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Effects of 7-Thia-8-Oxoguanosine Alone and in Combination with Ribavirin on Punta Toro Virus Infections in Mice. D.F. Smee, J.H. Huffman, J. Coombs, J.W. Huggins*, and R.W. Sidwell. Antiviral Program, Utah State University, Logan, Utah, and *U.S. Army Medical Research Institute of Infectious Diseases, Ft. Detrick, Maryland, U.S.A.

7-Thia-8-oxoguanosine (7-TOGuo) was evaluated in a murine model of Phlebovirus (Bunyaviridae) infection using the hepatotropic Adames strain of Punta Toro virus. When administered i.p. in divided doses at different starting times, 7-TOGuo conferred significant protection from death at 50-100 mg/kg/day (given -24 and -17 h relative to virus challenge), 25-100 mg/kg (given -4 h and +3 h), 12.5-100 mg/kg (given +24 and +31 h), and 100 mg/kg (given +36 and +43 h). Doses that prevented death also reduced liver icterus scores, serum glutamic oxalate transaminase and serum glutamic pyruvate transaminase levels, and liver and serum virus titers significantly. Combination studies were performed using 7-TOGuo and ribavirin (Rbv), by administering 7-TOGuo i.p. at +24 and +31 h, and Rbv p.o. twice a day for 3 days starting at +24 h. Under these conditions, Rbv alone protected most animals from mortality at 25 mg/kg/day, as did 7-TOGuo at 12.5 and 25 mg/kg. All combinations having either Rbv (25 mg/kg) or 7-TOGuo (12.5 and 25 mg/kg) were also highly protective against lethal infection. These doses also inhibited other infection parameters such as liver and serum virus titers. Each compound by itself was ineffective at 6.25 mg/kg. An improvement of survival from 0% (Rbv alone at 12.5 mg/kg) to 50% (Rbv, 12.5 mg/kg plus 7-TOGuo, 6.25 mg/kg) was achieved with the combination, but no increased benefit was evident using Rbv (6.25 mg/kg) plus 7-TOGuo (6.25 mg/kg). Of particular interest was the observation that 7-TOGuo reversed the toxicity in uninfected and infected mice treated with a high p.o. dose (1250 mg/kg/day) of Rbv. These data suggest that 7-TOGuo may be useful to increase the therapeutic index of Rbv by reducing toxicity and by enhancing antiviral activity. This work was supported by U.S. Army Contract No. DAMD 17-86-C-6028.

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Comparison of Ribavirin Analogues in Hantaan-Infected SCID Mice

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Evaluation of antiviral compounds against hemorrhagic fever with renal syndrome has been hampered by a lack of adequate animal models. Efforts to mimic the clinical syndrome have been unsuccessful, both in rodents and primates. Infection of adult mice does not produce clinical illness with prototype Hantaan. Hantaan-infected suckling mice are currently used for drug testing, but the model has several limitations. The immune-deficient SCID mouse provides a potential model for evaluation of inhibition of viral replication by an antiviral compound in an adult animal. Hantaan infection of adult SCID mice produces a uniformly lethal infection in animals 4 to 12 weeks old. After infection, virus can be recovered from all major organs by day 6 post infection and reaches peak titer by day 14 to 21. Animals die with a mean time to death of 33 days. Infection with 100 PFU (approximately 100 LD_{50}) resulted in a model where ribavirin therapy at optimum dose resulted in a delay in viral replication but no protection. Infection with 10 PFU (approximately 10 LD_{50}) produced a model where ribavirin treatment begun 2 hours post infection resulted in 90% survival. Ribavirin and ribamidine (AVS-000206), the carboxamidine of ribavirin, both demonstrate significant activity against several members of the Bunyaviridae, and provided equivalent protection at 50 and 75 mg/kg/day, respectively, in this model. The Hantaan- infected SCID mouse model allows evaluation of drug inhibition of viral replication and is useful in the optimization of drug dose, route and schedule.