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Lack of retinal toxicity of the anti-CMV drug (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC)

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HPMPC is an anti-herpes compound which has a higher potency and a longer duration of action against cytomegalovirus (CMV) than ganciclovir (DHPG) or phosphonoformate (Foscarnet). Twenty eyes of 10 New Zealand white rabbits received 0.1 ml intravitreal injections of either normal saline or HPMPC at doses of 10, 50, or 100 μg. The animals were sacrificed at days 14 and 28. Toxicity was assessed by indirect ophthalmoscopy, electroretinography (ERG) and by light and electron microscopy. The A and B wave ERG morphology and indirect ophthalmoscopic appearance of the retina in all groups was normal. Light and electron microscopy of perfusion-fixed retinal tissue revealed no morphologic changes. These results indicate that HPMPC is not toxic to the rabbit retina at 500-1000 times the dose that is effective in suppressing CMV replication *in vitro*. Intravitreal injections of HPMPC may be efficacious in the inhibition of CMV retinitis when administered at longer dosing intervals.

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Evaluation of Immunotoxic Potential of Antiviral Drugs: Effects of DHPG and HPMPC on lymphocyte transformation and delayed-type hypersensitivity (DTH) responses.

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Antiviral drugs that have activity against herpesviruses, particularly for CMV, are often used in patients that have a compromised immune system due either to an immunosuppressive agent prior to transplantation or to an underlying disease process such as AIDS. In the development and evaluation of a new antiviral drug, it is important to determine whether drug therapy alters the normal immune responses. In the present studies, we have evaluated the *in vitro* and *in vivo* effects of ganciclovir (DHPG) and (5)-1-(3-hydroxy-2-phosphenyl methoxypropyl) cytosine (HPMPC), on lymphocytes responses to T cell mitogens and DTH responses to dinitrofluorobenzene (DNFB). Initially, responses of C3H mouse splenic and human peripheral blood lymphocytes to PHA and con A were evaluated *in vitro* in the presence of the drugs. Both drugs at concentrations of ≥ 5 μg/ml were found to inhibit responses to each mitogen. Although mouse and human responses were both decreased, slightly higher drug levels were needed for mouse lymphocytes. Next, mice were treated daily i.p. with 5, 15 or 50 mg/kg/day. After 7d, spleen cells were collected and stimulated *in vitro* with mitogens. Overall, there was an inconsistent inhibition by drug treatments on mitogenic responses as compared to mice given no drug. However, drug treatment of mice decreased the development of DTH responses as measured by increased ear thickness 24 hours after challenge. HPMPC treatment had a greater inhibitory effect than DHPG treatment. At a dose of 15 mg/kg/day, HPMPC-treated mice had 60-75% of the response of control mice while DHPG-treated mice had 70-95% of the control response. Further studies are planned to evaluate the immunotoxic effects of these drugs in vivo, particularly in CMV infected animals. In summary, the results from the present studies suggest that these drugs may have a detrimental effect on the development of immunity; however, the effects are probably minimal at therapeutic doses of the drugs in normal animals.