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Acyclovir as prophylactic antiviral therapy in recurrent herpes simplex infection

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ABSTRACT

Background: Recurrent herpes simplex virus (HSV) infection is one of the most common viral infections worldwide. Oral herpes is an infection of the lips, mouth, or gums due to the herpes simplex virus. It causes small, painful blisters commonly called cold sores or fever blisters. Acyclovir is the most frequently prescribed antiviral agent. It has been available for clinical use for over two decades and has demonstrated remarkable safety and efficacy against mild to severe infections caused by HSV in both normal and immunocompromised patients. In this case report, Acyclovir as an antiviral agent for prophylactic therapy has shown good results. Objectives: To emphasize the importance of prophylactic therapy to prevent the recurrence of herpes simplex infection. Case Report and Management: A 49-year-old woman admitted to Oral Medicine Department with chief complaint of sore mouth for about a week. She had been diagnosed with recurrent HSV infection 4 years ago and since the last 2 years, the recurrence has been more often. She was treated with antiviral (Acyclovir) and anti-inflammation (Ibuprofen) orally for a month and the oral lesions were resolved. Prophylactic therapy was given for the next 3 months in a maintenance dosage and no recurrence reported. Conclusion: The current evidence demonstrates that prophylactic treatment of oral Acyclovir can prevent the recurrence of herpes simplex infection.

Keywords: Recurrent Herpes Simplex Infection, Acyclovir, Prophylactic therapy

INTRODUCTION

Herpes simplex virus (HSV) infections cause a wide variety of illness, depending on the antigenic type of the virus, site of infection, and host immune response. Most HSV infections in immunologically normal individuals are asymptomatic. The most common clinically apparent diseases are recurrent episodes of orolabial or genital diseases that are localized to cutaneous or mucosal surfaces and last from 4 to 10 days. Immunocompromised patients develop HSV episodes that may last more than 30 days, produce extensive necrotic lesions, and disseminate viscerally.¹

Herpes viruses are a large family of parasites able to infect humans. All are DNA viruses capable of latency. Among human herpesviruses there are two variants - Herpes
Simplex Virus type-1 (HSV-1) and type-2 (HSV-2), which can be – as well as other clinical signs and symptoms – responsible for oro-facial disease. Usually HSV-1 infections affect the face and mouth while HSV-2 infections occur genitally. Both viruses may cause recurrent disease.  

Recurrent herpes simplex infection (RHI) affects 16% to 38% of the population. In elderly patients, the frequency of RHI sinks to approximately 20%. The recrudescence of HSV infections require simultaneous viral reactivation at the trigeminal ganglia level as well as a cutaneous permissivity allowing intra-epidermal viral replication that lead to lesion formation. Recrudescence is usually occurring at the same anatomical site and often presents similar clinical course in terms of duration, pain and lesion severity.  

Commercially available since the 1980s, acyclovir remains in many regards the prototypic antiviral agent. The notable safety profile of acyclovir relates to its initial activation by the virus-encoded enzyme thymidine kinase (TK). Acyclovir is most active against HSV. At present, there are two types of antivirals for the treatment of herpes labialis, topical and oral, which are available over the counter or as prescription-only. The aim of antiviral therapy is to block viral replication to enable shortening the duration of symptoms and to accelerate healing of the lesions associated with herpes labialis.  

Case report and management

A 49-year-old female was reported to Oral Medicine Department complaining severe pain on her lips, cheeks and tongue since a week before admitted that made it very difficult for her to eat and drink. She has the same complaint about 4 years before and was diagnosed with Herpes simplex virus infection, since the last 2 years, the recurrence has been more often. About two months before admitted, she also has the same complaint which diagnosed with recurrent herpes simplex virus infection and has been resolved after a month of treatment but didn’t have the prophylactic antiviral treatment after the lesion was healed.

Extra oral examination revealed lymphadenopathy on both submandibular lymph glands, multiple ulcer on lower lip and red-blackish crust on upper lip. Intra oral examination revealed multiple erosive ulcer on upper and lower labial mucosa, left and right buccal mucosa, ventral and anterior tip of the tongue. Dorsal of the tongue is covered with white pseudomembran that can be scrapped off leaving an erthyema area. The examination also revealed superficial calculus deposit on lingual part of lower anterior teeth. Based on history and clinical presentation a provisional diagnosis of recurrent herpes simplex infection, oral candidiasis and chronic generalised gingivitis was made.

On the first visit, the patient was treated with Acyclovir tab 200 mg 5 times a day, Ibuprofen tab 400 mg 3 times a day, Vit B12 50 mcg twice a day, Folic acid 1 mg once a day and application of sterile gauze soaked with Chlorhexidin 0.2% gargleon tongue 3 times a day. Laboratory examination was then suggested for diagnosis confirmation.
DISCUSSION

Herpes simplex virus-type 1 (HSV-1) is a neurotropic member of the alpha herpesvirus family with worldwide seroprevalence rates ranging from between 50-90%. Primary infection with HSV-1 typically occurs in childhood or adolescence following inoculation of mucosal epithelial surfaces and is usually mild or asymptomatic in the immunocompetent host. Initial infection of epithelial cells results in a lytic replicative cycle during which the virus infects sensory neurons proximal to the site of primary infection. Virions are then transported retrograde axonally to neuronal cell bodies in the trigeminal ganglia resulting in the establishment of a lifelong latent infection. Subsequent reactivation of latent HSV-1 leads to renewed lytic infection at epithelial surfaces fed by infected sensory nerve fibers within infectious virus released either through asymptomatic viral shedding or the formation of fluid-filled vesicles.  

Primary infection with HSV-1 may be mild and inapparent and occur in early childhood. In approximately 10% of primary infections, overt disease may appear as an illness of varying severity, marked by fever and malaise lasting a week or more; it may be associated with gingivostomatitis accompanied by vesicular lesions in the oropharynx, severe keratoconjunctivitis, a generalized cutaneous eruption complicating chronic eczema, meningoencephalitis, or some of the fatal generalized infections in newborn infants (congenital herpes simplex).  

Reactivation of latent infection commonly results in herpes labialis (fever blisters, cold sores), manifested usually on the face or lips, by superficial clear vesicles on an erythematous base that crust and heal within days. Reactivation is precipitated by various forms of trauma, fever, physiological changes or intercurrent disease, and may also involve other body tissues; it occurs in the presence of circulating antibodies, which are seldom elevated by reactivation. Severe and extensive spread of infection may occur in those who are immunodeficient or immunosuppressed. The onset of reactivation is heralded by tingling prior to the onset of vesicles; if patients learn this sign, they can prevent or shorten the clinical course of reactivated infection through the use of antivirals.  

Diagnosis of herpes labialis is usually based on the patient history of this condition, the clinical signs and symptoms. Laboratory confirmation, however, may be required in immunocompromised patients if the clinical presentation is atypical. Many patients neither require nor use any treatment because the disease is self-limiting. For individuals with frequent recurrences, application of a sunscreen or zinc oxide to decrease the probability of recurrent outbreaks may help.  

The discovery of acyclovir seemed to offer great promise in the treatment of herpes labialis. Acyclovir acts as a substrate for the thymidine kinase enzyme of the herpes virus and thus selectively inhibits viral replication. It was found to be effective in suppressing recurrent herpes labialis in immunocompromised patients; however, in non-immunocompromised people it was more effective against herpes genitalis (due to herpes simplex virus type 2) than herpes labialis, which is typically caused by herpes simplex virus type 1.
Acyclovir is a guanine nucleoside analoguemost effective against HSV-1 and HSV-2, but it has some activity against VCV, CMV, and EBV. Acyclovir is converted to its active metabolite via threephosphorylation steps. First, viral thymidine kinase converts acyclovir to acyclovir monophosphate. Next, hostcell enzymes convert the monophosphate to the diphosphate and then to the active compound, acyclovirtriphosphate. Because viral thymidine kinase has a much greater affinity for acyclovir triphosphate than does mammalian thymidine kinase, acyclovir triphosphate accumulates only in virus-infected cells.\(^{10,11}\)

![Figure 4. Acyclovir Mechanism.\(^{12}\)](image)

The active metabolite of acyclovir inhibits herpesvirusDNA replication in two ways. Acyclovir triphosphate acts as a competitive inhibitor for the incorporation of deoxyguanosine triphosphate (dGTP) into the viral DNA. In addition, acyclovir that is incorporated into viral DNA acts as a chain terminator because it lacks the 3' hydroxyl group necessary for further chain elongation. Viral DNA polymerase becomes irreversibly bound to an acyclovir-terminated DNA chain and is unavailable for further replicative activity. The effect of acyclovir on host cell DNA synthesis is much smaller than its effect on the viral enzyme. Concentrations of acyclovir significantly beyond the therapeutic range are required to inhibit host cell growth.\(^{10}\)

Antiviral agents can be used to treat disease (a therapeutic strategy), to prevent infection (a prophylactic strategy), or to prevent disease (a preemptive strategy). Prophylaxis refers to the administration of an agent to patients at risk of contracting infection (e.g., acyclovir given to HSV-seropositive renal transplant recipients).\(^{9}\)

Acyclovir has few mild side effects and is generally very safe to use. After prolonged high doses, acyclovir can cause bone marrow depression but this is not likely to be encountered in normal clinical practice. Acyclovir resistant strains of HSV have been reported. These resistant strains fall into 3 categories: 1) Naturally occurring thymidine
kinase negative variants, 2) Thymidine kinase resistant mutants (Tk-); 3) pol mutants with a DNA polymerase resistant to inhibition by acyclovir triphosphate. Only Tk- variants have emerged in nature following the therapeutic use of acyclovir. However, both types of mutants are associated with reduced pathogenicity. Forskarnet and ara-A are the drugs of choice for the treatment of acyclovir resistant HSV.⁹

Oral acyclovir has modest effect in the treatment of recurrent herpes labialis, and treatment of these patients should be individualized. In general, therapeutic benefit is enhanced if treatment is initiated as soon as possible after onset of symptoms, preferably within 24 to 48 hours of onset of the recurrence. Among patients who start treatment in the prodrome or erythema lesion stage, acyclovir therapy (400 mg five times a day for 5 days) reduces the duration of pain by approximately one-third, and the healing time to loss of crust by approximately one-fourth. Topical acyclovir cream may also modestly decrease the duration of a clinical recurrence of herpes labialis by approximately half a day (approximately 4½ days for topical acyclovir recipients, compared with approximately 5 days for placebo recipients), although benefit of topical acyclovir is not conferred by acyclovir ointment, which has a polyethylene glycol base.⁹

Prophylactic acyclovir also has been used to prevent reactivation of herpes labialis following exposure to ultraviolet radiation, facial surgery, or exposure to sun and wind while skiing. Topical acyclovir cream also is effective in preventing recurrent herpes labialis in skiers and in persons with a history of frequent recurrences of herpes labialis. Long-term suppressive therapy reduces the number of recurrences of oral infection in those with histories of frequent recurrence. In one study of 400 mg of oral acyclovir administered twice daily for 4 months, clinical recurrences were reduced by more than half, and culture-confirmed recurrences were reduced by more than two-thirds.⁹

CONCLUSION

The current evidence demonstrates that prophylactic treatment of oral Acyclovir can prevent the recurrence of herpes simplex infection.

REFERENCES


