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Ganciclovir Does Not Antagonize the Anti-Human Immunodeficiency Virus Activity of AZT in A3.01 Cells *in vitro*.

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Human cytomegalovirus (CMV) is a common opportunistic pathogen in patients with AIDS. Therapy with ganciclovir (GCV) impedes the progress of this sight-threatening infection while AZT is useful for treatment of the human immunodeficiency virus itself. Clinical indications often necessitate the prolonged concomitant use of both GCV and AZT. Previous studies by Medina et al. have reported an antagonism by GCV of the anti-HIV effect of AZT *in vitro*. Their studies were limited in scope by the use of fixed molar ratios of the compounds and by the statistical methods utilized for data analysis. We sought to further define the interactions of GCV and AZT against HIV-1 *in vitro* by examining a full spectrum of concentration effects of the two compounds, and by applying a more definitive 3-dimensional analytical method to analyze the results. The effects of AZT and GCV were studied, alone and in combination, in A3.01 cells infected with HIV-1(LAV). AZT was tested at concentrations between $6x10^{-11}$M and $1x10^{-6}$M, while GCV was varied from $5x10^{-6}$M to $3x10^{-5}$M. In all, eight concentrations of each compound were tested: each concentration of AZT was tested with all concentrations of GCV. Antiviral activity was determined by assaying for viral reverse transcriptase levels. When AZT and GCV were used in combination, GCV had no significant effect on the anti-HIV activity of AZT: at all combinations of concentrations there was no evidence for antagonism or synergy. We have further analyzed our results by methods similar to those utilized by Medina et al., and again find no evidence for synergy or antagonism in our data. We conclude that in our hands, utilizing *in vitro* studies, we find no evidence to contraindicate the combined use of AZT and GCV.

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Zidovudine (AZT)-induced Down Regulation of Transcripts of Erythropoietin Receptor (Epo-R), *c-fos* and ß-Protein Kinase C (PKC) in Human Erythroid Progenitor Cells (EPC): Reversal with a combination of Erythropoietin and Interleukin-3. K.C. Agrawal, S.R. Gogu, B.J. Rider and C.A. Leissinger. Depts. of Pharmacology and Medicine, Tulane University School of Medicine, New Orleans, LA. 70112, USA.

Previously we have reported that exposure of EPC to AZT results in a decrease in the levels of Epo-R mRNA and in inhibition of PKC activity in a time and concentration dependent manner. We have extended these studies to demonstrate that AZT induces inhibition of a series of multiple events necessary for erythroid differentiation which includes down regulation of the mRNA levels of Epo-R, *c-fos* and ß-PKC. Enriched erythroid cells ($2x10^6$ cells/ml), isolated from the human bone marrow were treated with AZT at 5 and 10 μM for 24 hr. The total RNA was isolated and the mRNA levels were monitored by the slot blot hybridization with the specific oligonucleotide probes end-labelled with α-^{32}P-dCTP. The levels of mRNA of Epo-R, *c-fos* and ß-PKC were decreased to 36, 51 and 50 percent of control, respectively, at 10 μM AZT. In contrast, the levels of mRNA of *c-myc* and α-PKC remained unchanged. Simultaneous addition of a combination of rEpo (1.0 U/ml) and *r*IL-3 (100 U/ml) during exposure of EPC to AZT overcame the inhibitory effect of AZT on the levels of the mRNAs, whereas Epo or IL-3 as a single agent caused only partial protection. These results suggest that AZT induces a series of multiple events at the level of transcription and that these effects can be overcome by treatment with a combination of Epo and IL-3.