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Dose-Escalating Study of Safety And Efficacy of Dideoxy-didehydrothymidine (d4T) For HIV Infection. L. Dunkle, A. Cross, R. Gugliotti, R. Martin, M. Browne, H. Murray. Bristol-Myers Squibb, Wallingford, CT; University of Rhode Island, Providence, RI; Cornell Medical Center, New York, NY, and NIAID, USA.

In a dose-escalating study using 3 or 4 daily doses, d4T was administered to 33 HIV infected patients, with and without prior Rx with AZT, with $\leq$ 400 CD4 cells in doses of 2, 4, 8 and 12 mg/kg/day. 4 patients had AIDS and 29 had ARC with CD4 counts $\leq$ 100 in 10 and > 100 in 23. 5 patients entered at each dose level on each schedule. Dose-limiting toxicities of peripheral neuropathy and hepatotoxicity were reached at 4 mg/kg/day (qid) and 8 mg/kg/day 1 (tid). Anemia was encountered at 8 and 12 mg/kg/day. At 2 mg/kg/day 1 (tid) or (qid) and 4 mg/kg/day 1 (tid), 14 patients have tolerated d4T for x 28 wks (8.5 - 48 wks). Nausea, diarrhea, insomnia and dizziness were reported occasionally. Efficacy data from 33 subjects analyzed after 6 months (median F/U 12.3 wks) showed responses at all doses. Antiviral activity, determined by sustained fall in p24 was demonstrated in 10/11 p24+ patients, and sustained rises in CD4 counts of $\geq$ 50 cells over baseline occurred in 11/31 patients. Clinical improvement was defined by sustained weight gain of $\geq$ 2.5 kg in 12/33 patients and improved symptom scores in 20/30 patients. Combined, response of biological markers was seen in 17/31 patients and clinical response in 24/33 patients. Response of the 4 variables at non-toxic dose levels (2 mg/kg/day and 4 mg/kg/day 1 (tid) occurred 7/7, 7/9, 5/9 and 9/13 patients respectively. Combined biological or clinical improvement was detected in 10/13 and 9/13 patients respectively at these doses. In summary, d4T in doses of 2 mg/kg/day or 4 mg/kg/day 1 (tid), is safe for prolonged dosing and demonstrates evidence suggesting antiviral activity as promising clinical efficacy. This drug warrants further evaluation for treatment of patients with varying stages of HIV infection.

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Continuous Intravenous Dextran Sulfate in Patients with ARC and AIDS. C. Flexner, P. Barditch-Crovo, D. M. Kornhauser, L. Nerhood, B. G. Petty, and P. S. Lietman, Division of Clinical Pharmacology, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

Dextran sulfate is a polysulfated polysaccharide which inhibits HIV infectivity and syncytium formation in vitro. Oral dextran sulfate has been used in HIV-infected subjects, but is very poorly absorbed. We have designed a study to assess the safety, pharmacokinetics, and efficacy of parenteral dextran sulfate by administering the maximum safe dose of drug in a short period of time, with serum p24 antigen levels serving as a surrogate marker of anti-HIV activity. Since this drug is an anticoagulant, dosing is limited by the degree of anticoagulation achieved. In this open-label study, patients received a continuous infusion of dextran sulfate (avg. M.W. 7500) adjusted to maintain an activated partial thromboplastin time (APTT) of 65 to 80 seconds for 14 days. All subjects receiving drug for greater than four days developed significant thrombocytopenia which was readily reversible when the drug was discontinued. No other serious adverse reactions were observed. The infusion rate required to maintain a constant APTT fell with time in all patients, from a mean of 24 mg/hr (range 16 - 41 mg/hr) after 24 hours to 8 mg/hr on day 10. Plasma levels of dextran sulfate did not fall significantly once steady state was achieved, suggesting that total clearance of the drug may diminish over time as has been implied for intravenous heparin. The mean plasma level of drug for five subjects during the infusion was 7.6 mcg/ml (range 4.2 - 13.5 mcg/ml); the in vitro ED_{50} of the drug ranges from 0.1 - 10.0 mcg/ml. This study demonstrates pharmacokinetic and pharmacodynamic principles which should be applicable to other polysulfated polysaccharides.