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Comparison of the Viral Pharmacodynamics of 3TC in Chronically Infected Woodchucks and Humans. Hurwitz, S.J.,[1] Tennant, B., Korba, B.E.,[3] and Schinazi, R.F.[1*] Lab. Biochem. Pharmacol., Dept. Pediatrics, Emory Univ. Sch. Med. and VAMC, Atlanta, GA;[1] Dept. of Cli. Sciences, College of Vet. Med., Cornell Univ., Ithaca, NY;[2] and Georgetown Univ, Washington DC.[3]

A pharmacodynamic study was performed in woodchucks that were chronically infected with woodchuck hepatitis virus and treated with 3TC at 1 mg/kg twice daily (n = 4), 5 mg/kg/day (n = 30), and 15 mg/kg/day (n = 6) over a 12 wks period. The decline in fraction plasma virus during treatment (dF/dt) was modeled as the sum of an exponentially declining virus input and a first order elimination. The data were fit to the integrated form of the equation: $F = K/(D - K)*(e^{-K*t} - e^{-D*t}) + e^{-Kt}$ using nonlinear regression, were K = virus decline rate in plasma (wk^{-1}), D = decline rate for the net virus input into plasma (wk^{-1}), and t = time. Fits to averaged data from each dose group is shown in the table below.

Dose	K	D	r^2	$t_{1/2}$ D	$t_{1/2}$ K	# of obs.
1 mg/kg,bid	0.42	0.41	0.97	11.6	11.8	9
5 mg /kg/day	6.87	0.32	0.92	0.7	15.2	5
15 mg /kg/day	3.0	5.0	> 0.99	1.6	0.97	3

($t_{1/2}$ values in days: $t_{1/2}D = 0.693/D \times 7$ and $t_{1/2}K = 0.693/K \times 7$)

Plasma virus rebounded to pretreatment levels when 3TC was discontinued. Remodeling of HBV loads in humans [PNAS, 93, 4398, 1996], suggested a multiphasic decline, without noticeable shoulders. A biexponential fit to these data produced an r^2 value = 0.95, with an initial $t_{1/2}$ = 1 day, comparable to virus decline in woodchucks treated with the highest 3TC dose. The latter phase accounted for 22 % of the area under the curve and had a $t_{1/2}$ = 7 days, comparable to the virus decline in woodchucks treated with the lowest dose. This analysis provides insight for comparing the viral pharmacodynamics of 3TC in woodchucks and humans, and has immediate relevance for the management of hepatitis infections.

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Antiviral Activity of Famciclovir Therapy on HBV Replication in Patients with Chronic Hepatitis B. F. Zoulim, Z. Wang, C. Pichoud, C. Trépo. Liver Unit and INSERM U271, Lyon, France.

Prolonged administration of nucleoside analogs for therapy of chronic hepatitis B may result in the emergence of HBV mutants resistant to antivirals. Here, we have analyzed HBV genome variability during famciclovir therapy in relation to antiviral response. The study group consisted of 21 patients with liver biopsy proven chronic hepatitis B (HBeAg +) who had been included in a placebo controlled clinical trial. Duration of antiviral therapy was 16 weeks and the dosage of famciclovir was : 500 mg (7 patients), 250 mg (3 patients), 125 mg (5 patients) or placebo (6 patients) thrice daily. Antiviral response was assessed by determination of HBV DNA levels in serum. Structural analysis of HBV genomes was performed blindly by the determination of HBV genotypes, the detection of pre-core mutants, sequence analysis of the HBV POL gene, and full length genome amplification by PCR. The results showed no correlation between antiviral response and viral genotypes. No case of emergence of pre-core mutants was observed. Full length genome analysis after PCR amplification showed genomes with deletions prior to therapy in 5 cases and the emergence of such defective genomes during therapy in 2 cases. 6 of these 7 patients showed a spontaneous or drug induced decrease in viral DNA titers. These deletions were mapped to splice sites on viral pregenomic RNA. HBV POL gene sequence analysis of 2 conserved domains including the YMDD motif did not show any nucleotide change during therapy, in 10 patients. Our results indicate that : 1) antiviral response to a 16 week famciclovir therapy was independent of HBV genotypes, 2) no HBV pre-core or polymerase mutants were selected during a 16 week famciclovir therapy, 3) the role of defective viral genomes in the antiviral response warrants further studies.