-1 (ICAM-1) and endothelial leucocyte adhesion molecule (ELAM-1) while it had no significant effect on the expression of vascular cell adhesion molecule (VCAM-1). Expression of HLA class I and class II was not influenced by DFO treatment. The results showed that DFO is both effective in inhibition of HCMV replication and expression of ICAM-1 and ELAM-1 in endothelial cells, a combination that warrants attention to its potential use to prevent HCMV-induced allograft complications in transplant recipients.