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Evaluation of Retinal Toxicity of the anti-CMV compound 2-Amino-7-[(1,3-dihydroxy-2-propoxy) methyl] purine

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This is the first known antivirally active nucleoside analogue with the side chain substituted at the N7-position of the purine ring system. *In vitro*, this compound is active against HSV-1 and HSV-2 at concentrations comparable to those of ganciclovir (GCV) or acyclovir (ACV). It has a stronger effect than GCV against murine cytomegalovirus (MCMV), human cytomegalovirus (HCMV) and varicella-zoster virus (VZV). Its IC 50 for HSV is 14 µM and for HCMV is 0.05 µM. *In vivo*, the efficacy of intravenous treatment of MCMV infected mice is in the same range as with ganciclovir, while oral treatment is more effective than with ganciclovir. Intravitreal injection of this compound may be useful as a local treatment for HCMV retinitis. In addition, oral administration of a well absorbed pro-drug (2-Amino-7-[(1,3-bis-acetoxy-2-propoxy) methyl] purine) makes this compound especially interesting. In order to evaluate and quantitate retinal toxicity, five different concentrations of the drug, ranging from 0.5 to 2000 µM, were injected into the vitreous cavity of New Zealand white rabbits. Electroretinography was performed at the baseline and before sacrifice. Clinical toxicity was assessed through slit-lamp and indirect ophthalmoscopy examinations. Animals were sacrificed two and eight weeks after injection and the eyes were fixed to optimize morphology for light and electron microscopy . Fundoscopic, histologic and electrophysiologic data revealed no evidence of toxicity even at the highest dose of the compound. These results show that the compound has a very high therapeutic index in the eye and indicate that studies of treatment in an animal model of retinitis may be worthwhile. Such studies using a focal herpetic retinitis model have begun and the results will be reported.

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Pharmacokinetics and Bioavailability of Cygalovir (BMS-180194) in Asymptomatic HIV- and CMV-Seropositive Volunteers. BG Petty, H Saito, RS Summerill, H Burgee, J McDowell, and MB Stewart. The Johns Hopkins University School of Medicine, Baltimore, MD, and Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ and Syracuse NY, USA.

Cygalovir is a promising new drug with activity against CMV and with good bioavailability in animal studies. This was the first human study of cygalovir. Forty clinically stable HIV- and CMV-seropositive subjects participated in a double-blind, placebo-controlled study to assess the safety and pharmacokinetics (PK) of single doses of cygalovir. Groups of 8 subjects received cygalovir (n = 6) or placebo (n = 2) at dose levels of 0.3, 1.0, 3.0, 6.0 and 10.0 mg/kg. Subjects were randomized to receive the intravenous (IV) or the oral (PO) formulation on Day 1, and the alternate formulation on Day 4. Plasma and urine samples were collected before and for 48 hours after each dose and assayed for cygalovir content by HPLC to assess pharmacokinetics. Following IV administration, the pharmacokinetics of cygalovir were linear, and mean values for C_{max} and $AUC_{0-\infty}$ increased in proportion to dose; the plasma half-life was about 2 hours, clearance about 22L/hr/m^2 and Vd_{ss} about 41 L/m^2. Oral bioavailability was about 40% with possible saturable absorption. Clinical evaluations and laboratory testing were performed with each dose, and on Days 7, 10 and 14. The most frequently reported events were headache, localized itching, nausea, vomiting and diarrhea, but there was no clear relationship of Adverse Events (AE's) to drug or to dose administered. All events were transient and were of mild or moderate intensity. No serious AEs were reported. Neutropenia or thrombocytopenia were not observed. Single doses of cygalovir were well tolerated and orally absorbed, indicating that further clinical development is warranted.