Poster Session III

Animal Models, Pharmacology, Toxicity, Clinical Studies

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Efficacy of short term continuous Zidovudine infusion at early stages of retroviral infection in mice.

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We studied the pharmacokinetics of zidovudine (AZT) in mice after twice-daily subcutaneous (sc) bolus injections and during continuous infusion with subcutaneous ALZET mini-osmotic pumps. We also compared the antiretroviral efficacy of these two modes of administration against Friend leukemia virus (FLV) infection. Mice were infected by retro-orbital inoculation of about 50 ffu FLV and treatment was started 1 or 4 h later with AZT at 40 mg/kg/day for 5 days. Efficacy was evaluated in terms of spleen weight gain and infectious virus titer 3 weeks after virus inoculation in comparison with untreated infected mice. In one experiment, survival time after infection was also evaluated. Plasma concentrations of AZT were determined by means of high-performance liquid chromatography. Following bolus administration, the peak plasma AZT concentration (30.5 µg/ml) was reached within 10 min and elimination was rapid (mean half-life, 0.7h). During the continuous infusion, the mean concentration was constant at about 1.2 µg/ml. A significant reduction in splenomegaly and infectious virus titer was observed after 5 days of AZT therapy, regardless of the mode of administration. Continuous AZT infusion consistantly inhibited virus-induced splenomegaly by more than 97%; bolus injection was less effective with inhibition ranging between 13 and 98%. These results suggest that moderate constant levels of AZT may have greater antiretroviral efficacy than short periodic high concentrations.