117

Safe coadministration of Famciclovir and Zidovudine to HIV Positive Patients S. Siederer[1], S. Scott[2], F. Rousseau[3], S. Fowles[1], P. Sparrow[2], C. Lascoux[3], V. Lehner[3]and D. Serini[3] SmithKline Beecham Pharmaceuticals, Welwyn[1] and Harlow[2], UK and Hopital Cochin, Paris, France[3]

Famciclovir (FCV), the oral dose form of penciclovir (PCV), may be coadministered with zidovudine (AZT). The potential for an interaction was assessed because both PCV and AZT are eliminated by active tubular secretion. In a crossover study, 14 HIV + patients on stable AZT (400-1000 mg/day) received a single dose of 200 mg AZT with 500 mg FCV or placebo (single dose) 3-5 weeks apart. Plasma concentrations of PCV (following FCV+AZT; n=8) and AZT (after both doses; n=12) were determined (UV-HPLC) and submitted to model-independent pharmacokinetic analysis. AZT pharmacokinetic parameters were subjected to analysis of variance to determine point estimates and 95% CIs for the comparison AZT+FCV: AZT alone. AZT Tmax was analysed using the Wilcoxon matched pairs method. Clinical laboratory values and adverse events were recorded. Following AZT+FCV, mean (SD) Cmax for PCV was 4.57 (1.45) ug/mL and occurred at a median time of 0.75 [range 0.50-2.03] h. The mean (SD) PCV T1/2 was 1.55 (0.32) h, with a mean (SD) AUC(0-inf) of 8.12 (1.95) ug.h/mL. These PCV pharmacokinetic parameters were consistent with historical values in healthy volunteers. Mean (SD) Cmax for AZT were 1.24 (0.68) and 0.93 (0.44) ug/mL, reached at a median [range] time of 0.5 [0.25-1.25] and 0.88 [0.25-2.03] h following AZT and AZT+FCV, respectively. Mean (SD) T1/2 were 1.45 (0.59) h after AZT and 1.29 (0.57) h after AZT+FCV, the mean (SD) AUC(0-inf) were 1.10 (3.4) [AZT] and 1.06 (3.84) [AZT+FCV] ug.h/mL. On average, decreases in AZT Cmax and AUC(0-inf) following AZT+FCV were less than 20%. The median increase in Tmax was 24 mins, with the increase in T1/2 on average 6 mins following AZT+FCV. These changes in AZT pharmacokinetics are unlikely to be of clinical significance. Furthermore, single dose FCV with AZT was well tolerated. In conclusion, FCV can be safely coadministered with AZT to immunocompromised HIV positive patients.

118

Anti-HIV Agent 935U83 - Preliminary Clinical Assessment .

S.M. DALUGE, M.H. ST. CLAIR, L. WANG, P.M. SAVINA, W. SPREEN, J. YEO[1], B.A. LARDER[1], N. PARRY[1], D.J. M. PURIFOY[1], and T.A. KRENITSKY. Wellcome Research Laboratories, Research Triangle Park, NC 27709, USA and [1]Beckenham, Kent BR3 3B5, UK.

5-Chloro-2',3'-dideoxy-3'-fluorouridine (935U83) is a selective anti-HIV (human immunodeficiency virus) agent which is presently undergoing clinical evaluation. When tested in PHA-stimulated normal human peripheral blood lymphocytes against fresh clinical isolates of HIV-1 obtained from AZT (3'-azido-3'-deoxythymidine)-naive patients, 935U83 inhibited virus growth with an average IC_{50} of 1.8 μM; corresponding IC_{50}s were 0.23, 0.49, and 0.03 μM for the approved agents AZT, ddI, and ddC, respectively. Importantly, 935U83 retained activity against HIV strains that were resistant to AZT, ddI, or ddC. We were unable to generate virus which was resistant to 935U83 by passaging either HXB2 (AZT-sensitive) or RTMC (AZT-resistant) strains in the presence of high concentrations of 935U83. The safety profile of 935U83 in animals (monkeys and mice) is much-improved over that of any of the anti-HIV drugs approved to date. In HIV-infected patients, no adverse events or abnormal laboratory values were observed after single doses of 100 to 1500 mg 935U83. A single dose of 300 mg of 935U83 resulted in plasma levels which were above the IC_{50} for approximately 5 hours and systemic exposure (AUC) was about 5- to 6-fold higher than that observed for an equal dose of AZT. Peak plasma concentrations and AUC values were nearly dose-proportional for doses of 935U83 from 100 to 1500 mg. Multiple dose studies of 100 to 500 mg 935U83 three times daily for up to 12 weeks or longer, with or without ddI, in 80 HIV-positive patients are nearing completion. 935U83 has been very well-tolerated at all dose levels. Clinical safety, pharmacokinetics, virology, and immunology data will be presented.