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Efficacy of 2-Amino-7-[1,3-dihydroxy-2-propoxy)methyl]purine for the Treatment of Vaccinia (Orthopox-) Virus Infections in Mice

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We have previously shown that the N-7 substituted acyclic nucleoside analog 2-amino-7-[1,3-dihydroxy-2-propoxy)methyl]purine (compound S2242) is, both in in vitro and in animal models, a potent inhibitor of the replication of several herpesviruses (Neyts *et al.*, Antimicrob. Agents Chemother. 38:2710-2716; Neyts *et al.*, Antimicrob. Agents Chemother. 39: 56-60). Compound S2242 was shown to inhibit the replication of vaccinia virus (EC_{50}: 0.4 μg/ml) in cell culture. Next the efficacy of S2242 was studied in vaccinia virus-infected mice. Immunocompetent NMRI mice that had been inoculated intraveneously with 10^3 PFU vaccinia virus (VV) developed tail lesions. Animals that had been treated once daily for 5 consecutive days, starting at 2 hr post infection via intraperitoneal (ip) route with 100 mg/kg of the diacetate ester prodrug of S2242 (compound H961) did not develop any lesions and demonstrated no signs of adverse effects. When treated with 10 mg/kg of compound H961, the number of lesions was reduced by 69 % as compared to the untreated control. Next, severe combined immune deficient (SCID) mice were inoculated intraperitoneally with 10^3 PFU of VV. Untreated animals became sick and died 28 ± 5 days post infection. VV-chalenged SCID mice were by treatment with H961 at 100 mg/kg for 10 consecutive days (either via oral gavage or ip injection) completely protected, for at least 6 months, against virus-induced morbidity and mortality. Compound S2242 and its oral prodrug H961 could thus be considered as possible drug candidates for the treatment of poxvirus infections.