Combination Treatment with Famiclovir and a Topical Corticosteroid Gel versus Famiclovir Alone for Experimental Ultraviolet Radiation–Induced Herpes Simplex Labialis: A Pilot Study

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To investigate the efficacy of corticosteroids for the treatment of herpes labialis, we compared famciclovir (Famvir, 500 mg 3×/day po [per os] for 5 days) and topical fluocinonide (0.05% Lidex Gel 3×/day for 5 days) with famciclovir and topical vehicle control for experimental ultraviolet radiation–induced herpetic recurrences. We irradiated 49 volunteers, and 29 (60%) of 48 developed signs or symptoms of a recurrence. They self-initiated treatment, and we were able to evaluate them. There was a trend in the combination group toward more aborted lesions, compared with those who received antiviral therapy alone (7 [41%] of 17 vs. 1 [8%] of 12; P = .09). Combination therapy significantly reduced the median maximum lesion size (48 vs. 162 mm2; P = .02) and the number of patients who experienced lesion pain (10 [59%] of 17 vs. 12 [100%] of 12; P = .02). Adverse events were minimal. Corticosteroids in combination with an antiviral agent may be safe and beneficial for episodic treatment of herpes labialis. Larger studies are needed to confirm these findings.

Treating herpes labialis with antiviral drugs has been a major challenge for investigators over the past 3 decades [1, 2], and the treatment benefits to date have been modest [3–6]. Other approaches to therapy need to be considered.

Corticosteroids have been used as an adjunct to anti-infective agents in several bacterial and fungal diseases, to reduce inflammation associated with the immune response that contributes to the pathogenesis of the illness [7, 8]. Corticosteroids have a modest additive benefit when used in conjunction with antiviral drugs in herpes zoster [9]. There have been no published clinical trials of the use of corticosteroids in recurrent herpes genitalis or labialis. However, the severity of ultraviolet radiation (UVR)–induced herpetic recurrences has been shown to correlate with herpes simplex virus (HSV) antigen–induced peripheral blood mononuclear cell interferon–γ and interleukin–2 production [10]. More recently, Awan et al. [11, 12] constructed a murine model of recurrent HSV disease by adoptive transfer of sensitized leukocytes and found treatment with anti-inflammatory drugs to be beneficial.

We conducted a pilot trial of the combination of topical corticosteroids and a systemic antiviral agent for the treatment of herpes labialis. Our primary objective was to determine the safety of topical corticosteroids in the treatment of this disease. To carefully control patient self-medication and lesion severity assessments, we used the experimental UVR-induced herpes labialis model system [13], in which the recurrence develops within 1 week of enrollment in the study.

Methods

Study synopsis. Patients with a history of sunlight-induced herpes labialis were located by advertisement and were screened for eligibility, as detailed below. Patients were exposed to UVR on a portion of the lips to induce a recurrence of herpes labialis and were given medication with instructions to start treatment within 1 h of the first signs or symptoms of a recurrent episode developing in the 7-day period after UVR exposure. Patients received the topical corticosteroid and the systemic antiviral agent or the systemic antiviral agent and a topical vehicle control in a double-blind fashion. Lesion severity was assessed by patient diary cards and by scheduled follow-up visits to the clinic.

Study medication. Patients received famciclovir (Famvir, 500 mg 3×/day po [per os] for 5 days) and topical fluocinonide (0.05% Lidex Gel 3×/day for 5 days) or identical dosing with famciclovir and topical vehicle control. The 2 treatment groups were of equal size. All study medication was obtained commercially. Famciclovir came as 500-mg tablets. Fluocinonide and the gel vehicle control were provided in identical white plastic tubes by Richard Rasmuson (University Pharmacy, Salt Lake City, UT). The appearance of the 2 gels was the same. The tubes were randomized and serially numbered by
Brett Sower (University of Utah Health Sciences Center). There was no stratification. The tubes were dispensed by the study coordinator in such a way that neither the patients nor the investigators knew the treatment assignment. The treatment code was held by the research pharmacist and the Data Safety and Monitoring Board. Patients were given study medication in a blinded manner immediately after UVR exposure. They had instructions to self-initiate treatment within 1 h of the appearance of the first signs or symptoms of a recurrent episode within the next 7 days (episodic therapy). Whereas both prophylactic and preemptive drug administration have been used successfully in previous treatment studies with experimental UVR-induced lesions [13–15], timing therapy in either of these fashions was not considered appropriate to assess the value of corticosteroids. In addition, administration of corticosteroids in the absence of lesions might decrease UVR-induced inflammation and interfere with the induction of a recurrence.

**Patient population.** The study was conducted at the University of Utah Health Sciences Center, Salt Lake City. To be eligible, patients had to be ≥18 years old and had to have a self-described history of recurrent herpes labialis (vesicular lesions on the vermilion border of the lips or perioral skin) after sun exposure. In addition, women of childbearing age could not be pregnant or breast-feeding and must have been using an accepted method of birth control. Patients were not eligible if they had a history of or laboratory evidence of a significant medical disorder; if they had received any antiviral drug, investigational drug, or vaccine; if they had an episode of herpes labialis within the 30 days before enrollment; if they had a psychiatric disorder; or if, in the opinion of the investigator, they were considered unreliable or unable to follow protocol directions.

**Clinic visits.** At a screening visit, the inclusion and exclusion criteria were reviewed, the patient’s history of herpes labialis was recorded, a limited physical examination was done, and, for women, a urinary pregnancy test was done (Clearview HCG II; Wampole Laboratories, Carter-Wallace, Inc., Cranbury, NJ). Within 1 week of the screening visit, the patient’s sensitivity to UVR was evaluated by determination of the minimal erythema dose. Within 1 week of the minimal erythema dose determination, patients underwent UVR exposure (study day 0). Patients returned to the clinic on study days 1, 2, 4, 8, and 21 after UVR exposure and were evaluated for the development of lesions, as described below. If lesions developed, the patients were followed daily for 3 days and then 3 times a week until the lesions healed. A final visit to assess lesion development in the second week was done between days 13 and 15 after UVR exposure.

**Patient diary.** Patients were given a diary in which they recorded their assessment of lesion stage and pain 3 times a day until the lesions healed.

**Minimal erythema dose determination and exposure of the lips to UVR.** Patients were evaluated for UVR sensitivity and irradiated as described elsewhere [15].

**Evaluation of lesions.** Only lesions that developed during the 7-day period after UVR exposure were treated and evaluated. The first lesion to develop was termed the primary lesion. Lesions that developed subsequently and that were located >1 cm from the primary lesions were termed secondary lesions. Lesions that developed later and that were within 1 cm of the primary lesions were considered extensions of the primary lesion and were included in the primary lesion evaluation. Lesions were further categorized as aborted (those progressing no further than the papule stage) and classical (those progressing to vesicles, ulcers, hard crusts, or a combination of these). Lesions that developed during study days 8–14 were termed posttreatment lesions. Posttreatment lesions and secondary lesions were noted but not measured or followed.

Clinical assessment of lesion severity was made by use of investigator and patient observations of lesion stage, size, and pain. Lesion stages were as follows: prodrome, erythema, papule, vesicle, ulcer/soft crust, hard crust, residual swelling/dry flaking, and normal skin. Lesions were defined according to the most advanced stage present, with the following exceptions: a lesion was at the hard crust stage when ≥50% of the lesion area had a hard crust, residual swelling/dry flaking required that the hard crust be completely gone, and “normal skin” meant the absence of any abnormalities other than residual erythema. Two definitions of lesion healing were used: a return to normal skin or a loss of hard crust. When there were discrepancies between the investigator’s and patient’s assessments of lesion stage, the investigator’s assessment was used.

Lesion area was determined for papular aborted lesions and for classical lesions as the product of lesion length and width; since this excluded lesions for which the most advanced stage was erythema, the numbers of cases used in calculations of lesion area were less than the total number of lesions.

Patients determined the presence and intensity of pain. For those patients in whom pain came and went more than once, the duration of pain was recorded from its first occurrence until the first record of its permanent absence. Pain intensity was recorded on a visual analog scale.

**Virus isolation and titration.** Lesion specimens for virus isolation and procedures for virus identification and quantification have been described elsewhere [15, 16].

**Data analysis.** All patients who received ≥1 dose of medication were included in the intent-to-treat population. The intent-to-treat population was used to analyze safety. We performed efficacy analysis on patients who did not have major protocol violations. Efficacy variables included time to healing, lesion maturation (the proportion of patients who developed aborted lesions), maximum lesion area, the proportion of patients with pain, time to loss of pain, the proportion of patients with a positive virus culture, and maximum lesion virus titers.

The proportions of patients in each treatment group that developed a safety or efficacy event were compared by Fisher’s exact test. Other measures of lesion severity, which were continuous variables, were examined by the Mann-Whitney rank sum test. For time to healing, time 0 was the start of medication. For the duration of individual lesion stages, pain, and virus excretion, time was calculated from the appearance of the event in question (stage, pain, or virus) until the first record of its permanent absence. All probability determinations were 2-tailed, and \( P < .05 \) was considered significant.

**Results**

**Characteristics of the study population.** Forty-nine patients were assigned randomly to study treatment and took study medication, and these patients comprised the intent-to-treat
population. Seventy-one percent of the intent-to-treat patients were women, the mean age was 41 years, and all subjects were white. There were no differences in these demographic features between the treatment groups. There was a trend toward a history of more-frequent herpes labialis episodes in the famciclovir plus corticosteroids group, compared with the famciclovir-alone group (6 ± 4 episodes per year vs. 4 ± 2 episodes per year, respectively; P = .07). Compliance with study medication and clinic visits was excellent, except for 1 patient who failed to start medication until 2 days after lesion onset. This patient was excluded from the efficacy analysis.

Induction of lesions. Overall, 29 (60%) of 48 patients developed lesions during the 7 days after UVR exposure (figure 1) and could be evaluated for drug efficacy. Of these 29 patients with lesions, 8 experienced aborted lesions, and 21 developed classical lesions. Twenty-eight of 29 lesions developed in the UVR-exposed skin site, and 1 occurred within 1 cm of the exposed area. Seven of 29 patients had secondary lesions that developed ≥1 days after the primary episode. Seventeen lesions developed among 23 patients randomized to combination therapy, and 12 lesions developed among 25 subjects assigned to famciclovir alone (P = .08), possibly a reflection of the history of more-frequent lesions in the combination therapy group. Three (18%) of 17 patients in the combination group and 5 (42%) of 12 in the control group had lesions that began with a prodrome (P = .22), a hypothetical marker of susceptibility to antiviral drugs [17]. There were 2 posttreatment lesions, 1 in a patient who received corticosteroids and 1 in an individual who never used study medication.

Initiation of therapy. The time from the first sign or symptom of a recurrence to initiation of trial medication ranged from 0 to 11 h. There was no significant difference between the combination therapy and control groups in the median time to start of therapy (0.5 vs. 0.6 h, respectively; P = .42). At the start of treatment, 5 (29%) of 17 patients in the corticosteroid group and 7 (58%) of 12 patients in the control group (P = .15) had lesions in an “early” pathologic stage (prodrome or erythema), lesions potentially more susceptible to antiviral drugs [3, 4]. The remaining lesions were in the papular or vesicular stage at the start of treatment.

Lesion maturation. There was a trend toward a higher frequency of aborted lesions in the combination therapy group. Seven (41%) of 17 lesions were aborted lesions in the combination therapy group, compared with 1 (8%) of 12 among those treated with famciclovir alone (P = .09).

Lesion area. Maximum lesion area was markedly reduced in the combination therapy patients, compared with the group that received famciclovir alone. As shown in figure 2A, the median maximum lesion area for those treated with famciclovir and corticosteroids was 48 mm², compared with 162 mm² for the control group (P = .02). Because this difference might have been due to the higher frequency of aborted lesions among those treated with famciclovir and corticosteroids, we repeated the calculations among only those patients who developed classical lesions. As shown in figure 2B, a strong trend toward smaller lesions for those on combination therapy still was apparent in the classical lesion subgroup, although the difference did not reach statistical significance (P = .09).

Lesion healing time. As shown in figure 3A, there was a trend toward a faster healing time to normal skin among patients on combination therapy, compared with that of famciclovir alone (5.3 vs. 8.9 median days, respectively; P = .06). Because this difference might have been because of the higher frequency of aborted lesions among those treated with famciclovir and corticosteroids, we repeated the calculations among only those patients who developed classical lesions. As shown in figure 3B, the difference between treatment groups persisted but no longer was statistically significant (6.6 vs. 10.3 median days; P = .32). When the definition of healing was changed to loss of crust (figure 3C), our usual end point in herpes labialis trials, time to healing of classical lesions was the same for the 2 treatment groups (6.6 vs. 5.2 median days; P = .86).

Figure 1. The development of herpes labialis in 29 patients after ultraviolet radiation exposure among 48 drug- and placebo-treated subjects. Top, Results for 17 subjects treated with famciclovir and corticosteroids are shown. Bottom, Results for 12 subjects treated with famciclovir alone are presented. Aborted lesions are shown (hash-marked squares), and classical lesions are also represented (solid squares). Definition of lesion types is discussed in Methods.

Figure 2. The maximum lesion area is presented by treatment group. Horizontal bar, the median value. A, All lesions. B, Classical lesions.
Lesion healing time is presented by treatment group. Horizontal bar, the median value. A, Healing time for all lesions from the start of medication to normal skin. B, Healing time for classical lesions from the start of medication to normal skin. C, Healing time for classical lesions from the start of medication to loss of crust.

Lesion pain. There was a marked difference between the treatment groups in the frequency of patients who reported lesion pain. Only 10 (59%) of 17 patients in the combination group reported pain, compared with 12 (100%) of 12 in those who received famciclovir alone (P = .02). This difference persisted among the subgroup of patients with classical lesions (6 [60%] of 10 vs. 11 [100%] of 11, respectively; P = .04). Among those who reported pain, there was no difference between treatment groups in the maximum degree of pain, the duration of pain, or the area under the curve of pain intensity and time (data not shown).

Lesion virology. Twenty-seven of 29 patients had ≥1 swab specimens taken from their lesions for virus isolation. There was no difference in the frequency of virus culture-positive cases between the combination treatment group and the group treated with famciclovir alone (7 [44%] of 16 and 5 [45%] of 11, respectively; P = 1.0). Similarly, there was no difference between the two groups in the maximum lesion virus titers (medians, 3.7 and 3.2 log₁₀ plaque-forming units [pfu]/mL, respectively; ranges, 1.9–5.3 and 1.2–4.9 log₁₀ pfu/mL, respectively; P = .81).

Adverse reactions. Nine (53%) of 17 patients in the combination therapy group and 8 (67%) of 12 patients in the control group that received famciclovir alone (P = .70) reported ≥1 events. Five (29%) of 17 patients in the combination therapy group and 2 (17%) of 12 patients in the control group (P = .70) reported local application-site symptoms (stinging and burning). These were of mild intensity and did not result in any interruption of therapy. Five (29%) of 17 patients in the combination therapy group and 7 (58%) of 12 patients in the control group (P = .70) reported mild- to moderate-intensity central nervous system disorders (such as headache), or gastrointestinal, respiratory, or constitutional symptoms. No serious adverse reactions were reported.

Discussion

Corticosteroids have anti-inflammatory and immunosuppressive effects through many molecular mechanisms, including synthesis of lipocortins, enzyme inhibition, modulation of transcription, including down-regulation of genes for a variety of inflammatory cytokines, mRNA stability, leukocyte migration inhibition, adhesion molecule expression, and apoptosis of immature thymocytes [18–20]. The suggestions of efficacy in this trial are consistent with an anti-inflammatory and immunosuppressive activity (more aborted lesions, smaller lesions, and fewer persons with pain) and are different from the effect of antiviral drugs (faster healing). There may be more aborted lesions among patients treated with corticosteroids because the intraepithelial pressure is less and because protease activity, which could degrade the stratum corneum, is reduced.

This study found no increase in adverse events attributable to topical corticosteroids. Corticosteroids might increase the magnitude and duration of lesion virus shedding, but virus excretion was not increased significantly in the steroid arm, probably because a potent antiviral drug was used also. The question of whether corticosteroids could be used safely alone was not addressed in this study. Topical corticosteroids can cause thinning of the skin with long-term use and generally are not recommended for use on the face [21]. Whether repeat, intermittent, short-term use of topical corticosteroids would have this complication needs to be evaluated in a larger, longitudinal study.

The choice of therapeutic agents for this proof-of-concept pilot study was made on the basis of several considerations. High-dose peroral famciclovir was chosen because it is the most potent antiviral drug regimen studied to date in our clinic and, therefore, offered the best guarantee to corticosteroid-treated patients that the immunosuppressive activity of the corticosteroid would not increase virus replication and lesion severity [15]. Peroral administration of corticosteroids was not considered appropriate or necessary. We chose a high-potency, topical class II steroid to ensure good anti-inflammatory and immunosuppressive activity in the lesion. We selected a gel formulation because gels are less substantive than creams and ointments and are, therefore, less likely to be licked or wiped off...
the lips inadvertently by the patient [22]. A treatment course of 5 days is our standard for experimental therapy and corresponds to the average duration of recurrent herpes labialis lesions. Whether less antiviral drug, a less-potent steroid, and a shorter course of therapy for one or both moieties could be equally or more effective is a valid subject for speculation, but the point presently is moot.

There was a mixed effect of combination therapy on lesion healing time depending on the way we defined healing (figure 3). If the subgroup of patients with classical lesions was examined and time to loss of crust was used as the end point (figure 3C), then there was no suggestion of any benefit in the corticosteroid group, compared with those receiving famciclovir alone (6.5 vs. 5.2 days, respectively). The healing times were similar to what we have reported elsewhere in a dose-ranging study of famciclovir [15]. This is not surprising, since in this construction, the pathophysiologic process to be ameliorated by corticosteroids would be primarily wound healing, an event potentially prolonged, not hastened, by corticosteroid administration. We have used this definition of healing time routinely in our studies of antiviral agents because we think it reflects the end of the morbidity for most patients and is assessed easily and reliably. As shown in figure 3B and 3C, the value for median healing time of classical lesions in the control group was prolonged 2-fold when “normal skin” instead of “loss of crust” was used as the end point (10.3 vs. 5.2 days, respectively). Accordingly, corticosteroids might benefit healing time in a larger study if “normal skin” were the end point, but this should not be confused with wound healing, and the clinical significance of the effect might be unclear.

In conclusion, analysis of these data shows that topical corticosteroid and antiviral therapy together appear to produce a major improvement in the clinical course of herpes labialis, compared with treatment with the antiviral agent alone. Although a double-placebo arm was not part of the study, it is logical to expect that combination therapy would show an even greater degree of benefit against no treatment. There were no significant adverse reactions. Because this was a pilot study, it is essential to confirm these results in larger, definitive trials. Application of these results to the treatment of recurrent herpes genitalis is premature and unwarranted until specific data for this different disease are forthcoming.

References