65

Didox and an Analog Are Effective Against Retrovirus in a Murine Model (FeLV). D.L. Mills, H.L. Elford*, B. van't Riet*, and S.R. Webb, Biology Dept., Virginia Commonwealth U.,Richmond, VA and *Molecules for Health, 3313 Gloucester Rd., Richmond, VA 23227.

Didox (N,3,4-trihydroxybenzamide), a ribonucleotide reductase inhibitor, currently in clinical trials based on its anticancer activity in animal tumor models, was tested in a retrovirus murine model to determine the requirement for deoxynucleotide synthesis for retrovirus replication and to investigate the potential of Didox to enhance the effectiveness of deoxynucleoside analogs in combination protocols for retrovirus induced diseases like AIDS. Mice infected with the Friend Leukemia Virus (FLV) complex were treated with Didox for 12 days starting one day after virus infection. The mice were sacrificed on day 14 and the degree of splenomegaly was measured to indicate the amount of FLV replication. In addition, the blood cell profile was examined as a second indicator of the disease state. FLV infection caused an 8-fold increase in spleen wt. and a 4-fold increase in reticulocytes. Both increases were completely prevented by the optimum dose of Didox. Although the daily x 12 treatment with Didox prevented splenomegaly, the mice were not cured, since a group of Didox treated mice allowed to live 28 days exhibited spleen wt. above uninfected mice. A more potent analog Amidox (N,3,4-trihydroxybenzimidamide) significantly inhibited the FLV induced splenomegaly on day 14 with the 12 daily treatment regimen with a lesser effect on the blood cell components than Didox. These results indicate a potential for Didox in retroviral caused disease.

66

Antiviral Phosphate Prodrugs. A.Glazier,Drug Innovation and Design Inc.,Newton,Mass.; C.Kwong, J.Rose, R.Buckheit, Southern Research Institute; Birmingham,Alabama; B.Korba; Georgetown Univ. Rockville,MD.; M.Abou-Donia, Duke Univ. Medical Center, Durham, North Carolina; E.Smith, G.E.Wright; Univ. Mass. Medical School, Worcester, Mass.

We have developed a pharmacologically viable class of neutrally charged lipophilic phospho-ester prodrugs. In order to avoid both anticholinesterase activity and alkylating activity the prodrugs were designed to undergo transformation to the parent phosphorus drug by an elimination reaction. A prototype of this prodrug class was prepared by the reaction of ethyl 3-hydroxy-3-(4-acetoxy-phenyl)propanoate with methylphosphonic dichloride to yield the corresponding bis ester. This bis ester was stable in D_2O buffer. Treatment with pig liver esterase cleaved the 4-acetoxy groups and triggered an elimination reaction which led to the rapid liberation of methylphosphonic acid and ethyl p-hydroxy-cinnamate. A prodrug for AZT-5'phosphate was synthesized by the reaction of diethyl-phosphoramidous dichloride with 2 equivalents of ethyl 3-hydroxy-3-(4-acetoxy-phenyl)propanoate. Treatment with AZT and 1-H-tetrazole followed by oxidation with m-chloroperbenzoic acid yielded the AZT phosphotriester prodrug. This prodrug was on a molar basis equipotent to AZT (IC_{50} = 5 nanomolar) when pre-incubated with CEM cells for 8 hours prior to HIV infection. The AZT prodrug at 33 micromolar inhibited hepatitis B virus replication in tissue culture about 95 %. AZT at 100 micromolar was essentially inactive against hepatitis B. The AZT prodrug did not inhibit hen or eel acetylcholinesterase. No acute neurotoxicity was noted in mice given 300 mg/kg of the AZT prodrug IP.