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Inhibition of Duck Hepatitis B Virus Replication by Ganciclovir and Supercoiled DNA Active Compounds. Tim Shaw, Yanyan Wang, Scott Bowden, Gilda Civitico and Stephen Locarnini. Hepatitis Research Unit, Macfarlane Burnet Centre for Medical Research, Fairfield Hospital, Fairfield, Victoria 3078, Australia.

Hepatitis B virus (HBV) supercoiled DNA (SC DNA) is both the main transcriptional template for hepadnaviral replication and the replicative species most resistant to therapy with conventional antiviral agents such as interferon and nucleoside analogues. In this study we investigated the effects of the prokaryotic DNA gyrase inhibitors nalidixic acid and coumermycin A1 on replication of duck HBV DNA in vivo. Congenitally infected 5 week old ducklings were treated for 4 weeks with nalidixic acid or coumermycin A1 in combination with ganciclovir. Sera obtained at weekly intervals before, during and after treatment were tested for DHBV DNA by dot-blot hybridization. Liver specimens for analysis by Southern hybridization were obtained at the beginning and end of treatment and also four weeks later. Within the first week of treatment serum DHBV DNA decreased to levels which were undetectable by conventional dot-blot hybridization and remained so for the duration of therapy. Analysis of liver tissue revealed a 20-40 fold decrease in total viral DNA levels compared to placebo-treated ducks, with significant and reproducible decreases in viral SC DNA. These results demonstrate that the prokaryotic DNA gyrase inhibitors, nalidixic acid and coumermycin can inhibit SC DNA generation and processing and in combination with conventional antiviral agents such as ganciclovir, can reduce the generation and stability of all the recognised DNA replicative intermediates of DHBV.

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Inhibition of Ebola Virus replication *in vitro* and in a SCID Mouse Model by S-Adenosylhomocysteine Hydrolase Inhibitors

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Primary human outbreaks of the filoviruses Ebola and Marburg cause the most severe viral hemorrhagic fever known, with mortality of 40-90% in sporadic outbreaks. Recent viral hemorrhagic fever outbreaks among imported macaques in the U.S. lead to the discovery of a new filovirus, Reston virus, that is pathogenic for macaques but apparently less pathogenic for man. Reston or related viruses appear to have a wide geographic distribution in macaques. Safe handling of Ebola and Marburg requires maximum biological containment (BL-4) facilities. *In vitro* antiviral activity in permissive Vero E-6 or FRL-103 cells was assayed by a reduction, on formalin-fixed cell monolayers, of viral antigen detected by monoclonal ELISA. Inhibitors of S-adenosylhomocysteine hydrolase, which mimic a transition state intermediate, inhibited Ebola virus replication, generally as predicted by their inhibition constants. Of multiple murine strains evaluated for a potential model, only the immune-deficient SCID mouse produced a lethal infection. Infection with 100 LD_{50}'s of Ebola virus (Mayinga strain) produced a uniformly lethal infection with a mean time to death of 27 days, but no hemorrhagic disease. Initial prophylactic studies with carbocyclic 3-deazaadenosine and 3-deazaneplanocin A, potent inhibitors of Ebola *in vitro*, resulted in increased mean time to death and a delay in virus replication both in circulation and in major organs (heart, lung, liver, spleen, kidney, brain).