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Phosphonylmethoxyalkylpurines and -Pyrimidines in the Treatment of HSV Keratitis

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Phosphonylmethoxyalkyl derivatives represent a class of new broad-spectrum antiviral agents that are active against herpes simplex virus (HSV), varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, adenoviruses, iridoviruses, poxviruses and hepadnaviruses. We have previously reported the efficacy of (*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA) in the treatment of TK^+ and TK^- HSV-1 experimental keratitis. We have now evaluated two other congeners, 9-(2-phosphonylmethoxyethyl)adenine (PMEA) and (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC), for their anti-herpes activity in the rabbit keratitis model. Both compounds induced a rapid healing of epithelial disease caused by TK^+ McIntyre strain of HSV type 1, as compared with placebo treatment ($p < 0.005$). The healing effect of these two drugs was similar to that of bromovinyldeoxyuridine (BVDU), which was used as a reference compound. PMEA was also evaluated in the TK^- HSV-1 keratitis model. Unlike BVDU, PMEA induced significant healing of TK^- HSV-1 keratitis, as compared with placebo treatment ($p < 0.05$).

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Activity of Cyclobutyl Adenine and Cyclobutyl Guanine in Experimental Models of Infection with Herpes Simplex Type 1 and Type 2 Virus.

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Two new carbocyclic analogues of adenine (cyclobutyl adenine, CBA) and guanine (cyclobutyl guanine, CBG) were evaluated *in vitro* and *in vivo* against HSV-1 and HSV-2 and were compared to both acyclovir (ACV) or Ara-A. The *in vitro* IC_{50} values of CBA, CBG, ACV and Ara-A against HSV-1 in Vero cells were 16.5, 0.46, 1.08 and 12.5 μg/ml as determined by a vital dye microtiter assay. The IC_{50} values of these same agents against HSV-2 were 21.2, 1.0, 1.0 and 7.8 μg/ml. In a murine model of systemic HSV-1 infection at a 10 LD_{50} virus exposure, ED_{50} values for 30 day survival for CBA, CBA and ACV were <4.7, 1.9 and 190 mg/kg/day for intraperitoneal dosing. In a similar model of systemic HSV-2 infection, the ED_{50} values for CBA, CBG and Ara-A were 4.1, 1.6 and 15.3 mg/kg/day. CBG was orally active in the systemic models of HSV-1 and HSV-2 infections, having ED_{50} values of 33.3 and 35.8 mg/kg/inj, respectively. CBA and CBG were active in an HSV-2 encephalitis model in which mice were inoculated intracranially with a 100 LD_{50} dose of virus followed by ip administration of agent. CBA and CBG had ED_{50} values of 9.7 and 39.8 mg/kg/inj while Ara-A had no effect at doses below 125 mg/kg/inj. CBG was further tested as an oral agent against HSV-1 dermatitis in mice and HSV-2 genital herpes in guinea pigs and as a topical agent against HSV-1 rabbit ocular keratitis, mouse cutaneous HSV-1 infection and guinea pig HSV-2 genital infection. CBG was active in each of these models when applied orally or topically and was superior or equal in efficacy to ACV or Ara-A.