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Penciclovir: A Novel Nucleoside Analogue with Potent Activity against Duck Hepatitis B Virus in vivo. S Locarnini, E Lin, C Luscombe, P Edwards, D Anderson, T Shaw. Victorian Infectious Diseases Reference Laboratory and Macfarlane Burnet Centre for Medical Research, Fairfield Hospital, Fairfield, Victoria 3078, Australia.

The antiviral activity of penciclovir (9-[4-hydroxy-3-hydroxy methylbut-1-yl] guanine) and its oral form famciclovir has been established for the duck and human hepatitis B viruses (HBV). The aim of this study was to examine in more detail the antiviral effects of penciclovir on the intrahepatic expression of duck HBV replication markers in vivo. Congenitally infected ducks, positive for DHBV, were treated with a range of doses of penciclovir via the intra-peritoneal (IP) route. The maximum antiviral effect in liver and serum was achieved using a dosage of penciclovir of 5mg/kg twice daily (bd). Pharmacokinetic studies demonstrated that this antiviral effect of penciclovir was achieved at doses which can be readily generated in man by oral famciclovir. Four weeks of penciclovir therapy at 5mg/kg bd IP, resulted in a greater than 90% reduction in the level of intrahepatic viral DNA. Southern blot analysis revealed significant effects on all replicative intermediates including the viral supercoiled DNA form. Quantitative immunoblot studies revealed that treatment resulted in a 50% reduction in the expression of intrahepatic viral proteins, including the Pre-S1 and core antigen levels. This level of inhibition was confirmed by immunohistochemistry. There was no systemic or hepatic toxicity associated with the four weeks of penciclovir treatment. These studies confirm that penciclovir is an effective anti-hepadnaviral agent in vivo and further clinical studies are warranted.

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Inhibition of HPV-11 Gene Expression with Chimeric Methylphosphonate Oligomers

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Certain human papillomaviruses [HPV] are found in oral and genital mucosa lesions where they cause warts, dysplasias and carcinomas. HPV types 11 and 6b are usually associated with benign genital warts (condylomata acuminata) and with proliferative lesions of the oral mucosa. Two early HPV proteins, E6 and E7 are thought to play a role in establishing the cellular environment required for vegetative viral replication and wart formation. In high risk HPVs these proteins have oncogenic properties. To explore antisense technology as a treatment for genital warts, an RNA secondary structure analysis in combination with biological assays was utilized to identify sequences for antisense targeting within the polycistronic E6/E7 mRNA of HPV-11. A pseudoknot structure present just upstream from the translation initiation site of E7 was identified. Oligonucleotides with different backbones complementary to HPV-11 E7 sequences dowstream from the pseudoknot exhibited potent antisense inhibition of HPV-11 E7 and E6 protein production in cell-free reactions. Moreover, potent inhibition of transient expression of HPV-11 E7 in COS-7 cells was achieved with novel chimeric methylphosphonate [MP] derivatives that make use of Rp-stereoisomer MP dimers. HPV-11 E7 protein levels as well as mRNA levels were reduced by treatment of the cells with these oligomers, identifying them as strong candidates for the treatment of genital warts.