193

Pharmacokinetics and Metabolic Disposition of (-)-5-Fluoro-3'-thia-2',3'-dideoxycytidine in Mice, Rats, and Monkeys. L. W. Frick, L. St. John, L. C. E. Taylor, and D. J. Nelson. Wellcome Research Laboratories, Burroughs Wellcome Co., Research Triangle Park, NC, 27709, USA.

(-)-3'-Thia-2',3'-dideoxy-5-fluorocytidine (FTC) is an analog of the unnatural 'L' isomer of 2',3'-dideoxycytidine. FTC has potent anti-HIV and anti-hepatitis B virus (HBV) activities, and is currently undergoing active preclinical evaluation as a therapy for AIDS and HBV infection. The pharmacokinetics and metabolic disposition of FTC were studied in CD-1 mice, CD rats and cynomolgus monkeys. In monkeys given a 10 mg/kg IV dose of [6-^{3}H] FTC, the total body clearance rate (CL_T) was 0.7 l/kg/hr, and the volume of distribution at steady state (V_{ss}) was 0.8 l/kg. The ß elimination phase half-life of the plasma clearance ($t_{1/2}ß$) was 43 min. These data indicate that FTC permeates tissues well but is rapidly cleared in the monkey. Oral bioavailability of a 10 mg/kg dose was 39 % in fasted monkeys. The plasma C_{max} was 9 µM and the T_{max} was 95 min. Average recovery of radioactivity after PO and IV doses in fasted animals was 45 and 39 %, respectively. Unchanged FTC was 61 % of the recovered radioactivity after the IV dose. A ß-glucuronide of FTC (2 % of dose), 5-fluorocytosine (0.3 % of dose), and two sulfoxides of FTC (33 and 6 % of dose), were also observed in the urine. There was apparently no first-pass metabolism in the liver. In mice given a 10 mg/kg dose of [6-^{3}H] FTC, the (CL_T) was 2.3 l/kg/hr, the V_{ss} was 0.9 l/kg, and the $t_{1/2}ß$ was 23 min. Recovery of radiolabel in the urine of mice was 100 % of the IV dose and 84 % of the PO dose. After the IV dose, 94% of the dose was recovered as unchanged FTC; only traces of the sulfoxides, 5-fluoro cytosine and a ß-glucuronide of FTC were observed in the urine. In rats given 10 mg/kg [6-^{3}H] FTC, CL_T was 1.8 l/kg/hr, the V_{ss} was 1.5 l/kg, and the $t_{1/2}ß$ was 44 min. Oral bioavailability was 90 %, with C_{max} of 11 µM, and T_{max} at 43 min. At 100 mg/kg FTC, the CL_T was lowered to 1.5 l/kg/hr and oral bioavailability to 65 %. The metabolic disposition of FTC in the rat was similar to that in the mouse. Penetration of the blood-brain barrier of rats by FTC was poor, with brain concentration less than 5 % of plasma concentration 30 min post-dose. The CL_T rates of FTC in rats and mice are close to the estimated renal plasma flows in these species, suggesting that FTC is actively secreted by the kidney in rodents. The good oral availability and minimal metabolism of FTC encourage its further evaluation.

194

Antiviral Effect of DNA Gyrase Inhibitors on the Replication of Duck Hepatitis B Virus in vivo. S Locarnini[1], S Bowden[1] and Y Wang[2]. [1]Virology Department and [2]Hepatitis Research Unit, Fairfield Hospital, Fairfield, Victoria 3078, Australia.

Hepatitis B virus (HBV) supercoiled DNA (SC DNA) is the main transcriptional template for hepadnaviral replication and the major replicative species resistant to antiviral therapy with agents such as interferon and nucleoside analogues. The aim of this study was to examine the effect of the supercoiled DNA active compound nalidixic acid (a prokaryotic DNA gyrase inhibitor) alone and in combination with the nucleoside analogue, ganciclovir, on the replication of duck HBV in vivo. Congenitally infected 5 week old ducklings were treated with nalidixic acid alone or in combination with ganciclovir for 4 weeks. Weekly serum samples were collected before, during and after treatment and were tested for DHBV DNA by dot-blot hybridization. Specimens of liver were obtained at the beginning and end of treatment and also 4 weeks later, and tested for DHBV-specific viral DNA by Southern hybridization. In ducks treated with nalidixic acid alone, serum DHBV DNA was found to disappear within one week of treatment and remained negative for the duration of therapy. Analysis of liver tissue revealed an 8-10 fold decrease in total viral DNA levels with a relative reduction in the SC DNA species. In ducks treated with the combination of nalidixic acid and ganciclovir, the amount of viral DNA was reduced 20-40 fold by the end of the 4 week combination treatment and Southern analysis revealed a significant decrease in the SC, relaxed circular and single-stranded DNA species. In conclusion, for the first time a group of compounds have been identified, the prokaryotic DNA gyrase inhibitors, which inhibit DHBV SC DNA generation and processing when used either alone or in combination with conventional antiviral agents such as ganciclovir.