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Evaluation of HPMPC Therapy for Primary and Recurrent Genital Herpes in the Guinea Pig. F. J. BRAVO AND L. R. STANBERRY. Children's Hosp Res Foundation, Cincinnati, OH.

(S)-1-(3-Hydroxy-2-Phosphonylmethoxypropyl) Cytosine (HPMPC) is an antiviral compound with in vitro and in vivo activity against HSV-1 and HSV-2. The purpose of these experiments was to evaluate the efficacy of topically administered HPMPC in guinea pig models of primary and recurrent genital herpes. Female Hartley guinea pigs were infected by intravaginal inoculation of 5.7 $\log_{10}$ pfu HSV-2, MS strain. For primary infection, animals were randomized to receive 5% HPMPC (0.2cc intravaginal/topical) twice daily for 10d beginning either 3hr post inoculation (PI) or 3d PI, or serve as vehicle-treated or untreated controls. HPMPC therapy initiated 3hr PI significantly reduced the severity of genital skin disease while treatment begun 3d PI was ineffective. Control animals survived primary infection while all HPMPC treated animals exhibited weight loss and other non-specific signs and died by 17d PI. Histopathologic examination of 10 morbid and pre-morbid HPMPC treated animals revealed evidence of glomerulonephritis and vascular congestion and focal hemorrhages in lung and liver. In an effort to avoid the toxicity associated with 5% HPMPC we examined the efficacy of topically applied 0.1% and 1% HPMPC in the control of recurrent disease. Treatment given daily for 7d beginning 43d PI had no effect on the incidence or severity of spontaneous recurrent infections. Likewise, treatment of animals 78d PI with 1% HPMPC twice daily for 2 days did not reduce the incidence of recurrent disease induced by ultraviolet radiation. Topical treatment with lower dose HPMPC was not associated with mortality or clinically apparent morbidity. These results indicate that topical therapy with 5% HPMPC was effective in the treatment of primary genital herpes however, treatment with lower concentrations were ineffective in preventing spontaneous or UV radiation induced recurrent infections. The toxicity of HPMPC may limit its clinical utility.

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Treatment of Genital Herpes Simplex Virus Infections of Mice and Guinea Pigs with Famciclovir, an Oral Prodrug of Penciclovir.

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Penciclovir has activity against herpes simplex virus types 1 and 2 (HSV-1, HSV-2) and Varicella Zoster Virus in tissue culture and HSV infections in animal models that is comparable to acyclovir (ACV). Although penciclovir has good activity when administered to rodents parenterally or topically, it has poor oral bioavailability. In contrast, famciclovir, which is the diacetate ester of the 6-deoxy derivative of penciclovir, is rapidly absorbed and converted to penciclovir when administered by the oral route. Since famciclovir acts as a prodrug it has little activity in tissue culture, and must be evaluated in animal model infections. The purpose of our studies was to compare the efficacy of oral famciclovir and ACV in genital HSV-2 infections of mice and guinea pigs. In mice inoculated intravaginally with HSV-2, oral treatment with 30 or 100 mg/kg of famciclovir or ACV twice daily for five days beginning at +24h or +48h significantly reduced vaginal virus titers and extra-genital disease. In a genital infection of guinea pigs, a similar treatment regimen initiated 6h or 24h after infection significantly altered the severity of genital lesions but both compounds failed to inhibit viral replication in the vaginal tract. These data indicate that oral famciclovir has activity similar to oral ACV in experimental genital HSV-2 infections and suggests that it may have activity against genital HSV infections of humans.