Recurrent Herpes Simplex Labialis: Selected Therapeutic Options

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Abstract

Recurrent infection with herpes simplex virus 1 (HSV1), called herpes simplex labialis (HSL), is a global problem for patients with normal immune systems. An effective management program is needed for those with frequent HSL recurrences, particularly if associated morbidity and life-threatening factors are present and the patient's immune status is altered. Over the past 20 years, a variety of antiviral compounds (acyclovir, penciclovir, famciclovir, valacyclovir) have been introduced that may reduce healing time, lesion size and associated pain. Classical lesions are preceded by a prodrome, but others appear without warning, which makes them more difficult to treat. Various methods of application (intravenous, oral, topical) are used, depending on whether the patient is experiencing recurrent HSL infection or erythema multiforme or is scheduled to undergo a dental procedure, a surgical procedure or a dermatological face peel (the latter being known triggers for recurrence). This article outlines preferred treatment (including drugs and their modes of application) for adults and children in each situation, which should assist practitioners wishing to use antiviral therapy.

MeSH Key Words: *antiviral agents/therapeutic use; drug administration routes; herpes labialis/drug therapy*

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Infection with herpes simplex virus 1 (HSV1), called herpes simplex labialis (HSL), is a continuing global public health problem for which various forms of treatment have had minimal impact. The most common form of infection with this virus, primary gingivostomatitis (the precursor of recurrent HSL infection), usually occurs in preschool or kindergarten children, adolescents and young adults, and does not recur in the same form.[1] However, recurrences of HSL manifesting as cold sores can continue throughout adulthood (**Fig. 1**). Typically, the primary infection is more severe than the recurrences, and viral shedding is greatest in the initial episode, although the amount of virus shed appears unrelated to the severity of the attack.[2] The patient may experience fever, loss of appetite and general malaise, along with multiple intraoral vesicles that quickly burst, leaving painful ulcerations. Children especially may become dehydrated because of the pain associated with swallowing.

After the primary infection, the virus ascends the sensory nerve axons and establishes chronic, latent infection in various ganglia, including trigeminal, facial and vagus ganglia.[2] There is evidence that latent infection also develops in tissues such as the epithelium of the lips.[3] The dormant virus then awaits a "trigger" to reactivate it. Triggers may include sun exposure, psychological stress, onset of menses, illness and physical trauma.[1] Many patients experience a burning, tingling or itching sensation (a prodrome) at the location where a lesion later appears. HSL can recur frequently or infrequently. There is much less viral shedding during HSL recurrence than during the initial episode, but pain, ulceration and swelling may occur at each affected site. Currently available therapies have not been particularly effective in reducing these symptoms once the lesion has formed. This is reasonable, given that a classical ulcerated HSL lesion must heal by secondary intention.

A "skin trigger" model for HSL infection has been proposed to explain why some lesions occur immediately after the trigger, are difficult or impossible to block and are associated with increased susceptibility of the lip to lesion formation.[3] On the basis of this theory, it has been suggested that "nonclassical" lesions, those not preceded by a prodrome, are caused by dormant virus resident in epithelium dendrites.[4] This dormant virus has an anatomical "head start" in the race to the mucosa, and lesions appear

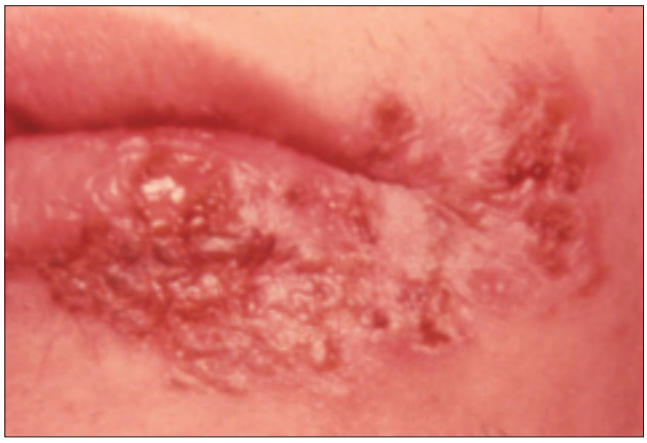

Figure 1: *Herpes simplex labialis on a 19-year-old man. Eruption followed a prodrome within 24 hours. The lesions first appeared as vesicles that ruptured. The episode was similar to 3 others experienced by the patient and was accompanied by a low-grade fever and malaise. University of Alberta department of dentistry teaching slide.*

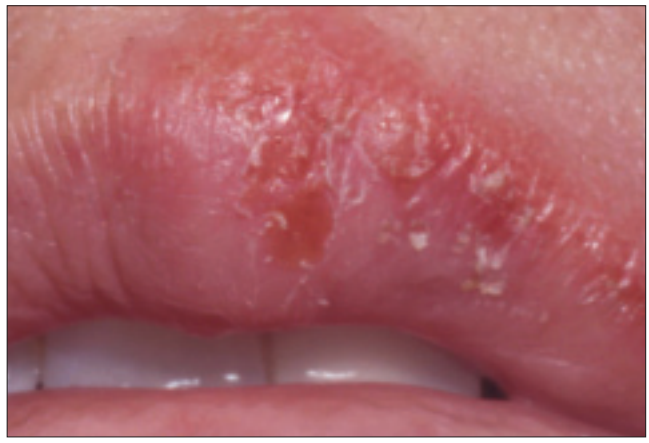

Figure 2: *Lesion that appeared on the maxillary vermilion border of the lip of a 22-year-old woman 48 hours after the lip was irradiated with an artificial ultraviolet light source. American Dental Association oral pathology teaching slide.*

within 24 to 36 hours after a trigger such as ultraviolet light. These so-called immediate lesions have no warning prodrome and respond less favourably to treatment, as the patient has no opportunity to begin treatment before the lesion appears. Once the lesion has formed, the normal healing process occurs, and resolution can take up to 14 days. Consequently, this type of lesion responds only to prophylactic therapy, if it responds at all.[5]

It has been suggested that classical lesions (those preceded by a prodrome) be monitored to understand their pattern of development.[6] It is postulated that these lesions arise from dormant virus harboured in the ganglia. When a trigger occurs, the dormant virus begins to replicate, leaves the ganglion and makes its way along peripheral nerves to cause vesicles at the specific mucosal site. Repeated viral waves can affect other branches of a single neuron, causing a larger lesion to form as smaller vesicles coalesce.

Preventive therapy such as sun block or an antiviral drug would be the management program of choice for patients experiencing frequent recurrences. Such therapy could suppress an individual patient's response to a specific trigger. However, such suppression would not be recommended for patients experiencing just 1 or 2 lesions a year[2,7] to reduce the possibility of developing a drug-resistant viral strain. For patients experiencing 3 to 5 episodes yearly, suppression might be considered, depending upon disease history, lifestyle, employment issues and possible exposure to susceptible, immune-suppressed associates. For certain patients, prevention and suppression are essential and can save lives or reduce morbidity: patients with 6 or more recurrences each year,[8] those in whom recurrence triggers erythema multiforme (EM)[9] and those whose immune systems have been suppressed by disease or transplant management protocols.

Antiviral drugs are approved for a variety of conditions caused by herpes simplex virus, including recurrent HSL and EM, as well as recurrences triggered by dental trauma, surgical (ganglion) trauma and dermatological procedures (face peels). Recurrent HSL is the most common problem, often triggering EM.[9] Dental procedures often cause intraoral HSL recurrence on the epithelium adjacent to the teeth. Manipulations such as surgery or injections into the ganglions where dormant virus resides can cause massive outbreaks of recurrent HSL. Likewise, facial dermatological manipulations can trigger oral–facial HSL recurrences.[10] Finally, therapy for fever and epidural administration of morphine may trigger recurrent HSL.

The occasional recurrent HSL lesion does not have a serious impact on the health of a patient whose immune system is normal, and the patient should allow the lesion to run its course or use an over-the-counter remedy. However, for patients with altered immune status, an unchecked viral episode can have life-threatening consequences.[11]

Management

The selection of an appropriate antiviral compound and drug delivery format (intravenous [IV], oral or topical) for HSL patients with normal immune systems presents a dilemma for practitioners. Numerous prescription drugs and over-the-counter preparations are available throughout the world, most of which focus on treating the symptoms. These drugs have been tested in a variety of doses and preparations, both in patients who have experienced a natural occurrence of HSL and in others in whom lesions have been induced by ultraviolet radiation (**Fig. 2**). Information to assist in decision making is now available for certain drugs and is summarized here.

Table 1 **Dosages of antiviral drugs for treatment of herpes simplex labialis in adults**

	Patient's condition or situation; dosage				
Drug	**Recurrent HSL**	**EM**	**Dental trauma[a]**	**Surgical trauma[a]**	**Dermatological peel[a]**
Oral					
Acyclovir	400 mg 2 times daily[b]; begin 24 hours before planned procedure	400 mg 2 times daily[b]	400 mg 2 times daily; begin 24 hours before planned procedure	400 mg 4 times daily; begin 24 hours before planned procedure	400 mg 4 times daily; begin 24 hours before planned procedure
Famciclovir	500 mg 3 times daily	500 mg 2 times daily[b]	500 mg 2 times daily	500 mg 2 times daily; begin 12 to 24 hours before planned procedure	500 mg 2 times daily; begin 24 hours before planned procedure
Valacyclovir	NTD	NTD	NTD	NTD	500 mg 2 times daily; begin before procedure and give 14 days of treatment
Topical[c]					
Acyclovir	5% cream, 5 times daily	NTD	NA	NA	NA
Penciclovir	1% cream, every 2 hours	NTD	NA	NA	NA

Recurrent HSL = recurrent herpes simplex labialis, EM = erythema multiforme, NTD = no clinical trial data available, NA = drug not usually applicable for this situation.
[a]*Planned procedure.*
[b]*Administration of oral acyclovir and oral famciclovir is recommended up to 5 days.*
[c]*Valacyclovir does not have a topical formulation.*

Antiviral compounds for the treatment of HSL infection and recurrence have been examined in laboratory and clinical trials. Despite recent positive results in large trials with oral valacyclovir, topical penciclovir and topical acyclovir,[12–14] no overwhelming "winner" has emerged. Certain regulatory groups have approved 2 antiviral medications (acyclovir and penciclovir for topical application) for prevention or suppression of recurrent HSL in patients with normal immune systems. An over-the-counter formulation (e.g., acyclovir cream for topical application, which is available over the counter or without prescription in numerous countries) is used by most patients, because of concern about delays related to obtaining prescriptions, which are required for oral acyclovir, valacyclovir and topical famciclovir.

Acyclovir was touted as effective in preventing HSL in 1983,[15] but further trials[16] cast doubt about whether it can significantly alter the course of disease and normal healing. Suppression studies produced promising results,[17] notably clinical trials[18,19] that demonstrated significant differences favouring acyclovir in terms of healing time. However, no advantage in preventing recurrent HSL was demonstrated with acyclovir 800 mg orally twice a day.[20]

Results obtained in the treatment of HSL have not equalled those obtained in the suppression of herpes genitalia.[21] Several theories have been postulated to explain the difficulty in treating HSL. For example, disease severity varies in the same patient on successive occasions, and some lesions are preceded by an aurora or prodrome, whereas others appear without warning.[2] Furthermore, if the patient develops more than one lesion, each lesion may follow a different pattern.

Treatment Options

A variety of drug models have been used for HSL, with variable success.

Acyclovir

A 1993 review discussed clinical trials, published over a 10-year period, that had studied either topical or oral acyclovir in the prevention or suppression of HSL; small sample sizes and methodological flaws of these studies were noted.[4] One trial involving skiers who used 5% topical cream reported positive results,[19] while another trial involving skiers who took a two 800-mg dose of oral acyclovir each day revealed no beneficial effect.[22] Possible reasons for these inconsistent results ranged from altitude differences

Table 2 **Dosages of antiviral drugs for treatment of herpes simplex labialis in children**

	Patient's condition or situation; dosage				
Drug	**Recurrent HSV**	**EM**	**Dental trauma[a]**	**Surgical trauma[a]**	**Dermatological peel[a]**
Oral					
Acyclovir	20 mg/kg per day	20 mg/kg per day for 6 months	NA	20 mg/kg per day; begin 24 hours before planned procedure	NA
Famciclovir	NTD	NTD	NTD	NTD	NTD
Valacyclovir	NTD	NTD	NTD	NTD	NTD
Topical[b]					
Acyclovir	5% cream, 5 times daily	NTD	NA	NA	NA
Penciclovir	1% cream, every 2 hours	NTD	NA	NA	NA

Recurrent HSL = recurrent herpes simplex labialis, EM = erythema multiforme, NTD = no clinical trial data available, NA = drug not usually applicable for this situation.
[a]Planned procedure.
[b]Valacyclovir does not have a topical formulation.

at the trial sites to the timing of application of the medication. In another study, infrared thermography was used to track lesions treated with acyclovir 5% topical cream, and the treatment was successful in preventing HSL from progressing beyond the prodrome.[23]

The therapeutic effects of antiviral drugs in treating HSL are evident when the cellular concentration of the drug approaches an optimum level. However, oral acyclovir (even in high doses) does not produce the concentration necessary to generate that level of response consistently, despite positive results.[24]

Penetration of topical preparations of acyclovir through the stratum corneum has proven difficult.[25] Trials of 2 ointment concentrations (10% and 5%) failed to demonstrate effective healing.[26,27] The cream formulation has exhibited greater penetration in HSL and has been accepted for over-the-counter use in a number of countries and by prescription in North America. In 2 large trials, acyclovir in topical cream format had a more favourable result than previous trials.[14] These new data suggest strongly that dosing frequency may overcome less-than-optimal penetration by acyclovir cream.

A retrospective case series evaluation of cream and oral acyclovir in prepubertal children concluded that "Childhood HSV-associated erythema multiforme (EM) may be unresponsive to treatment with oral steroids or oral or topical acyclovir. Frequent recurrences of EM may be abrogated by prophylactic treatment with acyclovir."[28]

Famciclovir

Famciclovir, an oral prodrug of penciclovir, has been reported to suppress HSL virus shedding in those with HIV,[29] and the same drug in topical formulation has been reported as efficacious in treating recurrent HSL.[30] Oral famciclovir reportedly establishes an effectively higher concentration of active antiviral drug (i.e., penciclovir) at the cellular level, and there is a carryover effect after drug delivery has ceased. The half-life of penciclovir in cells infected with herpes simplex virus is reportedly 10 to 20 times longer than the half-life of acyclovir.[31]

There have been 2 international pivotal trials of topical 1% penciclovir in the treatment of HSL.[32,33] In total, 4,500 patients were enrolled in these 2 studies, and over 3,000 that qualified were randomly assigned to initiate treatment with 1% penciclovir cream or placebo at the first sign of the prodrome. Penciclovir significantly influenced the disappearance of classical lesions, resolution of pain and cessation of viral shedding. A unique finding in both trials was the experience of significant benefits from penciclovir even when therapy was initiated late in the progression of a classical lesion (after the prodrome), and both pain and viral shedding were reduced.[13]

Orally administered famciclovir has also shown promise in experimental ultraviolet-induced HSL, based on a trial of 125, 250 or 500 mg famciclovir given 3 times daily, the largest dose producing the best results.[34]

Valacyclovir

Valacyclovir, the metabolic precursor of acyclovir, provides significantly higher therapeutic availability of acyclovir when administered orally, 3 to 5 times that of a high oral dose of acyclovir. Valacyclovir 500 mg daily, given orally, was moderately effective in preventing herpes gladiatorum in wrestlers.[35] Time to lesion healing and to

cessation of pain were significantly less with oral valacyclovir, and the adverse events were similar to placebo in 2 trials with 1-day and 2-day regimens respectively.[12]

Combination Therapy

A topical formulation combining antiviral action with suppression of inflammatory response might prove useful for the treatment or suppression of recurrent HSL. Previously, patients have been warned not to use steroids to treat HSL lesions, the rationale being that suppression of the inflammatory response could cause a larger lesion through coalescence.[2] However, a combination of antiviral and corticosteroid could overcome this problem, in that the antiviral compound could suppress the infection by interrupting viral replication, thus controlling lesion spread, and the corticosteroid could accelerate healing and suppress the inflammatory response.

A model is required that combines the best features of suppressing the inflammatory response in conjunction with controlling viral replication. This would theoretically minimize symptoms and reduce the number of episodes. Although findings were favourable in a pilot study with a combination treatment,[34] larger trials are needed to confirm safety and efficacy. A new drug combining acyclovir with an immune modulator in the treatment of radiation-induced HSL significantly influenced the healing process as indicated by 3 of 4 clinical endpoints.[35]

Discussion

Tables 1 and **2** provide suggested dose and dosage forms for adults and children respectively, to assist the practitioner in using antiviral therapy for suppression or treatment of recurrent HSL. Acyclovir has the most detailed history, is safe for most patients and has been studied more often, although results have been inconsistent. However, recent results for a topical acyclovir cream in adults have been encouraging.[12] It is the only drug with a track record for children, and suggested treatments are available for recurrent HSL, EM and surgical trauma. In choosing a topical agent for children or adolescents, the safety data for acyclovir and penciclovir are excellent, and topical application at the adult dosage is recommended. Combination therapy involving acyclovir or penciclovir along with various immune modulators holds great promise. In the near future, patients will be given options, including instructions specific to their own medical history and propensity for acquiring either classical or immediate lesions. Penciclovir and valacyclovir have both shown definite promise in large trials for HSL recurrences.

Studying individual patterns of prodrome detection, healing rates of lesions and size of lesions could determine methods that limit the impact and duration of the cold sore. Some patients in whom HSL lesions were induced have reported experiencing fewer subsequent episodes or none at all, even after several years, regardless of the treatment received in the trials.[36] This effect might result from other factors in their lives, such as limited exposure to triggers or some modification in the immune response. It is possible that the induction process itself, within a controlled environment, could produce long-term positive effects. Vaccine trials and research into viral latency with a view to developing treatments that can target and attack dormant virus should be explored.

Noteworthy reductions in healing times and lesion size have been reported in well-designed trials, with significant differences in some and positive trends in others. Consequently, a patient has numerous treatment options. Topical therapy with a penciclovir or acyclovir cream may offer the advantage of being specific to the lesion site, whereas an oral drug may be more effective for prevention or suppression.

Continued development of new treatment forms, particularly combination drugs, and the reporting of a broader range of objectives and results in trials has improved the situation for patients with recurrent HSL. ◆

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