Comparison of Foscarnet Cream, Acyclovir Cream, and Acyclovir Ointment in the Topical Treatment of Experimental Cutaneous Herpes Simplex Virus Type 1 Infection

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Received 6 January 1986/Accepted 15 April 1986

Topical foscarnet (PFA) and acyclovir (ACV) were compared in the dorsal cutaneous guinea pig model of herpes simplex virus type 1 infection. The relative order of efficacy was PFA cream > ACV cream > ACV ointment. In vitro studies demonstrated that PFA and ACV formulated in cream vehicles penetrated through guinea pig skin 7- to 10-fold faster than did ACV in ointment.

Foscarnet cream (sodium phosphonofluoridate [PFA]), acyclovir (ACV) cream, and ACV ointment are topical antiviral preparations which have received extensive clinical evaluation as treatments for recurrent herpes simplex labialis and genitalis in normal, nonimmunocompromised subjects. Modest success has been claimed for PFA cream (19, 26) and ACV cream (6, 7, 15, 25), while the majority of studies with ACV ointment in recurrent disease have failed to demonstrate any clinical benefit (3, 17, 20, 21, 24, 27). The present report compares these three treatments in the dorsal cutaneous guinea pig model of herpes simplex virus type 1 (HSV-1) infection.

ACV cream (5%), ACV ointment (5%), and the vehicles without ACV were provided by Burroughs Wellcome Co., Research Triangle Park, N.C. PFA cream (3% and 0.3%), the cream vehicle, and [14C]PFA were provided by Astra Lakemedal AB, Sodertalje, Sweden. The final specific activity of [14C]PFA in the present experiments was 540 cpm/μg of PFA. The concentrations of PFA and ACV inhibiting HSV-1 E115 plaque formation by 50% in Vero cells (8) were 14.2 and 0.14 μg/ml, respectively. Sixteen Hartley strain, outbred female albino guinea pigs weighing 350 to 400 g each were inoculated with HSV-1 E115 in six different areas on the depilated dorsal by multiple shallow punctures as originally described by Hubler et al. (14). Treatment of each infection site with 200 to 250 mg of cream or ointment was begun 24 h after inoculation and continued once per day for 3 days. The frequency of dosing was limited because some formulations were irritating to the skin. This protocol allowed for 12 comparisons between each drug and its contralaterally applied vehicle as well as comparisons of efficacy between each of the four different antiviral formulations. The severity of the infection at each treatment site was evaluated on the day after completion of the treatment regimen by examining the number of lesions, the diameter of lesions, the total lesion area, and the quantity of virus in excised skin. Further details of these procedures have been previously described (8, 22).

Full-thickness dorsal guinea pig skin was excised, and a portion of the skin was clamped across a Franz single-chambered glass diffusion cell (Crown Glass Co., Somerville, N.J.). The temperature of the receiver chamber was maintained at 37°C, and the top of the cell was open. A 200-mg amount of 0.3% [14C]PFA cream was applied to the exposed epidermal surface. Samples (200 μl) were withdrawn periodically from the receiver chamber and assayed for [14C]PFA with a Beckman liquid scintillation counter. Drug flux was determined from a steady-state plot of drug concentration versus time. Further details of these procedures are available elsewhere (8, 22, 23).

Lesion severity between drug and vehicle control-treated sites were compared by the Wilcoxon signed-rank test. The percent efficacies of different drug formulations were compared by the Mann-Whitney rank-sum procedure and in vitro flux values by Student’s t test. All probability determinations were two tailed, and a P of ≤ 0.05 was considered to be significant.

The results of the in vivo studies are shown in Table 1. Compared with lesion severity at vehicle control-treated sites, reductions of the mean number of lesions by 3% PFA, 0.3% PFA, ACV cream, and ACV ointment were 54, 36, 19, and -8%, respectively; reductions in the mean lesion area were 73, 52, 31, and 19%; and the reductions in mean lesion virus titer effected by these treatments were 90, 80, 75, and 60%. The greater reduction in number of lesions by 3% PFA, 0.3% PFA, and ACV cream compared with that of ACV ointment was statistically significant (P ≤ 0.03). Both 3% and 0.3% PFA were significantly more effective in reducing lesion area than was ACV ointment or ACV cream (P ≤ 0.05). PFA (3%) had a significantly greater effect on lesion virus titer than did ACV ointment (P = 0.03).

The penetration of 0.3% PFA from cream formulation through excised guinea pig skin is compared with prior data (9) on the skin penetration of 5% ACV in cream and in ointment (Fig. 1). The mean fluxes ± standard error of the mean of 0.3% PFA (0.51 ± 0.13 μg/cm² per h) and 5% ACV (0.36 ± 0.12 μg/cm² per h) from cream formulation were similar (P > 0.4) and were significantly greater than the flux of 5% ACV from ointment formulation (0.05 ± 0.01 μg/cm² per h, P < 0.05). ACV in cream exhibited a substantially longer lag period than did PFA before achieving steady-state penetration kinetics (Fig. 1).

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TABLE 1. Effects of topical therapy with 3% and 0.3% PFA creams, 5% ACV cream, and 5% ACV ointment on an experimental cutaneous HSV-1 infection of guinea pigs

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of lesions</th>
<th>Total lesion area (mm²)</th>
<th>Lesion virus titer (log₁₀ PFU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3% PFA cream</td>
<td>16 ± 9b</td>
<td>34 ± 20b</td>
<td>3.4 ± 0.8b</td>
</tr>
<tr>
<td>Cream vehicle</td>
<td>35 ± 9</td>
<td>127 ± 44</td>
<td>4.4 ± 0.3</td>
</tr>
<tr>
<td>0.3% PFA cream</td>
<td>25 ± 8b</td>
<td>62 ± 30b</td>
<td>3.9 ± 0.3b</td>
</tr>
<tr>
<td>Cream vehicle</td>
<td>39 ± 11</td>
<td>129 ± 32</td>
<td>4.6 ± 0.4</td>
</tr>
<tr>
<td>5% ACV cream</td>
<td>30 ± 13</td>
<td>83 ± 43</td>
<td>3.9 ± 0.8</td>
</tr>
<tr>
<td>Cream vehicle</td>
<td>37 ± 12</td>
<td>120 ± 58</td>
<td>4.5 ± 0.4</td>
</tr>
<tr>
<td>5% ACV ointment</td>
<td>41 ± 13</td>
<td>116 ± 52b</td>
<td>4.0 ± 0.6b</td>
</tr>
<tr>
<td>Ointment vehicle</td>
<td>38 ± 13</td>
<td>144 ± 47</td>
<td>4.4 ± 0.3</td>
</tr>
</tbody>
</table>

* Each antiviral formulation was tested 12 times.

* Significantly different from the vehicle control value.

The present studies demonstrate that the relative order of efficacy of the different formulations was as follows: 3% PFA cream > 0.3% PFA cream > ACV cream > ACV ointment. These findings show that topical PFA cream is more effective in the cutaneous guinea pig model than ACV cream, and we confirm prior reports that topical PFA cream (1) and ACV cream (2) are superior to ACV ointment in this experimental system. Our in vitro skin penetration studies indicate that the better results with topical PFA cream and ACV cream compared with ACV ointment are likely because of better drug delivery by the cream preparations.

The superior effect of PFA over ACV cream in our experimental animal model is paradoxical, considering the comparable rates of skin penetration of PFA and ACV from cream and the 100-fold greater virus-inhibitory potency of ACV against the HSV-1 strain used in these studies (see above) and other HSV-1 isolates (4). While we have recently demonstrated a good correlation for six nucleoside antiviral agents among drug flux through skin, in vitro virus-inhibitory potency, and in vivo drug efficacy by topical application (10), it is apparent from the present report and another recent study (5) that prediction of efficacy for some topically administered compounds will require consideration of additional factors. One potentially influential factor may be relatively high concentrations of the ACV-inhibiting substrate thymidine in guinea pig skin (5, 12, 16). However, since concentrations of thymidine in green monkey kidney cells have been estimated to be of similar magnitude (11), it is not clear whether our in vitro-to-in vivo correlations with Vero cells and the guinea pig model are distorted by differences in drug susceptibility to thymidine. Matthews et al. (18) have suggested that the relatively rapid rate of catabolism of ACV triphosphate mitigates the in vivo efficacy of intermittent doses of this agent, a factor which would not be manifested in routine in vitro assays of drug potency. Harmenberg et al. (13) have recently reported that ACV may be more susceptible to an inoculum effect than is PFA. Lastly, although the steady-state rates of drug flux of 0.3% PFA and 5% ACV cream were similar in this present study, penetration of ACV was markedly delayed, which could have adversely affected the in vivo activity of this formulation.

The minimal efficacy of topical ACV ointment in the present studies (19% reduction in lesion area) and in other experiments (8, 22, 23) parallels the disappointing results with this preparation in recurrent cutaneous human HSV infections in normal hosts (3, 17, 20, 21, 24, 27). Similarly, the better results (31 to 73% reduction in lesion area) seen with topical PFA and topical ACV cream in our model system find parallels in the recent clinical reports which indicate that these formulations may be more effective than ACV ointment (6, 7, 15, 19, 25-27). The human experience does not support superiority of topical PFA over ACV cream, as was found in the guinea pig. This may be due to therapeutic limitations in recurrent human herpes simplex disease; i.e., greater antiviral activity is unable to produce a better clinical result. Alternatively, there may be important differences in drug metabolism or competitive substrate concentrations (12) between human and guinea pig skin that influence antiviral activity. While there does not appear to be a difference in the penetration of ACV through human versus guinea pig skin (9), the rate of penetration of PFA through human skin has not been examined.

We thank Mark McKeough for excellent technical assistance. This work was supported in part by a grant from Astra Lakemedel AB.

LITERATURE CITED