Therapeutic Options for Herpes Labialis, II: Topical Agents

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GOAL

To review the topical agents available for the treatment of herpes labialis

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Discuss the available topical agents for the treatment of herpes labialis.
2. Explain the research supporting use of topical agents for herpes labialis.
3. Describe the dosage regimens for topical agents in the treatment of herpes labialis.

CME Test on page 50.

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Herpes labialis is a common condition characterized by recurrent vesicular eruptions, primarily on the lips and perioral skin, causing pain and discomfort for millions of healthy adults each year. Over the last several years, the major focus of herpes research has been on the treatment of genital herpes. Recently, however, several studies have been conducted to evaluate the efficacy of therapies specifically for herpes labialis. In the second part of this series, we review topical therapeutic agents that are available in the treatment of herpes labialis and its associated symptoms.

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Herpes labialis is a common condition characterized by recurrent vesicular eruptions primarily on the lips and perioral skin. Most commonly caused by herpes simplex virus type 1 (HSV-1), this condition can significantly affect quality of life in patients with multiple recurrences, which may cause pain, embarrassment, and psychosocial distress. Oral HSV is the most easily acquired herpesvirus. Approximately 50% of Americans are seropositive for HSV-1 by the time they reach adolescence—by age 50 years, 80% to 90% carry the virus.[1] The first part of this series discussed oral antiviral agents in the treatment of herpes labialis. In the second part of this series, we review topical therapeutic agents that are available in the treatment of herpes labialis and its associated symptoms.

Topical Agents

For many years, acyclovir ointment was the only topical agent available for herpes labialis. Over the last several years, many new topical therapies have been investigated, and 3 have been approved by the US Food and Drug Administration (FDA). Currently, the 4 approved topical treatments available for herpes labialis include acyclovir ointment and cream (Zovirax®), penciclovir cream (Denavir®), and n-docosanol cream (Abreva®)(Table).

Acyclovir—Acyclovir *ointment*, which was first brought to market in 1982, is of questionable value in the treatment of recurrent herpes labialis.[2] Acyclovir *cream*, which appears to provide better absorption than the ointment, has been available in many countries outside the United States for more than a decade. To examine more comprehensively the safety and efficacy of this formulation, Spruance et al[3] conducted 2 independent, identical, parallel, randomized, double-blind, vehicle-controlled, multicenter clinical trials (N=686 in study 1 and N=699 in study 2). Healthy adults with a history of recurrent herpes labialis were randomized to receive acyclovir cream 5% or vehicle control and asked to self-initiate treatment 5 times a day for 4 days starting within 1 hour of recurrence onset. The mean duration of episodes was significantly decreased in both studies (study 1: 4.3 vs 4.8 days in treated vs placebo, respectively; study 2: 4.6 vs 5.2 days in treated vs placebo, respectively)($P \leq .05$). In addition, lesion pain was reduced significantly for subjects in both studies, though acyclovir cream did not prevent the development of classic lesions.[3]

In another study, Biagioni and Lamey[4] used infrared thermography to identify the prodromal stage of herpes labialis and treated the active area with acyclovir cream 5 times a day for 5 days. All patients (N=70) were evaluated at 72 hours thermographically and clinically, and localized increase in temperature over the symptomatic area was noted. The development of a clinical herpes lesion was prevented in 46% (32/70) of the patients. In the lesions that did develop (38/70), an 80% reduction in clinical lesion size was observed in 82% (31/38) of the subjects. The remaining 18% (7/38) of patients showed a reduction in healing time.[4]

In a recent publication, Seth et al[5] reported the use of a novel liposomal acyclovir topical *gel*. In this study, 10 patients with recurrent, mild facial infection were subjected to double-blind clinical evaluation, using a 1% liposomal acyclovir topical gel in a 5% hydroxypropylmethyl cellulose K4M gel base. The efficacy of plain acyclovir gel and liposomal acyclovir gel was compared by application to herpetic lesions 5 times a day for up to 8 weeks. In patients treated with liposomal acyclovir gel, a significant increase in the average percentage improvement of lesion healing was observed after 2 to 3 weeks of therapy ($P<.05$), along with a significant decrease in adverse events associated with acyclovir, including itching and burning ($P<.05$).[5]

Topical acyclovir also has been evaluated in combination with a topical steroid. Evans and colleagues[6] assessed the efficacy of a combination of acyclovir cream 5% and hydrocortisone cream 1% (ME-609) in treating experimentally UV radiation (UVR)–induced herpes labialis in patients with a history of recurrent herpes labialis. Starting on day 2, 380 subjects were randomized to receive ME-609 or vehicle control 6 times a day for 5 days. Fewer patients in the treatment arm developed delayed classic lesions. Statistically significant reductions in healing time (9.0 vs 10.1 days in treated and placebo groups, respectively; $P=.04$) and maximum lesion size (43 vs 60 mm in treated and placebo groups, respectively; $P=.07$) were noted in treated patients compared with patients given placebo. Overall, combination treatment with an antiviral and anti-inflammatory agent led to a reduction in the incidence of classic lesions, healing time, lesion size, and lesion tenderness.[6]

Penciclovir—Penciclovir, famciclovir's active metabolite, is FDA approved for episodic treatment of herpes labialis. Topical penciclovir cream 1% applied every 2 hours for 4 days can decrease the duration of lesion healing, pain, and viral shedding, as evidenced by several studies, with

Topical Therapies for Herpes Labialis*

Drug	FDA-Approved Indications	Dosage for Orolabial HSV
Acyclovir ointment 5% (Zovirax®)	Management of initial genital herpes and of limited, non–life-threatening mucocutaneous HSV infections in immunocompromised patients	Every 3 h 6×/d for 7 d
Acyclovir cream 5% (Zovirax)	Treatment of recurrent herpes labialis in adults and adolescents (12 years and older)	5×/d for 4 d
Penciclovir cream 1% (Denavir®)	Treatment of recurrent herpes labialis in adults	Every 2 h during waking hours for 4 d
Docosanol 10% cream (Abreva®)(OTC)	Treatment of orofacial herpes simplex	5×/d until healed

*FDA indicates US Food and Drug Administration; HSV, herpes simplex virus; OTC, over-the-counter.

some benefit in the early and late stages of lesion development.[7-10] Penciclovir interferes with viral replication and significantly limits both the severity and duration of cold sores.

Spruance et al[7] conducted a randomized, multicenter, double-blind, placebo-controlled, 2-arm, parallel trial to compare the safety and efficacy of penciclovir cream 1% with vehicle control cream in the treatment of recurrent herpes simplex labialis in immunocompetent patients. Treatment was self-initiated by the patient within the first hour of the first sign or symptom of a recurrence. A total of 2209 patients were enrolled and given study medication, 1573 of whom initiated treatment for a recurrence. Patients applied the medication every 2 hours during waking hours for 4 days. Healing of classic lesions was 0.7 days faster in penciclovir-treated patients compared with placebo-treated patients (median, 4.8 vs 5.5 days; $P<.001$). Reduction in duration of lesion pain was observed in penciclovir-treated patients compared with placebo-treated patients (median, 3.5 vs 4.1 days; $P<.001$). Lesion viral shedding also resolved faster in penciclovir-treated patients compared with those who received vehicle control cream (median, 3 vs 3 days; $P=.003$). Statistically significant reductions in time to healing and pain resolution occurred with topical penciclovir cream when treatment was initiated in the early (prodrome or erythema) stage or late (papule or vesicle) stage of the lesion.[7]

Boon et al[8] evaluated the efficacy and tolerability of penciclovir cream versus placebo control (purified water) in treating sunlight-induced herpes labialis. Healthy patients (mean age, 38.3 years; range, 18–81 years) with a history of sunlight-induced herpes labialis self-initiated treatment with either penciclovir cream (n=266) or purified water (n=275) within one hour of development of the signs and symptoms of a recurrence.

A significant reduction in the time to lesion healing ($P<.001$), with a reduction in median time of up to 2 days, was noted. There was a significant reduction in maximum lesion area ($P=.008$), faster resolution of lesion-associated symptoms ($P=.026$), reduction in pain duration ($P\leq.040$), itching ($P\leq.032$), burning ($P\leq.028$), and tenderness ($P\leq.026$). The daily self-assessment of lesion attributes showed significantly fewer severe or extreme assessments of lesion size ($P\leq.003$),

noticeability ($P \leq .003$), amount of scab or crust ($P \leq .003$), raised or swollen area ($P \leq .040$), soreness or tenderness ($P \leq .043$), and overall severity ($P \leq .001$) throughout the study.[8]

Recently, Raborn et al[9] conducted 2 randomized, double-blind, parallel-group clinical trials to compare the efficacy and safety of topical penciclovir cream 1% for recurrent herpes labialis. Of the 4573 immunocompetent patients with a history of recurrent herpes simplex labialis (defined as 3 or more episodes per year) that were enrolled in the study, 3057 patients initiated treatment (1516 with penciclovir cream 1% and 1541 with placebo). Patients were instructed to apply medication 6 times a day for the first day and thereafter every 2 hours during waking hours for 4 consecutive days. In the treatment group, patients lost classic lesions 31% faster than did those in the placebo group and experienced 28% faster resolution of lesion pain. Significant benefits were achieved with penciclovir use whether treatment was initiated in the early stages ($P = .001$) or later stages ($P = .0055$) of the recurrence.[9]

Lin and associates[10] compared the efficacy of topical penciclovir cream 1% versus acyclovir cream 3% in the treatment of herpes labialis. In a randomized, double-blind, multicenter trial, 248 patients with a history of herpes labialis were randomly allocated to 1 of the 2 treatment groups (n=124 each) to receive either penciclovir cream 1% or acyclovir cream 3%. Before treatment (day 0) and at every visit (days 3, 5, and 7), signs and symptoms scores were recorded by the same physician. Two hundred twenty-five patients completed the study. No significant differences were noted in efficacy, clinical cure rate, and safety between the 2 groups; however, a trend toward a shorter time to resolution of symptoms, cessation of new blisters, and loss of crust ($P \leq .008$) was noted in penciclovir-treated patients compared with acyclovir-treated patients. In addition, signs and symptoms scores in penciclovir-treated patients were significantly lower than those in the acyclovir-treated patients on days 5 ($P < .01$) and 7 ($P < .05$), supporting the finding that topical penciclovir cream 1% is at least as convenient and effective as acyclovir cream 3% in the treatment of herpes labialis.[10]

A susceptibility program was established by Sarisky et al[11] to assess the resistance profile for serial HSV isolates from immunocompetent patients with recurrent herpes labialis. The isolates were obtained throughout a 4-day treatment period with topical penciclovir cream 1% or placebo. Two isolates (2/1035; 0.19%), representing 0.34% of the patients (2/585), were confirmed to be penciclovir resistant. These were highly resistant to penciclovir (50% inhibiting concentration [IC_{50}], >55 µg/mL) and were isolated less than 17 hours after the start of patient-initiated treatment. However, subsequent isolates on days 2 and 3 from the same patients were completely susceptible to penciclovir cream (IC_{50}, <2.0 µg/mL). None of the patients were found to have penciclovir-resistant species at the end of acute treatment, regardless of treatment group. Overall, the prevalence of penciclovir resistance was found to be similar to that of acyclovir resistance (ie, 0.3%) reported in immunocompetent untreated populations.[11]

N-docosanol—Docosanol is a compound that inhibits herpes virus replication by blocking fusion of the viral envelope with the plasma membrane and can potentially limit both the duration and severity of herpes labialis.[2] Presently, docosanol 10% cream is approved by the FDA as an over-the-counter agent for application 5 times a day during episodes of herpes labialis. In one small clinical trial with 63 patients, n-docosanol 10% cream significantly reduced the healing time of patients' herpes labialis episodes compared with stearic acid–containing placebo cream.[12] Application of n-docosanol 10% cream early in the prodrome or erythema stage of a recurrent episode of herpes labialis shortened mean healing time by approximately 3 days compared with late treatment with n-docosanol 10% cream and early or late treatment with the placebo. A subsequent larger study with 846 patients found no benefit.[13] Because of a concern that the vehicle may have had a beneficial effect on herpes labialis and masked an effect by n-docosanol, a polyethylene glycol control preparation was created.[14]

With this new preparation, Sacks et al[15] conducted studies to determine whether docosanol 10% cream is efficacious compared with placebo in the topical treatment of episodes of acute herpes simplex labialis. Two identical double-blind, placebo-controlled studies were conducted at a total of 21 sites. Otherwise healthy adults, with documented histories of herpes labialis, were randomized to receive either docosanol or polyethylene glycol placebo. Subjects were instructed to initiate therapy in the prodrome or erythema stage of an episode. Treatment was administered 5 times a day until healing occurred (ie, the crust fell off spontaneously, or there was no longer evidence of an active lesion) with twice-daily visits. The median time to healing in the 370 docosanol-treated patients was

4.1 days, 18 hours shorter than that observed in the 367 placebo-treated patients ($P=.008$). The docosanol group also exhibited reduced times from treatment initiation to (1) cessation of pain and all other symptoms (itching, burning, and/or tingling; $P=.002$), (2) complete healing of classic lesions ($P=.023$), and (3) cessation of the ulcer or soft-crust stage of classic lesions ($P<.001$). Aborted episodes were experienced in 40% of docosanol recipients versus 34% of placebo recipients ($P=.109$). Adverse experiences with docosanol were mild and similar to those with placebo. The authors concluded that docosanol applied 5 times a day is safe and effective in the treatment of recurrent herpes labialis.[15]

Because in vitro studies have shown that n-docosanol can enhance the antiviral activity of nucleoside analogs against the replication of herpesviruses, clinical studies of this combination will be of interest.[2]

Comparative Efficacy of Topical Treatments

McKeough and Spruance[14] evaluated the comparative efficacy of penciclovir cream, acyclovir cream, n-docosanol cream, and acyclovir ointment in a guinea pig model of cutaneous HSV-1 disease. The backs of guinea pigs were infected with HSV-1 using a vaccination instrument. Active treatments and corresponding vehicle controls were applied for 3 to 5 days beginning 24 hours after inoculation. After completion of treatment, the animals were killed, and the severity of the infection was assessed from the number of lesions, total lesion area, and lesion virus titer.[14]

Penciclovir cream effected modest reductions in lesion number (19%), area (38%), and virus titer (88%) compared with its vehicle control, and each of these differences was significantly greater ($P<.05$) than the reductions effected by acyclovir ointment (0%, 21%, and 75%, respectively). The acyclovir cream effect (reductions of 4%, 28%, and 77%, respectively) was less than that of penciclovir cream, and this difference was confirmed by 2 additional head-to-head experiments. Two experiments with n-docosanol cream failed to show statistically significant differences by any parameter between n-docosanol cream and vehicle control-treated sites or between n-docosanol and untreated infection sites.[14]

In this model, the efficacy of penciclovir cream was greater than acyclovir cream, acyclovir cream was greater than or equal to acyclovir ointment, and acyclovir ointment was greater than n-docosanol cream. The authors noted that because their model was designed to evaluate compounds that function primarily through antiviral activity, the negative findings with n-docosanol in these studies do not exclude that it might work clinically through other mechanisms.[14]

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