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Evaluation of HPMPC therapy for primary and recurrent genital herpes in mice and guinea pigs

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Summary

The nucleoside analogue (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) inhibited the replication of herpes simplex virus (HSV) types 1 and 2 in tissue culture cells at about 1.0 μg/ml, whereas Acyclovir (ACV) had an EC_{50} of about 0.10–0.50 μg/ml. The purpose of these studies was to evaluate the efficacy of topically applied HPMPC in animal models of primary and recurrent genital HSV-2 infections. Mice treated with 5%, 1% or 0.5% HPMPC three times daily, beginning 6 or 24 h after virus inoculation had reduced vaginal viral replication regardless of time of initiation of therapy. ACV at 5% also reduced vaginal viral replication, but not as effectively as HPMPC. In primary infection of guinea pigs, therapy with 5% or 1% HPMPC beginning at 24 h but not 72 h significantly altered lesion development. However, 5% HPMPC was highly toxic to guinea pigs. Vaginal viral replication was reduced significantly with either 1% or 0.3% HPMPC initiated at 24 h. In these studies, HPMPC was also more efficacious than 5% ACV. Topical treatment with 1% HPMPC did not reduce the incidence or severity of spontaneous or UV-induced recurrent genital lesions. These results indicate that topical therapy with 1%, 0.5% or 0.3% HPMPC was more effective than 5% ACV in the treatment of primary genital HSV-2 infections of guinea pigs and mice and suggest that HPMPC should be considered for topical use in humans.

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HPMPC; Genital herpes; Mice; Guinea pig

Introduction

(*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) is a potent and selective antiviral agent with activity against herpesviruses (De Clercq et al., 1987; Bronson et al., 1989a). Recent studies have examined the efficacy of HPMPC therapy in the treatment of acute and chronic murine cytomegalovirus infections (Kern, 1991), acute cytomegalovirus infection in severe combined immunodeficiency mice (Neyts et al., 1992), acute guinea pig cytomegalovirus infection (Li et al., 1990), rat cytomegalovirus infections, (Stals et al., 1991) simian varicella-zoster virus infection (Soike et al., 1991) and acute, non-genital herpes simplex virus (HSV) infections of mice and rabbits (Bronson et al., 1989b; De Clercq and Holy, 1991; Maudgal and De Clercq, 1991; Yang and Datema, 1991). While therapy was effective in all the model systems it was observed that systemic administration of HPMPC was toxic to guinea pigs (Li et al., 1990). To further explore its therapeutic and toxic properties we evaluated the effect of topically administered HPMPC in murine and guinea pig models of primary and recurrent genital herpes.

Materials and Methods

In vitro susceptibility

The origin and preparation of the HSV-1 and HSV-2 isolates has been described previously (Kern et al, 1978). The comparative susceptibility of five HSV-1 and five HSV-2 isolates to HPMPC and ACV was determined in low-passaged human foreskin fibroblast (HFF) cells using a plaque reduction assay. Confluent cell monolayers were inoculated with about 25 plaque forming units (PFU) of each virus and incubated for 60 min. The monolayers were then overlaid with an agarose-medium mixture containing six concentrations of the respective antiviral drug. After 3 days incubation, monolayers were stained with neutral red and plaques were counted. The plaque number in drug-treated wells was compared with untreated control wells and an EC_{50} was calculated using the dose effect analysis computer software (Elsevier, UK).

Animals

6-Week-old female Swiss Webster mice obtained from Charles River Breeding Laboratories (Portage, MI) were used in these studies. Hartley female guinea pigs (250–350 g) were purchased from Charles River Breeding Laboratories (Wilmington, MA) and housed for a week prior to virus inoculation.

Viral inoculation

All animals were inoculated with stock preparations of HSV-2, MS strain (ATCC VR #540) prepared in primary rabbit kidney monolayers. Mice were inoculated intravaginally (Ivg) with 5.0×10^5 PFU by using a dacron-tipped swab soaked in an appropriate virus dilution which was inserted into the vaginal tract and rotated approximately five times. 1 h prior to Ivg inoculation, animals were swabbed with a dry dacron swab for removal of vaginal secretions to facilitate HSV infection. In guinea pig experiments examining the effect of 5% HPMPC on primary infection and the effect of 0.1% and 1% HPMPC on recurrent infections animals were Ivg inoculated by rupturing the vaginal closure membrane with a moistened calcium alginate-tipped swab (Calgiswab #3, Spectrum Labs., Los Angeles, CA) and instilling 0.1 ml of a virus suspension (5.0×10^5 PFU) into the vaginal vault using a plastic catheter (Abbocath, Abbott Laboratories, North Chicago, IL). For guinea pig experiments examining the effect of 1% and 0.3% HPMPC on primary infection animals were Ivg inoculated with 2.5×10^5 PFU using the same method described above for mice.

Antiviral treatment

HPMPC was provided by Bristol-Myers Squibb Company, Wallingford, CT through the Antiviral Substances Program, NIAID, NIH, Bethesda, MD and was used as its monosodium salt. The 5% aqueous solution for the initial guinea pig study was prepared with 40% glycerol and 0.1% Tween 80. In other studies, concentrations of HPMPC were prepared in 70% glycerol and 0.2% Tween 80. The 5% Acyclovir in PEG (Zovirax) was purchased from the University of Alabama at Birmingham Hospital Pharmacy. Placebo-treated animals received vehicle without drug. Using a pipette (Microman, Gilson Medical Electronics, France) or a tuberculin syringe, 0.1 cc of drug or vehicle was applied both Ivg and topically to the perineal skin of guinea pigs. Groups of 10–12 guinea pigs were treated with 5%, 1%, 0.3% HPMPC or 5% ACV 1–3 times daily beginning at various times after viral inoculation. Groups of 10 mice were treated Ivg with 5% HPMPC, 1% HPMPC, 0.5% HPMPC or 5% ACV either three times or once daily. Treatment was begun 6 or 24 h after viral inoculation.

Clinical disease

After intravaginal HSV-2 inoculation guinea pigs were examined daily for 21 days for evidence of primary infection. Lesions developing on the external genital skin were quantified using a lesion score scale: 0 = no disease; 1 = redness or swelling; 2 = a few small vesicles; 3 = several large vesicles; 4 = several large ulcers with maceration (Kern et al., 1978; Stanberry et al., 1982). Severity of infection was assessed by determining the area under the lesion score-day curve. After recovery from primary infection, guinea pigs developed spontaneous recurrent herpetic lesions on the genital skin (Stanberry et al., 1985). The incidence and number of recurrences were quantified by daily

examination. When spontaneous recurrences became infrequent, recurrent herpetic lesions were induced by exposure to ultraviolet (UV) radiation (10 min, 8000 uW/cm^2 at 302 nm, UVP, San Grabiel, CA) (Stanberry, 1989). The incidence and number of UV radiation-induced recurrences were quantified by daily examination.

Evaluation of efficacy

Evaluation of drug efficacy in the guinea pig model of a genital HSV infection included effect on vaginal viral replication and external genital lesion development. To determine the effect of treatment on vaginal virus replication, swabs of vaginal secretions were obtained on days 1, 3, 5, 7 and 10 after HSV-2 inoculation, placed in tubes containing 2.0 ml of media, vortexed, and frozen at −70°C until titrated for HSV-2. When all samples were collected, they were thawed, diluted serially, and HSV-2 titers determined in rabbit kidney cells using a microtiter CPE assay. The magnitude of viral replication was assessed by determining the area under the virus titer-day curve. To determine the effect of treatment on lesion development, lesions were scored daily as described above.

Drug efficacy in the mouse model of genital HSV infection was assessed by determining the effect of therapy on vaginal viral replication. Vaginal swabs were taken on days 1, 3, 5, 7, and 10 post-inoculation. Procedures as outlined above were followed.

Histopathology

Sections were prepared from formalin-fixed, paraffin-embedded tissues harvested from selected animals. The tissue sections were examined for evidence of microscopic changes after hematoxylin and eosin staining.

Statistical evaluation

With all parameters used to determine efficacy, placebo-treated animals were compared with the untreated control animals. The animals that received drug were compared to the appropriate placebo-treated group. Lesion score-day areas and virus titer-day areas under the curve (AUC) and mean peak virus titers were compared using the Mann-Whitney U Rank Sum Test. Data on the incidence of recurrent infections were analyzed by the chi-square test. A *P*-value of 0.05 or less was considered significant.

Results

Effect of HPMPC or ACV on HSV replication in vitro

A comparison of the susceptibility of 5 HSV-1 and 5 HSV-2 strains to HPMPC or ACV in HFF cells shown in Table 1. The EC_{50} of the HSV-1 strains ranged from 0.6–2.7 μg/ml for HPMPC with a mean of 1.6 μg/ml and 0.2–0.4 μg/ml for ACV with a mean of 0.3 μg/ml. The EC_{50} of the HSV-2

TABLE 1

Effect of HPMPC or ACV on replication of herpes simplex virus type 1 or type 2 in human foreskin fibroblast cells

Virus strain	EC_{50} (μg/ml)[a]	
	HPMPC	ACV
HSV-1		
E-377	1.1 (0.77–1.40)	0.2 (0.22–0.25)
HL-3	1.7 (0.44–3.80)	0.3 (0.19–0.35)
E-115	2.7 (0.77– 6.3)	0.2 (0.18–0.33)
HL-34	1.7 (0.74– 3.6)	0.4 (0.25–0.62)
F	0.6 (0.32– 1.1)	0.2 (0.25–0.62)
Mean	1.6	0.3
HSV-2		
MS	1.2 (0.84–1.60)	0.8 (0.73–0.80)
X-79	2.2 (1.1 – 3.9)	0.5 (0.31–0.57)
Jensen	2.1 (0.92– 3.8)	0.3 (0.19–0.50)
Heeter	3.0 (1.1 – 5.8)	0.9 (0.77– 1.0)
SR	2.1 (2.1)	0.6 (0.39–0.74)
Mean	2.1	0.6

[a]Plaque reduction assay, mean of 2–4 assays (range).

strains ranged from 1.2–3.0 μg/ml for HPMPC (mean = 2.1 μg/ml) and 0.3–0.9 μg/ml for ACV (mean = 0.6 μg/ml).

Effect of treatment with HPMPC or ACV on vaginal viral replication in mice

We first evaluated the efficacy of a 5 day course of topically applied HPMPC in the murine genital HSV-2 infection using concentrations of 5%, 1% or 0.5% beginning 6 or 24 h after HSV-2 inoculation. Treatment with these concentrations of HPMPC three times a day given either 6 or 24 h after inoculation significantly reduced vaginal viral replication (Table 2). Utilizing the same regimen, 5% ACV also reduced virus titer-day AUC values and peak virus titers, but not as effectively as HPMPC. When therapy was limited to once daily, HPMPC was again highly effective at reducing vaginal viral replication at all concentrations and times tested. Although 5% ACV significantly reduced virus titer-day AUC when given once daily at 6 or 24 h after HSV inoculation, it was less effective than HPMPC.

Treatment of primary infection of guinea pigs with HPMPC

In an initial study, groups of guinea pigs were infected with HSV-2 and treated twice daily for 10 days with topical 5% HPMPC. The effect on lesion development is presented in Fig. 1. When treatment was initiated 3 h post HSV-2 inoculation, guinea pigs experienced significantly less severe primary disease compared to untreated or vehicle-treated animals ($P < 0.05$). When initiation of therapy was delayed until 72 h after virus challenge, topical 5% HPMPC had no effect on the course of primary genital infection. All animals that received 5% HPMPC exhibited signs of toxicity including weight loss and lethargy. No

TABLE 2

Effect of topical treatment with HPMPC or ACV on infection rates and vaginal virus titers during a genital HSV-2 infection of mice

Treatment[a]	# Virus positive/ # inoculated	Virus titer-day area under curve	*P*-value	Mean peak virus titer	*P*-value
Three times daily					
None	7/10	12.8	–	2.5	–
Placebo +6 h	9/10	17.3	NS[b]	3.4	NS
HPMPC 5% +6 h	1/10	0.1	<0.001	0.1	<0.001
HPMPC 1% +6 h	1/10	0.1	<0.001	0.1	<0.001
HPMPC 0.5% +6 h	1/10	0.1	<0.001	0.1	<0.001
ACV 5% +6 h	5/9	2.3	<0.001	1.1	<0.01
Placebo +24 h	9/9	18.1	NS	3.3	NS
HPMPC 5% +24 h	6/10	2.3	<0.001	1.4	<0.01
HPMPC 1% +24 h	7/10	1.4	<0.001	1.1	<0.01
HPMPC 0.5% +24 h	9/9	3.4	<0.001	2.3	0.06
ACV 5% +24 h	9/10	3.3	<0.05	1.8	<0.01
Once daily					
None	7/10	12.8	–	2.5	–
Placebo +6 h	9/10	15.2	NS	2.9	NS
HPMPC 5% +6 h	2/10	0.2	<0.001	0.1	<0.001
HPMPC 1% +6 h	2/9	0.2	<0.001	0.1	<0.001
HPMPC 0.5% +6 h	0/10	0.0	<0.001	0.0	<0.001
ACV 5% +6 h	3/10	2.3	<0.001	0.7	<0.01
Placebo +24 h	6/10	9.1	NS	1.9	NS
HPMPC 5% +24 h	5/10	1.4	<0.001	0.9	NS
HPMPC 1% +24 h	7/10	2.7	<0.01	1.6	NS
HPMPC 0.5% +24 h	6/10	1.7	<0.001	0.7	NS
ACV 5% +24 h	5/10	3.3	<0.01	1.3	NS

[a]Treatment was initiated at the times and concentrations indicated and continued three times or once daily for 5 days.
[b]NS – not statistically significant when compared to the untreated control or appropriate placebo-treated group.

deaths occurred in untreated groups, however, all HPMPC-treated animals died between days 10–17 post HSV-2 inoculation. Tissues were harvested from 10 dead or pre-morbid HPMPC-treated animals for microscopic evaluation. Examination revealed focal and multifocal hemorrhages, vasodilation and inflammatory changes in lung, liver and kidneys of HPMPC-treated animals but not in vehicle-treated controls. Photomicrographs illustrating the histologic changes are shown in Fig. 2.

Since 5% HPMPC delivered topically to guinea pigs resulted in unacceptable toxicity, we utilized 1% and 0.3% HPMPC for additional efficacy studies. Animals were treated for 7 days with either drug or placebo-administered either

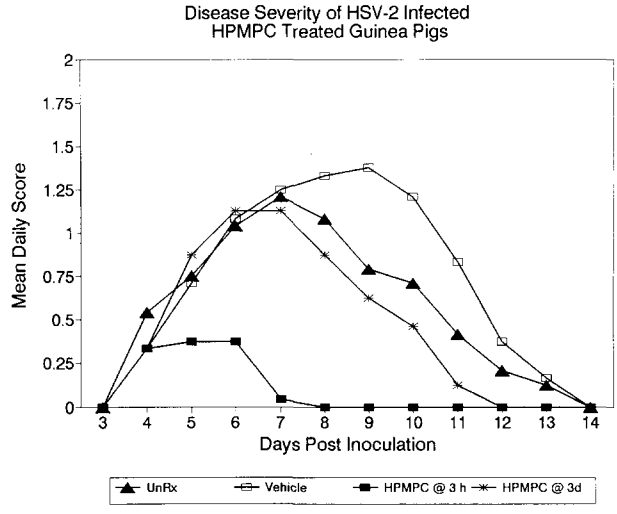


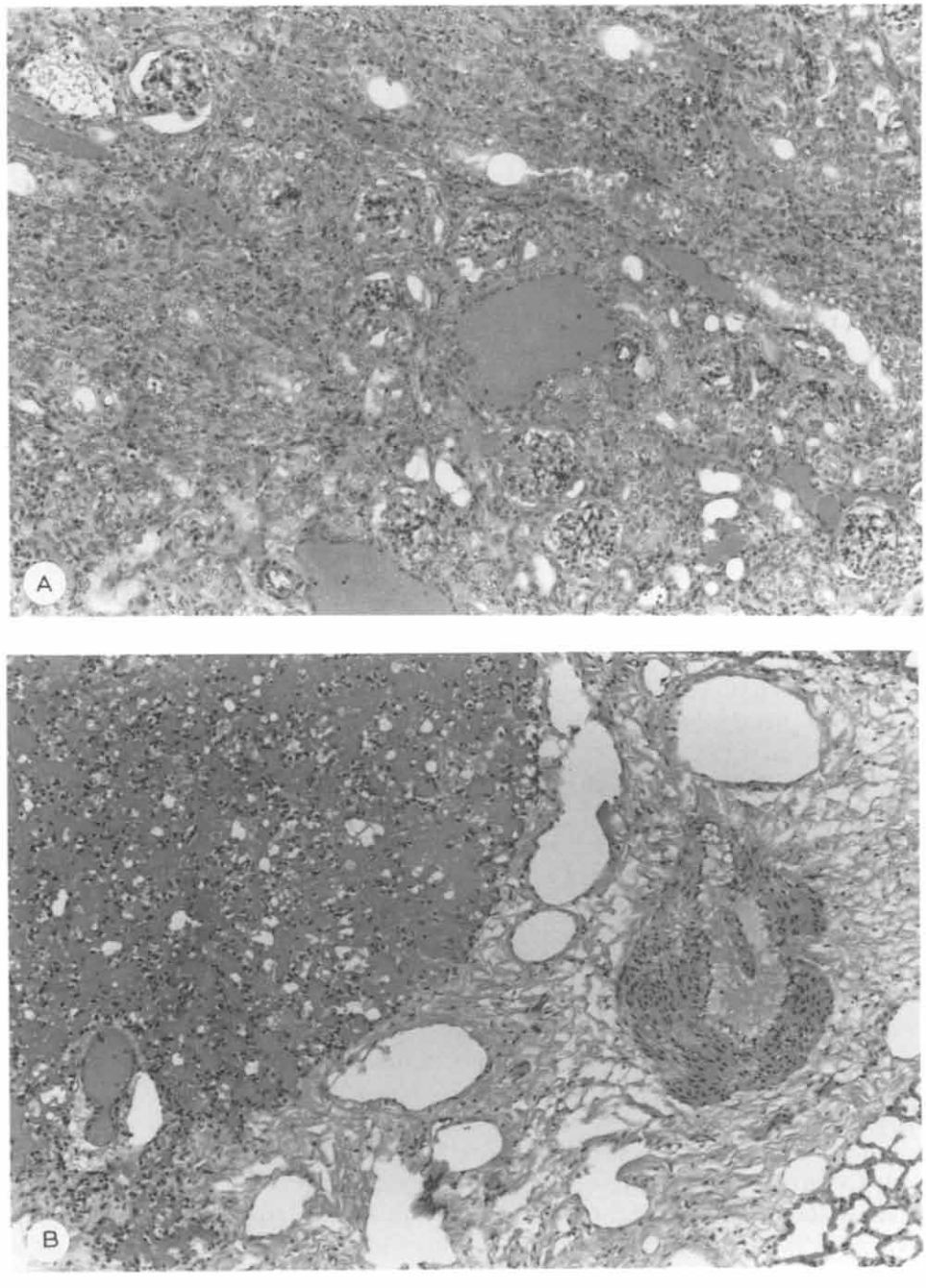
Fig. 1. The effect of topical 5% HPMPC on the course of genital skin disease in HSV-2 infected guinea pigs. Treatment was given twice daily for 10 days. Triangle = untreated control; open square = vehicle control; closed square = HPMPC initiated 3 h post HSV-2 inoculation; star = HPMPC initiated 3 day post HSV-2 inoculation.

three times a day or once daily. The effects of topical therapy with HPMPC or ACV on the virologic and clinical course of primary genital HSV-2 infection are shown in Table 3. Treatment with 1% or 0.3% HPMPC but not 5% ACV beginning 24 h after inoculation reduced significantly the virus titer-day AUC values ($P<0.05$). When therapy was delayed until 72 h post-inoculation, no significant differences were observed with any of the treatment regimens.

Treatment with 1% HPMPC either three times per day or once daily beginning 24 h after inoculation also significantly reduced the lesion score-day AUC. The lesion score-day AUC was also reduced with 0.3% HPMPC at 24 h, but only when compared to the 24 h placebo, which was greater than the untreated control. ACV, tested only at 5% three times daily beginning at 24 or 72 h, failed to alter the clinical course of primary infection. No other significant differences were observed and there was no evidence of HPMPC-associated morbidity or mortality.

Treatment of spontaneous recurrent disease in guinea pigs

The effect of HPMPC on spontaneous recurrent genital infection was studied in latently infected guinea pigs. After recovery from primary genital infection 36 animals were randomized to one of three experimental groups and observed for recurrent lesions for 7 days prior to treatment, during a 7 days treatment period (day 43–49 after HSV-2 inoculation) and for an additional 7 day period after discontinuing treatment. To minimize toxicity, 0.1% and 1.0% concentrations of HPMPC were used and the frequency of topical administration was reduced to once daily. As shown in Table 4 the topical HPMPC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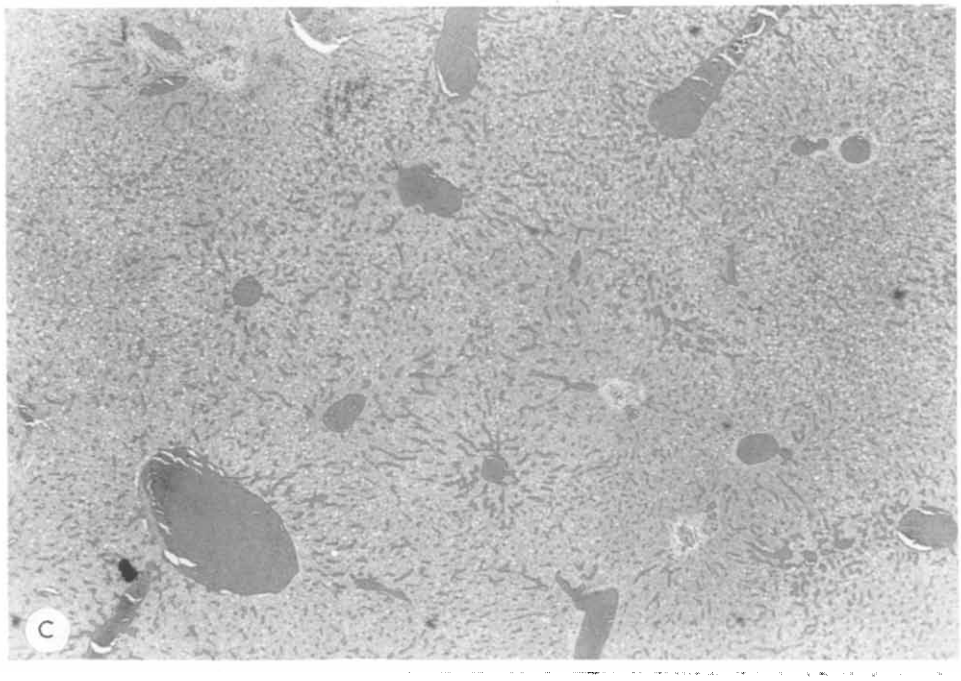

Fig. 2. Histopathological examination of tissues harvested from guinea pigs treated with 5% topical HPMPC b.i.d. x 10 days (hematoxylin and eosin stained). (A) Kidney: (10 x magnification) glomerular swelling, focal inflammation and vascular congestion. (B) Lung: (10 x magnification) alveolar hemorrhages and perivascular edema in an area of pneumonitis. (C) Liver: (4 x magnification) vascular and sinusoidal congestion, hemorrhage present but not obvious on the photograph.

regimens utilized did not reduce the incidence or severity of spontaneous recurrent genital HSV-2 infections. There was no evidence of HPMPC-associated morbidity or mortality.

Treatment of ultraviolet radiation-induced recurrent disease in guinea pigs

To examine the suppressive effect of HPMPC treatment on induced recurrent HSV infections, latently infected guinea pigs were randomized, 78 days after intravaginal inoculation with HSV-2, to receive treatment prior to UV exposure. Treated animals received either vehicle or 1% HPMPC administered topically twice daily for 2 days. Compared to the non-irradiated control group, UV radiation significantly increased the incidence of herpetic recurrences noted during the 7 day observation period (Table 5, $P<0.05$). Prophylactic administration of topical 1% HPMPC did not protect animals against UV radiation-induced recurrent HSV infections.

TABLE 3

Effect of topical treatment with HPMPC or ACV on vaginal virus titers or lesion development during a primary genital HSV-2 infection of guinea pigs

Treatment[a]	Virus titer-day area under curve	*P*-value	Lesion score day area under curve	*P*-value
Three times daily				
None	25.1	–	45.3	–
Placebo +24 h	25.2	NS[b]	46.4	NS
Placebo +72 h	23.0	NS	43.1	NS
HPMPC 1% +24 h	10.8	<0.05	37.0	0.01
HPMPC 1% +72 h	17.8	NS	43.1	NS
HPMPC 0.3% +24 h	11.4	<0.05	40.7	NS
HPMPC 0.3% +72 h	17.9	NS	39.5	NS
ACV 5% +24 h	17.3	NS	45.2	NS
ACV 5% +72 h	17.2	NS	40.1	NS
Once daily				
None	25.1	–	45.3	–
Placebo +24 h	25.5	NS	51.9	NS
Placebo +72 h	25.6	NS	45.2	NS
HPMPC 1% +24 h	10.0	0.01	23.3	<0.001
HPMPC 1% +72 h	17.7	NS	44.9	NS
HPMPC 0.3% +24 h	12.2	<0.05	40.5	0.01
HPMPC 0.3% +72 h	19.5	NS	44.2	NS

[a]Treatment was initiated at the times and concentrations indicated and continued three times or once daily for 7 days.
[b]NS = Not statistically significant when compared to the untreated control or appropriate placebo-treated group.

TABLE 4

Effect of HPMPC on spontaneous recurrent genital herpes in the guinea pig[a]

Group[d]	Animals with recurrences[b]			Mean lesion days[c]		
	D36-42 (before treatment)	D43-49 (during treatment)	D50-56 (after treatment)	D36-42 (before treatment)	D43-49 (during treatment)	D50-56 (after treatment)
1.0% HPMPC	8/12	8/12	8/12	1.67 ± 0.41	1.17 ± 0.37	1.33 ± 0.36
0.1% HPMPC	9/12	7/12	7/12	1.58 ± 0.42	0.92 ± 0.29	0.92 ± 0.26
Control	8/12	9/12	6/12	1.83 ± 0.49	1.25 ± 0.33	0.83 ± 0.35

[a]Animals observed for 3 weeks, days 36–56 post HSV-2 inoculation.
[b]Animals with recurrences per total animals.
[c]Mean number of days lesions were noted ± S.E.
[d]HPMPC administered once a day for 7 days (days 43–49 post-inoculation).

TABLE 5
Effect of HPMPC on UV induced recurrent genital herpes in the guinea pig

Group[a]	Animals with recurrences[b]
Untreated/No UV	3/14 (21%)
Untreated/UV	8/12 (67%)
Vehicle/UV	10/12 (83%)
1% HPMPC/UV	8/11 (73%)

[a]HPMPC administered twice daily on days 78 and 79 post-inoculation. Animals exposed to UV radiation 3 h after final drug treatment.
[b]Recurrences scored for 7 days (days 80–86 post-inoculation).

Discussion

These studies indicate that early initiation of topical HPMPC therapy was effective in the control of primary genital HSV-2 infection in mice and guinea pigs. When topical treatment for genital herpes was delayed until 72 h after intravaginal HSV-2 challenge, HPMPC therapy was no longer effective. These results extend previous reports of the efficacy of topically administered HPMPC in the treatment of HSV-1 cutaneous infections in guinea pigs (Bronson et al, 1989a), HSV-1 and HSV-2 cutaneous infections in mice (De Clercq and Holy, 1991) and HSV-1 keratitis in rabbits (Maudgal and De Clercq, 1991). Systemic administration of HPMPC has also been reported effective in the treatment of non-genital HSV infections (Bronson et al, 1989b; De Clercq and Holy, 1991).

In our experiments, HPMPC at concentrations as low as 0.5% was as active as 5% ACV in reducing viral replication in the murine model. While HPMPC reduced both HSV replication and lesion development in the guinea pig, 5% ACV had no effect on either viral replication or lesion development. In other experiments, topical ACV has been effective in controlling primary HSV-2 genital infection in guinea pigs even when treatment was delayed until 24–72h (Kern, 1982; Kern, unpublished results).

While HPMPC was effective in the treatment of primary infection we observed that low concentrations of HPMPC (0.1% and 1.0%) were not effective in reducing the incidence of spontaneous or UV radiation-induced recurrent infections. These results are consistent with other studies which have shown therapies effective in the management of primary genital HSV infection may be less useful in controlling recurrent disease. For example, topical ACV therapy is beneficial in first episode genital herpes but is ineffective in the treatment of spontaneous recurrent genital HSV-2 infections in guinea pigs (Kern, unpublished data) or in humans (Reichman et al., 1983; Luby et al., 1984). In contrast, with oral or parenteral ACV, the frequency and severity of recurrent episodes is reduced in both guinea pigs (Bernstein et al., 1986; Kern, 1984; Kern, 1990) and human (Corey et al., 1982; Douglas et al., 1984) infections. Topical ACV initiated prophylactically has been reported to

decrease the severity but not the incidence of UV induced genital HSV-2 recurrences in the guinea pig (Stanberry et al., 1990). In this study, low dose topical HPMPC administered prophylactically for 2 days before irradiation failed to prevent UV radiation-induced recurrent lesions. The benefit of continuing HPMPC treatment after UV radiation exposure was not assessed in our experiments because of the long half-life of the drug. Due to the toxicity observed in guinea pigs treated topically with 5% HPMPC or systemically with low concentrations (Li et al., 1990), we were not able to investigate whether concentrations higher than 1% HPMPC administered topically or systemically might be effective in reducing the incidence or severity of recurrent genital herpes in guinea pigs.

Topical 5% HPMPC was highly toxic to guinea pigs producing histopathologic changes in lung, liver and kidneys, and death. This appears to be a direct toxic effect of the drug rather than an effect mediated by drug-virus interaction because HSV does not infect these tissues following intravaginal virus inoculation in guinea pigs. Li et al. (1990) also reported significant toxicity in studies designed to evaluate the efficacy of HPMPC in the treatment of guinea pig cytomegalovirus infection. They observed pathological changes in kidney and bone marrow. Similar patterns of toxicity were not seen in our murine studies and have not been reported in studies using other species (De Clercq and Holy, 1991; Maudgal and De Clercq, 1991). Additionally, systemic treatment of mice with HPMPC was less inhibitory to immune functions in mice than ganciclovir (Simecka et al., 1992). The mechanism of HPMPC-induced toxicity in the guinea pig is unknown, but appears to be unique to this particular rodent. The drug is currently being evaluated in clinical phase I/II studies for toxicity and efficacy in the treatment of cytomegalovirus retinitis. Until these studies are completed, the toxicity and potential for use of HPMPC in humans remains uncertain.

We have shown that HPMPC is more effective than ACV as topical therapy for experimental primary genital herpes in both mice and guinea pigs when initiated soon after HSV challenge. However, low dose topical HPMPC therapy is not efficacious in the treatment or prevention of recurrent genital herpes. The topical efficacy of HPMPC in two species and its lack of toxicity in animals other than the guinea pig suggests that HPMPC may have clinical utility in the treatment of genital HSV infections in humans. Additionally, HPMPC has been shown to be effective in vitro and in vivo against ACV-resistant, thymidine kinase-deficient or altered HSV mutants (Kern, 1991). Combined, these studies suggest that HPMPC may have a role in the management of HSV infections, particularly in the treatment of ACV-resistant HSV infections of the immunocompromised host.

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