202

Protection of Zidovudine (AZT)-Induced Fetal Toxicity in Mice by Interleukin-3 (IL-3). S.R. Gogu, B.S. Beckman and K.C. Agrawal. Dept. of Pharmacology, Tulane Univ. Sch. of Med., New Orleans, LA. 70112, USA

Since AZT is in clinical trials for treatment of pregnant woman with AIDS, we have investigated the toxic effects of AZT on the fetus in pregnant mice (CD-1) by parameters such as fetal size and number, and fetal hepatic cell (FHC) survival. AZT-induced toxicity on hematocrit and on bone marrow cells (BMC) was also determined simultaneously. In this study, IL-3 was employed to ameliorate the inhibitory effects of AZT on the fetus since it has been shown to stimulate the growth of BMC. AZT treatment (0.5 mg/ml in drinking water) was initiated on day one of gestation in mice. A second group of animals received AZT in combination with IL-3 (100 U/day/mouse/S.C.). After 13 days of treatment, the animals were sacrificed. AZT caused 20% fetal abortions and a 35% decrease in the size of survived fetuses. In addition, the number of FHC CFU-E, BM CFU-E, BFU-E, and CFU-GM showed a significant decrease to 33, 51, 76, and 75% of control. The AZT toxicity was overcome by simultaneous administration of IL-3 as demonstrated by lack of fetal abortions, significant increase in fetal size to 97% of control and an increase in FHC CFU-E, BM CFU-E, BFU-E, and CFU-GM to 67, 100, 100 and 89% of control, respectively. The hematocrit in AZT treated pregnant mice dropped from 40.6 ± 0.6 to 36.9 ± 1.4 and in group treated with IL-3 combination to 37.8 ± 3.1. These results suggest that IL-3 can overcome the fetal toxicity induced by AZT and thus may be useful in the clinical management of pregnant women with AIDS.

203

In vitro Pharmacodynamic Modeling of Anti-retroviral Agents and Interferon. J. A. Bilello[1,2], M.N. Dudley[3] and G.L. Drusano[1]. Division of Infectious Diseases, Dept. of Medicine[1] and Dept. of Microbiology and Immunology[2], University of Maryland School of Medicine. Baltimore, MD and University of Rhode Island[3], Kingston, RI USA.

Understanding the pharmacokinetics and dynamics of therapeutic agents alone and in combination is key to having effective antiviral concentrations at the sites of infection. We have used an *in vitro* system to expose uninfected, *de novo* infected and chronically infected cells to antiviral agents and interferons. Drug dosing inputs were adjusted to simulate continuous infusion, or an intravenous bolus. The relative toxicity of each dosing regimen was established by measuring the protein synthesis, growth and viability of a human T cell line 8E5 in the presence and absence of drug. HIV replication and the synthesis and release of viral proteins were determined by western blotting or measuring p24 released into the tissue culture media. In an experiment with human recombinant beta-interferon (IFN) release of HIV-1 p24 from chronically infected HIV-1 producing, 8E5 cells was similar when 1000 Units/ml of IFN was administered either continuously or as a bolus delivered every 24 hours. Mechanistically this result appeared to be due to the slow "wash-out" kinetics of interferon. After removal of IFN from cells treated for 72 hours, there was a lag of nearly 20 hours until the rate of p24 release from the treated cells paralleled that of untreated cells.