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Combined Antiviral Effect and Cytotoxicity of Ganciclovir and Azidothymidine Against Cytomegalovirus Infection in Cultured Cells.
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The nucleoside analogues, ganciclovir (DHPG) and azidothymidine (AZT) are currently licensed for treatment of patients with human cytomegalovirus (HCMV) or human immunodeficiency virus (HIV) infection, respectively. Although concomitant usage of these two drugs is not recommended, it is tempting since cessation of either drug results in recrudescence of each virus infection. In the present studies, using HCMV infection in human embryo lung (HEL) cells and guinea pig cytomegalovirus (GPCMV) infection in guinea pig embryo cells, the antiviral and cytotoxic effects of DHPG and AZT, alone and in combination at various concentrations and ratios were examined. Our results showed that AZT alone was not significantly effective against HCMV or GPCMV infection. In combination with DHPG (0.1 uM), AZT (0.25-1.0 uM) reduced the antiviral activity of DHPG against HCMV by more than 50% in HEL cells. Similarly, a combination of DHPG (10 uM) and AZT (10 uM) reduced the antiviral activity of DHPG against GPCMV by 50% in GPE cells. Although these concentrations of DHPG/AZT each alone or in combination were not toxic to either cell type, higher concentrations of each (100-200 uM) at 1:1 ratio were toxic in replicating cells as determined by cytotoxicity tests. Combination Indices (CI) were < 1 indicating synergistic cytotoxic effects for both cell lines. These results suggest antagonistic anti-CMV effects and synergistic cytotoxic effects in cultured cells when DHPG/AZT are used in combination.

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Ganciclovir Antagonizes the Anti-HIV-1 Activity of Zidovudine In Vitro.
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Patients with the acquired immunodeficiency syndrome may have active cytomegalovirus infection necessitating concomitant treatment with ganciclovir (9-(1,3-dihydroxy-2-propoxymethyl)guanine, DHPG) and zidovudine (3'-azido-3'deoxythymidine, AZT). The potential interactions of these two nucleoside analogues in combination have not been throughly defined, however. In the present study, we examined the effect of DHPG on the anti-HIV-1 activity of AZT in H9 cells. Target cells were infected with the HIV-IIIB strain at an MOI of 0.01 and cultured for 5 days in medium containing either AZT alone (.001 uM to 1 uM), DHPG alone (.01 to 10 uM), or AZT combined with DHPG at a fixed concentration ratio of 1:10. This ratio was chosen for study based on peak and trough serum concentrations of the two drugs achieved in humans with standard dosing regimens (Hochster, H. et al., 1990, Ann Intern Med. 113:111). Viral replication was assessed by determining HIV-1 p24 antigen levels in culture supernatants. The 50% inhibitory concentration (ED50) of AZT alone was 0.014 uM (mean of 3 experiments). When combined with DHPG at a concentration ratio of 1:10, the ED50 of AZT increased greater than 40-fold to 0.58 uM (mean of 3 experiments). DHPG alone had no anti-HIV-1 activity and was not cytotoxic at the concentrations tested. These data indicates that DHPG antagonizes the anti-HIV-1 activity of AZT in vitro. This finding raises the possibility that concomitant administration of DHPG can reduce the clinical efficacy of AZT in patients with HIV-1 infection. Further investigation of this possibility and the mechanism of antiviral antagonism is warranted.