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Antiviral Efficacy of 9-(2-Phosphonylmethoxyethyl)-2,6-Diaminopurine (PMEDAP) Upon Oral Administration to Moloney Murine Sarcoma Virus (MSV)-Infected Mice

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9-(2-Phosphonylmethoxyethyl)-2,6-diaminopurine (PMEDAP) is a potent and selective inhibitor of DNA viruses and retroviruses *in vitro* and *in vivo*. We now investigated the antiviral efficacy of PMEDAP administered orally to mice infected with Moloney murine sarcoma virus (MSV). PMEDAP had high antiretroviral activity in mice infected with MSV when administered orally at a daily dose of 50 or 100 mg/kg during 5 subsequent days (mean day of MSV-induced tumor initiation: 9 and 12 days, respectively; as compared to 6 days for untreated mice). MSV-infected mice that were treated orally with PMEDAP at 250 mg/kg developed no tumors within 15 days after infection. PMEDAP was also effective in inhibiting splenomegaly in mice infected with Friend leukemia virus (FLV), when given orally at 50, 100 or 250 mg/kg/day during 5 days (inhibition of splenomegaly: 84%, 93% and 96%, respectively). To achieve a comparable antiretroviral efficacy, two- to five-fold lower PMEDAP doses were required if the compound was administered *via* the intraperitoneal route. Pharmacokinetic studies are in progress to determine the oral bioavailability of PMEDAP in mice. Also, the efficacy of orally administered PMEDAP in the treatment of herpesvirus (i.e. herpes simplex virus type 1 and murine cytomegalovirus) infections is under investigation.

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Anti-HIV activity of 5-hydroxymethyldeoxyuridine *in vitro* and *in vivo*. Gupta,V.S., Stuart, A.L., Kumar, S.V.P., De Clercq, E., Qualtiere, J., Cozens, R.M., Lazdins, J.K. and Qualtiere, L.F. Depts. Vet. Physiol. Sci., Chem., and Microbiol., Univ. of Saskatchewan, Saskatoon, Sk., Canada, CIBA-GIEGY Ltd., Basle, Switzerland and Rega Institute for Med. Res., Katholieke, Leuven, Belgium.

Modified nucleoside analogs such as AZT, ddCyd and ddI have proven to be effective anti-HIV agents *in vitro* and *in vivo*. Their usefulness in humans has been limited by various types of toxicity.

We have identified a new anti-HIV agent. 5-Hydroxymethyldeoxyuridine (HMdUrd), a naturally occurring nucleoside, protects cells from the cytopathic effects of HIV *in vitro*. Using the tetrazolium-based colorimetric method in MT-4 cells, the ED_{50} of HMdUrd was 0.75 μg/ml. In the blood derived monocyte-macrophage system by reverse transcriptase assay the ED50 was 2.5 μg/ml. Cellular toxicity was not observed in either system up to 25 μg/ml. HMdUrd has low mammalian toxicity and most significantly is devoid of bone marrow toxicity (Meldrum *et al.*, Tox. Appl. Pharmacol. 79:423-435(1985)). Efficacy studies were carried out with HMdUrd and AZT against Friend Leukemia Virus (FLV) in mice. Treatment was initiated one h after infection and continued by daily injections of 5 and 10 mg/kg i.p. for 21 days. Both compounds significantly prolonged survival ($p < 0.05$) of the FLV infected mice. Interestingly, there was essentially no difference observed between the AZT and HMdUrd treatments.

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