Early, Patient-Initiated Treatment of Herpes Labialis with Topical 10% Acyclovir

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Received 5 October 1983/Accepted 10 February 1984

To determine whether topical acyclovir in polyethylene glycol could reduce the severity of herpes simplex labialis if applied immediately after onset of a recurrence, 10% acyclovir in polyethylene glycol ointment or polyethylene glycol alone was prospectively dispensed to 352 patients in a double-blind, randomized trial. Sixty-nine subjects initiated treatment in the prodrome (57%) or erythema (43%) stage and were followed by clinical and virological criteria. The healing time (6.0 days), maximum lesion area (42 mm²), vesicle or ulcer formation (91%), and maximum lesion virus titer (4.8 log₁₀ PFU) in the drug recipients were not reduced in comparison with those who received the vehicle (5.2 days, 30 mm², 75%, and 4.5 log₁₀ PFU, respectively). Topical acyclovir in polyethylene glycol was ineffective for the treatment of herpes labialis despite an optimum therapeutic opportunity.

Topical 5% acyclovir in polyethylene glycol (ACV-PEG; Zovirax ointment; Burroughs Wellcome Co., Research Triangle Park, N.C.) was approved in 1982 by the U.S. Food and Drug Administration for the treatment of limited cutaneous herpes simplex virus (HSV) infection in immunocompromised patients with normal immune systems. Topical ACV-PEG has effected a 32% reduction in the time to complete crusting and a 41% reduction in the duration of virus shedding as compared with placebo treatment among primary first-episode cases of herpes genitalis (2). In nonprimary first-episode genital disease, recurrent herpes labialis and genitalis, and recurrent herpes infections in immunocompromised patients, topical ACV-PEG has mainly influenced the duration of virus excretion (2, 4, 8, 10).

The modest response of HSV infections to topical ACV-PEG may be related to delayed initiation of treatment, inadequate penetration of ACV into lesions from the PEG vehicle, or both (2, 4, 8, 10). In our previous study of topical 5% ACV-PEG in recurrent herpes labialis, treatment was given four times per day for 5 days after an initial clinic visit; 98% of patients had lesions in the papule, vesicle, or ulcer stage when treatment was begun (8). The present report describes a second study of topical ACV-PEG for herpes labialis, in which early treatment was realized by dispensing medication prospectively to patients and allowing them to initiate treatment at home. The concentration of ACV was increased to 10%, and the dosing frequency was increased to eight times per day, but there was no change in the drug vehicle.

(This work was presented in part at the 22nd Interscience Conference on Antimicrobial Agents and Chemotherapy, Miami, Fla., 1982.)

MATERIALS AND METHODS

Patient population. A pool of eligible subjects was identified who were healthy, non-immunosuppressed persons with a history of three or more episodes of herpes labialis per year and virus culture-confirmed disease on at least one prior occasion. All volunteers were 18 years of age or older. Women were not pregnant and employed adequate means of contraception. One group of volunteers was studied in Boston, Mass., and one in Salt Lake City, Utah.

Study design. At the onset of the study, members of the patient pool were contacted. The study was explained, an Institutional Review Board-approved document of informed consent was signed, demographic and medical data were recorded, and a pregnancy test was performed on all women with child-bearing potential. Each subject was then dispensed a 15-g tube containing either 10% ACV-PEG or PEG alone. The tubes were ordered on the basis of a table of random numbers and dispensed consecutively to the participants. The code was maintained by the National Institute of Allergy and Infectious Diseases; it was not broken until the completion of the study. The patients were instructed to initiate topical therapy of a recurrence of herpes labialis in the prodrome or erythema stage. If a lesion was in the papule, vesicle, or ulcer/crust stage, therapy was not to be applied and patients were instructed to wait and attempt early treatment of a subsequent episode. Lesions were treated by rubbing on a 0.25-in. (ca. 0.6-cm) strip of ointment eight times per day during waking hours for 5 days. Additional doses could be applied if the medication was inadvertently removed by licking or rubbing. If treatment of a new lesion was begun, the patient was instructed to call the clinic and make an appointment to be seen within 24 h.

The first clinic visit was designated study day 0. Patients were seen in the clinic for the first 4 consecutive days and then on days 5, 7, 10, 14, 18, and 22 as necessary until the lesion was healed. At the first follow-up visit, women received a second pregnancy test; patients with a positive test were excluded from further treatment. At each visit, lesions were washed with saline and sampled for identification and titration of virus, and the painfulness, size, and stage of lesions were noted according to previously described procedures (5). The patients did not record personal observations but were instructed to come to the clinic if a change in the stage of the lesion occurred during the interval.
between scheduled visits. Rates of recurrence of lesions were determined for 12 months after the end of the study by having patients return stamped, self-addressed postcards to us once per month.

Virology. The virological methods and conventions used have been described previously (5). In addition, inoculated cells were washed once with medium immediately after virus adsorption, and 1 mM thymidine was included in the viral transport medium to minimize the effect of residual ACV in the specimen on the recovery of virus.

Data analysis. The duration of various measures of lesion severity was timed from the first sign or symptom of a recurrence. The two-tailed Mann-Whitney rank sum test was used for comparison of sets of values, and the chi-square test was used for proportions. A difference was considered significant at \( P \leq 0.05 \).

RESULTS

Recruitment of appropriately treated subjects. Over an 18-month period, ointment tubes were prospectively dispensed to 352 subjects. Sixty-nine subjects (20%) initiated treatment of a suspected new lesion in the prodromal or erythema stage and received adequate follow-up evaluation in the clinic to determine the course of their disease.

Comparison of treatment groups. Thirty-three of the 69 treated subjects received topical ACV-PEG, and 36 were treated with the vehicle placebo. The patient characteristics are shown in Table 1 by treatment group. The study subjects were equally distributed with regard to sex, age, race, and measures of prior severity of herpes labialis. More people who received ACV-PEG (67%) began treatment in the prodrome than did those who received the placebo (47%), but this difference was not statistically significant (\( P = 0.17 \)). The time between the first sign or symptom of a new episode and the beginning of treatment was a median of 2 min among ACV-PEG patients and a median of 8 min among those who received the vehicle. This difference was not significant.

Effect of topical ACV-PEG on the course of the disease. Ten measures of lesion severity were used to assess the course of the disease and to compare drug-treated subjects with those receiving the placebo. Lesion area, lesion pain, and lesion virus titer were examined according to the maximum value attained during the course of the lesion, time until resolution, and rate of change as measured by the difference between the value obtained on study days 0 and 1. The percentage of patients whose lesions progressed to the vesicle or ulcer/crust stage (or both) describes the pathological evolution of lesions in each group.

The results are shown in Table 2. For the total population, no statistically significant differences were noted between the treatment and placebo groups with regard to maximum lesion values and duration of lesion features. There was no consistent trend in the data toward a benefit from topical ACV-PEG; some of the measures were reduced among the treated patients, while others were increased in comparison with the placebo patients. The rates of decrease in lesion area and lesion virus titer between days 0 and 1 were greater in the drug-treated patients, and these effects were of borderline significance if a one-tailed statistical test is employed (\( P = 0.04 \) and 0.06, respectively). Among the 47 Utah subjects, the differences in the rates of change of area (median, –9 versus 0 mm²) and virus titer (median, –0.7 versus 0.0 log₁₀ PFU) were statistically significant (two-tailed test, \( P = 0.03 \) and 0.04, respectively). No other significant differences were seen in the Utah subgroup, and none were found among Boston patients. Drug treatment did not affect the frequency of subsequent recurrences.

DISCUSSION

The present report demonstrates that topical 10% ACV-PEG was not of clinical benefit to persons with recurrent herpes simplex labialis despite initiation of treatment in the prodrome or erythema stage of the disease. Of 33 patients treated with ACV-PEG, 30 (91%) progressed to the vesicle or ulcer stage, and complete healing took 6.0 days. The values for lesion severity of both the drug- and placebo-treated subjects are of lesser magnitude than similar measurements in our other studies of herpes labialis (1, 5, 8). This is most likely related to the patient-initiated design of the present trial, which resulted in the selection of milder lesions than are likely to be seen in a clinical trial where therapy is initiated after a visit to the investigator. We conclude from these results that topical ACV-PEG is of no value for the treatment of recurrent herpes labialis.

### TABLE 1. Characteristics of study subjects by treatment group

<table>
<thead>
<tr>
<th>No. of subjects</th>
<th>Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>38</td>
<td>33</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>35 (23–69)</td>
<td>34 (20–70)</td>
</tr>
<tr>
<td>Yr with disease</td>
<td>19 (1–51)</td>
<td>15 (1–50)</td>
</tr>
<tr>
<td>Three or more lesions/yr (%)</td>
<td>97</td>
<td>92</td>
</tr>
<tr>
<td>Lesions usually last 9 or more days (%)</td>
<td>67</td>
<td>56</td>
</tr>
</tbody>
</table>

Initiation of treatment of the current lesions

<table>
<thead>
<tr>
<th>Treatment begun in prodrome (%)</th>
<th>Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to start of treatment (min)</td>
<td>2 (0–420)</td>
<td>8 (0–999)</td>
</tr>
<tr>
<td>Time to first visit (h)</td>
<td>19 (4–42)</td>
<td>19 (2–55)</td>
</tr>
<tr>
<td>No. of doses before visit</td>
<td>6 (0–17)</td>
<td>5 (0–12)</td>
</tr>
</tbody>
</table>

* Median (range).
In previous reports we have stressed the importance of early initiation of treatment and adequate penetration of topicaly applied antiviral agents through the skin (5, 8). The lack of clinical effect of topical ACV-PEG in the treatment of recurrent mucocutaneous HSV infections is most likely attributable to inadequate penetration of ACV into the skin from the PEG vehicle, for the following reasons: (i) the negative findings in the present study despite initiation of treatment at the earliest possible moment; (ii) recent success with oral ACV in the treatment of recurrent herpes genitalis (3; R. C. Reichman et al., J. Am. Med. Assoc., in press); and (iii) poor penetration of ACV in PEG through guinea pig skin and enhancement of skin penetration and clinical effect in experimental cutaneous HSV infection in guinea pigs when dimethyl sulfoxide is the vehicle (6).

We experienced an unanticipated difficulty in obtaining patients who had initiated treatment of an episode of herpes labialis in the prodromal or erythematous stage, despite dispensing medication prospectively to 352 individuals who had a history of three or more recurrent episodes per year. In a previous report on the natural history of recurrent herpes labialis (7), 85% of patients interviewed indicated that they usually had prodromal symptoms, and 60% described prodromal symptoms on admission to the study with a lesion. In two subsequent studies of investigator-initiated antiviral therapy for herpes labialis (5, 8), only 5 of 441 subjects studied were in the prodromal or erythema stage at the time of their first clinic visit, despite admonitions to report for treatment at the earliest possible moment. In the present study, patients who believed they were experiencing prodromal symptoms of a new episode were frequently determined to be in the papular stage. True prodromal symptoms appear to be less common than might be construed from histories supplied by patients.

The present study evaluated lesion severity by measuring lesion area, pain, and virus titer according to maximum value, time until resolution, and rate of change. The percentage of subjects progressing to the vesicle or ulcer stage was also described, since these stages are the most painful and disfiguring to the patient. A marginal effect of topical ACV-PEG on lesion virus excretion was seen by the change in lesion virus titer between days 0 and 1, similar to results of our earlier study of topical 5% ACV-PEG (8). Our failure to identify more pronounced antiviral effects in the present study may be due to the small number of subjects and the mild lesions that were encountered (1). The results also indicated that lesion areas decreased at a significantly greater rate among ACV-treated subjects in Utah. Measurement of the rate of change of lesion severity may be the most sensitive means of identifying statistically significant differences between treatment and placebo groups in trials of topical therapy, as we noted in our prior study (8) and as was found as well by Whiteley et al. (10) in their trial of topical ACV-PEG in immunocompromised subjects.

Despite the demonstration that an oral antiviral agent can be beneficial in recurrent herpes genitalis, topical therapy of mucocutaneous HSV disease in normal hosts should still be aggressively pursued. Topical therapy offers the benefit of lower cost, minimal systemic exposure of the patient to the agent, and a route of application for useful antiviral agents which cannot be given by a systemic route because of toxicity or poor absorption. Penetration-enhancing agents have not been adequately explored in the formulation of topical antiviral preparations. In addition to dimethyl sulfoxide, dimethylacetamide, N,N-diethyl-m-toluamide, and 1-dodecylazacycloheptan-2-one (Azone; Nelson Research, Irving, Calif.) have been shown to enhance percutaneous penetration (9, 11). Agents such as these should be combined with an effective antiviral agent as a next step in the attempt to realize the full potential of topical treatment of cutaneous HSV infections.

ACKNOWLEDGMENTS
This work was supported in part by contracts NO-1-AI-52532 and NO-1-AI-52530 with the Antiviral Substances Program, the National Institute of Allergy and Infectious Diseases, and the National Institute of Dental Research, and by the Charles H. Dana Research Institute.

We acknowledge the careful work of Gay Wenerstrom, Carla Burton, Pat Kowalsky, and Mary Ellen Katz in the conduct of this study.

LITERATURE CITED