REVIEW ARTICLE

Drug Safety 2000 Aug; 23 (2): 131-142
0114-5916/00/0008-0131/$20.00/0

A Risk-Benefit Evaluation of Aciclovir for the Treatment and Prophylaxis of Herpes Simplex Virus Infections

Stephani Leflore, Peter L. Anderson and *Courtney V. Fletcher*

Department of Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, Minnesota, USA

Contents

Abstract

The objective of this article is to review and evaluate risks and benefits associated with the use of aciclovir in the treatment and prophylaxis of common manifestations of herpes simplex virus (HSV) infections in immunocompetent and immunocompromised patients. Information was found through a MEDLINE search using keywords: herpes simplex virus, genital herpes, herpes labialis, aciclovir and acyclovir. Selected articles were randomised, double-blind, placebo-controlled, clinical trials. 30 such trials involving 3364 persons were evaluated. All articles were reviewed by the authors and the data were extracted and summarised. In both immunocompetent and immunocompromised hosts, aciclovir therapy demonstrated a high degree of clinical efficacy. None of the studies reported statistically significant differences between aciclovir and placebo for mild or major adverse events. This evaluation found that aciclovir is both effective and well tolerated for treatment and prophylaxis of genital, oral and mucocutaneous HSV infections in immunocompetent and immunocompromised patients. In most clinical scenarios, the benefit of aciclovir exceeded any risks by a comfortable margin. The availability of aciclovir as a generic preparation further improves the benefit to cost ratio.

The hallmarks of herpes simplex virus (HSV) infections of humans are ubiquity, latency and reactivation. Genital herpes is the most widespread sexually transmitted disease in the world, affecting 25 to 35% of sexually active adults.[1] It is estimated that 40 to 60 million North Americans have HSV-2 antibodies with approximately 500 000 new cases of genital HSV infection occurring annually.[2] HSV, like all members of the human herpes virus family, establishes latency after initial infection. Once latency is established, recurrent infections may occur throughout the lifetime of the host. More than one-third of the world's population has recurrent HSV infections.[2] Similarly, it is believed that one-third of the US population has recurrent herpes labialis with an annual incidence of 100 million episodes.[3] Viral infections caused by HSV have received much less attention since the era of human immunodeficiency virus (HIV), however, they remain a worldwide epidemic.

The clinical symptomatology associated with HSV infections range from asymptomatic infection to life-threatening diseases such as neonatal herpes, herpes simplex encephalitis and viscerally-disseminated infections in immunocompromised hosts. If untreated, 50% of neonates with HSV encephalitis and more than 80% with disseminated HSV infection will die.[2] HSV encephalitis is a common cause of fatal encephalitis and survivors usually develop permanent neurological impairment.[2] Immunocompromised hosts are much more susceptible to persistent mucocutaneous HSV infections,[4] which may progress and involve the oesophagus, respiratory tract or gastrointestinal tract. Before the availability of aciclovir, HSV infections in these patients caused death or serious morbidity.[5]

Beyond the direct manifestations of HSV infections, other health concerns have developed. Studies have shown that patients diagnosed with genital herpes often show high levels of anxiety and depression.[6,7] Childbearing women who acquire genital HSV late in pregnancy are particularly at risk for passing herpes to the neonate during vaginal delivery.[8] Caesarean deliveries are recommended in these circumstances, and for symptomatic recurrences peripartum or at labour onset.[9,10] It is believed that 25 to 30% of pregnant women in the US and Europe have HSV-2 antibodies,[4] which confer a risk of recurrence peripartum. Considerable emotional strain may result in monogamous sexual partners with discordant infection, where 1 survey estimates a yearly transmission rate of 10 to 15%.[2] More recently, HSV-2 has been identified as an independent risk factor for HIV seroprevalence.[11] Thus, substantial morbidity is associated with HSV infections.

The goals of antiviral drug therapy for HSV infections encompass prevention of virus transmission or recurrence, reduction in the severity of disease and its complications, prevention of damage to visceral organs and the central nervous system, and treatment of life-threatening disease. Aciclovir is the gold standard for therapy of HSV infections. It is the most effective and widely prescribed antiviral drug available, and has been used for more than 15 years in over 30 million people.[12] It is currently prescribed for the treatment of initial and recurrent mucosal and cutaneous HSV infections, suppression of genital HSV infections, treatment of HSV encephalitis, and treatment and suppression of mucocutaneous HSV infections in immunocompromised patients.[2]

The objective of this paper is to review common HSV infections, and to assess the benefits and risks of aciclovir therapy in both immunocompetent and immunocompromised persons. The discussion will be focused on treatment and suppression of oral and genital HSV infections in immunocompetent patients, and treatment and suppression of mucocutaneous HSV in immunocompromised patients. Efficacy and tolerability data regarding the use of aciclovir were found through a MEDLINE search using the keywords HSV, genital herpes, herpes labialis, aciclovir and acyclovir. Double-blind, placebo-controlled clinical trials were preferentially selected; all studies were reviewed by the authors and data were collectively summarised.

1. Epidemiology

Historically, HSV-1 has been associated with orofacial infections and HSV-2 with genital infec-

tions. Nevertheless, genital infections attributable to HSV-1 have been increasing[13] although they tend to be less severe and less likely to recur than genital HSV-2 infections.[2] While it is estimated that 45 to 98% of adults have HSV-1 antibodies,[13] the prevalence varies depending on geographic location, socioeconomic status and age.[2] Individuals from lower socioeconomic populations tend to have higher prevalence of HSV-1 antibodies and seroconvert earlier in life than individuals from middle income populations.[2] HSV-2 prevalence is also dependent upon various factors such as race, gender, marital status and place of residence. The overall HSV-2 seroprevalence is 10 to 40%[13] with a higher prevalence in Blacks, females, divorced individuals and city residents.[2] The rate of HSV-2 infection during pregnancy is 2.5% per gestation.[2] While distinctions may be made between HSV-1 and HSV-2 it is important to realise that they both cause oral and genital infections, they have the same mode of transmission and clinical presentation, and are essentially treated the same.

2. Pathophysiology

HSV is spread by person-to-person transmission and enters the body through direct contact with mucous membranes or abraded skin.[2] A person is susceptible to HSV-1 or HSV-2 infection if they do not already possess antibodies for the HSV type they contact. Primary infection refers to first time exposure to either HSV-1 or HSV-2. Initial infection refers to a person who has antibodies to 1 virus type and is exposed to the other type.[2] After infection, the replication process involves many elaborate steps including adsorption, penetration, viral component synthesis, maturation and release. This replication at the site of primary/initial infection causes cell lysis and subsequent fluid filled blisters or ulcers. However, these infections can be asymptomatic as well. Upon healing the blisters/ulcers form scabs which seldom lead to scarring.[2]

After viral replication at the site of infection, HSV is transmitted within sensory neurons via retrograde movement, usually to the trigeminal or sacral ganglia, where it undergoes another round of replication before establishing latency.[2] A latent virus may be reactivated by fever, tissue damage, emotional stress, ultraviolet light or other immunosuppressive triggers to cause recurrent infection.[2] During recurrent infection the virus travels back down the neuron and usually invades the same area where the primary/initial infection occurred.[2] Most recurrent infections are less severe than primary infections and many times no clinical symptoms are present at all.[13] Studies have demonstrated that HSV-2 is often transmitted during times of asymptomatic shedding,[14] which may partially explain the continued increase in HSV-2 transmission.

3. Clinical Presentation

In general, asymptomatic primary orofacial HSV infections occur more frequently than symptomatic primary infection.[2] Patients with herpes labialis usually experience less than 2 recurrent infections per year and most infections are very mild.[3] Primary genital HSV infections, however, are more commonly associated with clinical symptoms.[15] Recurrent infections tend to be less severe than primary infections[15] and it is interesting to note that pre-existing HSV-1 antibodies seem to make HSV-2 infections less severe.[2] The following discussion describes common symptoms of HSV infection, although the severity and frequency of symptoms vary greatly among individuals.

3.1. Orofacial Herpes Simplex Virus Infection

Symptomatic primary orofacial infection most commonly presents as fluid filled vesicles on the tongue palate, pharynx and buccolabial membranes (gingivostomatitis) and may produce red, swollen and bleeding gums.[2,15] Children may display fevers of 101 to 104°F (38.3 to 40°C) and have submandibular lymphadenopathy.[15] Adults commonly experience pharyngitis and mononucleosis-like syndrome.[2,15] Other symptoms of primary orofacial infections include sore throat, difficulty eating and swallowing, malaise and tender cervical lymphadenopathy. Recurrent orofacial infections are usually preceded by a prodrome of pain, burning, tingling or itching, which lasts for approximately 6

hours before vesicles appear.[2] Pain is most severe during the first 3 to 4 days while complete healing can take as many as 8 to 10 days.[2]

3.2. Genital Herpes Simplex Virus Infection

Primary genital infections are associated with systemic symptoms such as fever, headache, malaise and myalgia. Primary genital HSV infections present as macules and papules which progress to vesicles and ulcers before healing.[2] In women, lesions are extremely painful and appear bilaterally on the vulva and may also involve the cervix, vagina, buttocks and perineum.[2,15] Women are also more prone to experience urinary retention syndrome or aseptic meningitis.[2] Men usually exhibit lesions on the glans of the penis and/or the penile shaft although lesions may also appear on the thigh, buttocks and perineum.[2] Most lesions are associated with pain, burning, and/or itching and usually require approximately 3 weeks to resolve.[2] Severe primary infections are predictive of more frequent recurrences.[2] Recurrent infections are typically less severe than initial infections and may be preceded by prodromal symptoms prior to lesion formation. The lesions usually resolve in 8 to 10 days.

3.3. Mucocutaneous Herpes Simplex Virus Infections in the Immunocompromised Host

Mucocutaneous HSV infections in the immunocompromised population are most often the result of recurrent infection.[16] Immunocompromised patients, specifically transplant recipients and patients with HIV, are at a much higher risk for developing HSV-related morbidity and mortality.[17,18] HSV infections in immunocompromised patients resemble those described in sections 3.1 and 3.2 but are more frequent, severe, progressive and chronic. Lesions may be disseminated throughout the respiratory tract, oesophagus or gastrointestinal tract as well as the orofacial and genital areas.[17] HSV-associated morbidity increases proportionately with increased immunosuppression.[18]

4. Treatment

Antiviral drugs available to date are not able to cure HSV infections; however, they inhibit viral replication and thus impact the course of HSV disease. Therefore, the current strategy in HSV therapy consists of disease management rather than virus eradication. Antivirals are used in primary and recurrent infections to decrease pain, viral shedding and duration of symptoms. Prophylactic use of antivirals has proven useful in decreasing the frequency of recurrences, especially in immunocompromised patients and immunocompetent persons who experience frequent recurrences of oral or genital HSV infections. Long term use of antivirals is also thought to decrease asymptomatic viral shedding, which may have an impact on HSV transmission.[19] Antiviral drugs currently available to treat HSV infections include aciclovir, penciclovir, valaciclovir (prodrug of aciclovir), famciclovir (prodrug of penciclovir), cidofovir and foscarnet. Aciclovir is available as a tablet, capsule, suspension, topical ointment or cream, and powder for injection. In contrast, penciclovir is currently available as a topical cream, valaciclovir as a caplet, famciclovir as a tablet, and cidofovir and foscarnet as an injection for intravenous administration. Table I lists current treatment recommendations for herpes labialis infections and genital herpes infections in immunocompetent hosts, and mucocutaneous infections in immunocompromised hosts.[20,21]

5. Aciclovir Efficacy and Tolerability

The mechanism of action of aciclovir results in a high degree of clinical efficacy as well as good tolerability. Once aciclovir enters the cell it is monophosphorylated by virally-induced thymidine kinase.[12] Therefore, only cells harbouring HSV effectively phosphorylate aciclovir to its activated triphosphate moiety. Host cellular kinases are responsible for transforming the mono-phosphorylated aciclovir into the activated triphosphorylated form.[12] Aciclovir triphosphate then competitively binds irreversibly to viral DNA polymerase and thus prevents formation of a DNA replication complex.[12]

Table I. Current treatment recommendations for herpes labialis infections, genital herpes infections and mucocutaneous infections[20,21]

Disease	Treatment of choice	Alternative treatment	Prophylactic/suppressive
Immunocompetent host			
Herpes labialis	Penciclovir 1% cream applied every 2h (while awake) for 4 days	Aciclovir 200mg orally 5 times daily for 5 days[a]	Aciclovir 200mg orally 5 times daily and just before and during sun exposure[a]
Genital herpes			
initial episode	Aciclovir 200mg orally 5 times daily or 400mg 3 times daily for 7-10 days or Valaciclovir 1g orally twice daily for 7-10 days or Famciclovir 250mg orally 3 times daily for 5-10 days[a]	Aciclovir 5-10 mg/kg every 8h for 5-10 days (for severe cases only)[b]	
recurrent episode	Aciclovir 200mg orally 5 times daily or 400mg 3 times daily or 800mg twice daily for 5 days or Valaciclovir 500mg orally twice daily for 5 days or Famciclovir 125mg orally twice daily for 5 days		Aciclovir 200-400mg orally 2-3 times daily for 1 year or longer if necessary or Valaciclovir[c] 500-1000mg once daily for 1 year or longer if necessary or Famciclovir[c] 125-250mg twice daily for 1 year or longer if necessary
Immunocompromised host			
Mucocutaneous infections	Aciclovir 5-10 mg/kg IV every 8h for 7 days[b]	Aciclovir 400mg orally 5 times daily for 7 days[a] or Valaciclovir 1g 3 times daily for 7 days[a] or Famciclovir 500mg twice daily for 7 days[a]	Aciclovir 400mg orally 3 times daily for 2-3 months[a] or Valaciclovir 1g 3 times daily for 2-3 months[a] or Famciclovir 500mg twice daily for 2-3 months[a]

a Not approved by the US Food and Drug Administration for this indication.

b Reduce dose in renal failure according to package insert.

c Less long term safety and efficacy data are available for these agents compared to aciclovir.

IV = intravenous.

Aciclovir triphosphate may also be incorporated into the growing chain of viral DNA where it promotes chain termination because it lacks the 3′hydroxyl group required for incorporation of the next nucleotide.[12] While all acyclic nucleoside analogues inhibit herpesvirus DNA polymerase, aciclovir triphosphate has been found to be 100 times more potent an inhibitor of HSV polymerase than, for example, penciclovir triphosphate.[12]

Table II is a summary of clinical trials assessing the efficacy and tolerability of aciclovir for the treatment of herpes labialis infections and genital herpes infections in immunocompetent hosts, and mucocutaneous infections in immunocompromised hosts.[3,9,22-50] The following discussion summarises the findings reported in table II.

5.1 Oral Herpes

As discussed in section 3, herpes labialis infections are usually mild and self-limiting and therefore may not require drug therapy. Treatment of herpes

Table II. Randomised, double-blind, placebo-controlled trials assessing the efficacy and tolerability of aciclovir in the treatment of gingivostomatitis, herpes labialis, genital herpes and mucocutaneous herpes

Clinical scenario (no. of patients)	Regimen	Patient characteristics	Results: aciclovir *vs* placebo	Adverse effects
Treatment of gingivostomatitis				
Amir et al.[22] (n = 61)	15 mg/kg suspension PO 5 times daily for 7 days	Children aged 1-6 years presenting within 72h of symptom onset. Only culture or serology confirmed cases were included; all were HSV-1	60% ↓ in median days until oral lesion healing; 67% ↓ in median days to fever resolution; 100% ↓ in median days until extraoral lesion resolution; 75% ↓ in median days viral shedding. Significant ↓ in eating and drinking difficulties as well as drooling were also noted	No significant adverse effects noted. Stomach upset was reported in 1 patient from each group
Prophylaxis for recurrent herpes labialis				
Rooney et al.[3] (n = 22) Spruance et al.[23] (n = 147) Raborn et al.[24] (n = 237)	400mg PO bid for 4mo (cross-over design)[3] or 400mg PO bid for 7 days[23] or 800mg PO bid for 7 days[24]	Otherwise healthy adults with ≥6 recurrent infections in 1y, or at a self-reported risk of outbreak during sun exposure or skiing	61% ↓ in time to first clinical recurrence; 0-74% ↓ in mean number of clinical episodes; 71% ↓ of virologically determined episodes. 1 trial[24] found no aciclovir effect	Headache and nausea were reported more than once (1 patient withdrew because of headache and nausea)
Treatment of recurrent herpes labialis				
Shaw et al.[25] (n = 45) Fiddian et al.[26] (n = 13)	5% ointment[25] or cream[26] 5 times daily as soon as prodrome detected	Otherwise healthy men and women with ≥2 recurrences of diagnosed HSV labialis in the past year	**Ointment study:**[25] 25% ↓ in time to crusting all episodes; 25% ↓ in time to complete healing all episodes; 4-fold ↑ in % abortive lesions **Cream study:**[26] no significant differences were found	Some skin flaking noted. No other adverse effects were reported
Treatment of first episode genital herpes				
Mindel et al.[27] (n = 30) Thin et al.[28] (n = 40) Corey et al.[29] (n = 77)[a] Mertz et al.[30] (n = 119) Bryson et al.[31] (n = 48) Nilsen et al.[34] (n = 31)	5 mg/kg IV over 45-60 min every 8h for 15 doses[27] 5% ointment applied 4-5 times daily[28,29] 200mg PO 5 times daily for 5 or 10 days[30,31,34]	Otherwise healthy adults presenting 5-6 days after initial lesion onset Patients who required hospitalisation were included in the IV trial[27]	**IV study:**[27] 50% ↓ in median time to healing of all lesions; 100% ↓ in duration of new vesicle formation; 40% ↓ of mean vesicle duration; 24% ↓ in duration of all symptoms; 76% ↓ in mean viral shedding time of all lesions **Topical studies:**[28,29] 41-89% ↓ in mean duration of viral shedding; 50% ↓ in duration of all symptoms; 33% ↓ in healing time; 32% ↓ in time to crusting **Oral studies:**[30,31,34] 60-100% ↓ of viral shedding of all lesions; 30-67% ↓ in time to crusting of all lesions; 25-45% ↓ in time to healing of all lesions; 71-100% ↓ in % pts forming new lesions (first 48h); 29-56% ↓ in duration of pain and itching	1 patient had a transient increase in urea and creatinine levels after a bolus dose (returned to normal in 48h).[27] Otherwise, the incidence of adverse events was similar in both groups
Treatment of recurrent genital herpes episodes				
Corey et al.[29] (n = 111)[b] Reichman et al.[32] (n = 88) Reichman et al.[33] (n = 377) Nilsen et al.[34] (n = 85)	5% ointment applied qid for 5 days[29] or 5% ointment applied 6 times daily for 5 days[32] or 200mg PO 5 times daily for 5 days[33,34]	Otherwise healthy adults; patients presented within 48h from onset of lesions	**Topical studies:**[29,32] 38-48% ↓ in viral shedding in men – all lesions (no significant differences in women or other significant findings) **Oral studies:**[33,34] 32-50% ↓ in duration of viral shedding of all lesions; 89% ↓ in % pts with new lesion formation; 19-38% ↓ in time to crusting of all lesions; 15-21% ↓ in time to healing of all lesions	Transient irritation, 1 withdrawal (rash). Otherwise, no significant differences *vs* placebo

Continued over page

Suppression of initial and/or recurrent episodes of genital herpes in pregnant women				
Scott et al.[9] (n = 46) Brocklehurst et al.[35] (n = 63)	400mg PO tid[9] or 200mg PO qid[35] week 36 gestation until delivery	Otherwise healthy pregnant women with the 1st occurrence or 1st clinical recurrence of cultured genital herpes during pregnancy	88-100% ↓ in % patients with clinical herpes at delivery; 50-100% ↓ in caesarean delivery because of herpes	No reports of significant adverse effects in mothers or neonates
Suppression of recurrent episodes of genital herpes				
Thin et al.[36] (n = 88) Mertz et al.[37] (n = 1146) Goldberg et al.[38] (n = 389-950)[c] Douglas[39] (n = 143) Strauss et al.[40] (n = 32)	200mg PO 2-5 times daily until a recurrence (duration 84-125 days)[36-40] or 400mg PO bid for up to 5y[37,38]	Otherwise healthy adults with culture-proven genital herpes and 6 to 12 or more recurrences over 1y	**Oral studies:**[36,37,38,39,40] 4.6 to 13.6-fold ↑ in time to first recurrence; 63-86% ↓ in lesion recurrences; 58-77% ↓ in % viral isolation during episodes; 5.7 to 32-fold ↑ in the no. of patients with no lesions or symptoms; 53-70% all patients were episode-free over years 3-5; 20% of the original suppressive patients were episode free over entire 5 years. For year 5 (all patients):[38] 68.6%, no recurrences; 16.5%, 1 recurrence; 7.5%, 2 recurrences; 2.1%, 3 recurrences; 2.6%, 4 recurrences; 0.8%, 5 recurrences; 2.1%, ≥6 recurrences	Transient leucopenia (n = 1)[38], rash (n = 1), mean corpuscular volume of erythrocytes and mean corpuscular haemoglobin level slightly elevated with aciclovir. 5 patients had resistant virus (2 had not taken aciclovir before).[40] Otherwise, no differences beween groups
Treatment of mucocutaneous herpes infections in immunocompromised patients				
Shepp et al.[41] (n = 21) Meyers et al.[42] (n = 97) Wade et al.[43] (n = 34) Whitley et al.[44] (n = 59)	250 mg/m^2 IV q8h for 7 days[42,43] or 400mg PO 5 times daily for 10 days[41] or 5% ointment applied 6 times daily for 10 days[44]	Immunocompromised patients (organ transplant, malignancy, immunodeficiency disease, bone marrow transplant, or the treatment of these diseases) with mucocutaneous HSV infection confirmed by culture	**IV studies:**[42,43] 83% ↓ in median virus shedding time; 31-50% ↓ in median time to scabbing; 32-38% ↓ in median time to cessation of pain; 32-50% ↓ in median time to complete healing **Oral study:**[41] 78% ↓ in viral shedding; 90% ↓ in days with new lesion formation; 81% ↓ in time to first decrease of pain; 63% ↓ in resolution of pain; 45% ↓ in time to 50% healing; 62% ↓ in time to total healing **Topical study:**[44] 65% ↓ in viral shedding; 43% ↓ in median time to resolution of pain; 26% ↓ in time to healing	Phlebitis was more common with IV aciclovir than placebo in 1 study (5 *vs* 1)[42] Lightheadedness and substernal burning reported by 1 patient during rapid drug infusion. 1 report of aciclovir resistance (the isolate lacked thymidine kinase activity).[43] Otherwise, no differences found
Prophylaxis of mucocutaneous herpes infections in immunocompromised patients				
Saral et al.[45] (n = 29) Prentice et al.[46] (n = 59) Pettersson et al.[47] (n = 35) Saral et al.[49] (n = 20) Seale et al.[50] (n = 40)	250 mg/m^2 IV q8h for 18 or 32 days,[45,49] or 5 mg/kg IV q12h[46] 200mg PO qid for 28 or 180 days,[47,48] or 200mg PO q8h for 30 days[50]	Immunocompromised patients (organ transplant, malignancy, immunodeficiency disease, bone marrow transplant, or the treatment of these diseases). Patients had 1:16 or greater anti-HSV antibody titer[45,50]	**IV studies:**[45,46,49] 80-100% ↓ in culture-positive HSV infection **Oral studies:**[47,48,50] 92-100% ↓ in clinical HSV infections; 93-100% ↓ viral shedding episodes	1 herpes isolate with reduced aciclovir sensitivity.[46] Otherwise, adverse experiences were similar between groups

a 77 of 188 patients with first episode infection.
b 111 of 188 patients with recurrent infection.
c No. of patients varied: 950 (1st year), 683 (2nd year), 525 (3rd year), 433 (4th year) and 389 (5th year).

bid = twice daily; **HSV** = herpes simplex virus; **HSV-1** = herpes simplex virus-1; **IV** = intravenous; **min** = minutes; **PO** = orally; **q8h** = every eight hours; **q12h** = every 12 hours; **qid** = 4 times daily; **tid** = 3 times daily; ↑ = increase; ↓ = decrease.

labialis with aciclovir has produced inconsistent results. For gingivostomatitis in children, oral aciclovir reduced clinical symptoms such as drooling, fever, and dehydration by 43% or more, and decreased time to lesion healing by 60% or more.[22] In adults, aciclovir has been shown to be an effective prophylactic agent during high risk trigger events such as snow skiing. There was a 74% reduction in recurrent infections in patients who used oral aciclovir prior to and during skiing,[23] although this was not a universal finding.[24] For general suppression of frequent recurrences (6 or more per year), prophylactic oral aciclovir has been shown to reduce both the number of clinical episodes and the amount of viral shedding by 53 and 71%, respectively.[3] It also increased the time to first clinical recurrence by 2.5-fold.[3] The benefit of topical aciclovir for treatment and prophylaxis of recurrent episodes is equivocal.[25,26]

5.2 Genital Herpes

Aciclovir has become the mainstay of therapy for genital herpes. Topical aciclovir 5% ointment is more effective during primary episodes than initial (nonprimary) or recurrent episodes. When used during primary infection, topical aciclovir decreased duration of viral shedding, time of local pain and time to crusting.[28,29] It was less effective in preventing new lesion formation or decreasing time to overall healing.[29] Topical aciclovir, in general, did not prove beneficial for recurrent genital HSV infections. It significantly decreased viral shedding in men only, and did not reduce healing time, time to crusting or duration of symptoms.[29,32] In sharp contrast, intravenous aciclovir is very effective in decreasing the time of viral shedding, time to healing, the number of new vesicles and duration of symptoms.[27] However, intravenous aciclovir is usually reserved for severe disease in immunocompetent patients.

Oral aciclovir is the most commonly used preparation of aciclovir and is useful in primary/initial, recurrent and suppressive therapy of genital HSV infections. The course of disease during a first episode (primary and nonprimary) is greatly affected by oral aciclovir. It consistently decreased time of viral shedding by 60 to 100%, reduced time to crusting by 30 to 67%, reduced time to healing by 25 to 45%, decreased new lesion formation 71 to 100%, and reduced symptoms (pain and itching) by 29 to 56%.[30,31,33] During recurrent episodes, oral aciclovir has been shown to reduce time of viral shedding by 32 to 50% and reduce time to healing by 15 to 21%.[33,34] Early initiation of therapy has a greater impact on the course of the disease.[33]

More recently, oral aciclovir has been shown to be an effective suppressive therapy when taken for extended periods (up to 5 years) in patients with frequent recurrences of genital HSV. Long term suppressive therapy has decreased the number of recurrences by 63 to 86% and increased the time to first recurrence 4.6- to 13.6-fold.[36-40] Twice daily aciclovir appears to be as effective as 5 times daily therapy in this setting.[39]

In pregnant women, suppression of recurrences with oral aciclovir during the peripartum period resulted in an 88 to 100% reduction in recurrence at labour, and a reduction in caesareans because of herpes.[9,35] However, larger trials are needed to clearly define a role for aciclovir in HSV-infected pregnant women.

5.3. Immunocompromised Patients

Immunocompromised patients such as bone marrow transplant and organ transplant recipients benefit from both acute and suppressive intravenous aciclovir therapy of HSV infections. Acute treatment with intravenous aciclovir decreased the duration of viral shedding by ≈83%, the time to cessation of lesion pain by up to 38% and the time to crusting and healing by up to 50%.[42,43] Acute treatment with topical aciclovir decreased viral shedding, duration of pain, and lesion healing by 6 days compared with placebo; larger lesions were more susceptible to the drug's effects.[44] Oral aciclovir reduced time to healing and time to pain resolution by 63 and 62%, respectively, in immunocompromised patients.[41]

In 5 patients with severe chronic mucocutaneous HSV infections but different immunocompro-

mising aetiologies, both oral and intravenous aciclovir were found to be extremely effective, as shown by complete healing of the lesions.[51]

Prophylactic intravenous or oral aciclovir therapy for acutely immunosuppressed patients was extremely successful in several studies, and prevented 80 to 100% of patients from developing lesions and shedding virus; however, it did not prevent infection after therapy was discontinued.[45-50] Similar to other immunosuppressed patients, recurrent HSV disease is common in HIV-infected individuals. Before the advent and use of triple antiretroviral therapies, oral aciclovir (600 to 800 mg/ day) in combination with zidovudine was shown to reduce mortality in patients with AIDS.[52] Clinical experience indicates that oral aciclovir, in dosages ranging from 600 to 800 mg/day, is effective in suppressive therapy for frequently recurring HSV disease in HIV-infected people.[52]

Among antiviral agents, aciclovir has an envious tolerability profile. The drug has been used for over 15 years by over 30 million people worldwide, and yet there have been no reports of death or serious irreversible adverse reactions associated with its use. The most frequently reported adverse effects during aciclovir therapy are headache, nausea, diarrhoea, and abdominal pain/cramping. 30 clinical trials (table II) evaluating 3364 patients found no statistically significant differences between aciclovir and placebo for either mild or major adverse events. A transient increase in serum urea and creatinine levels was reported in 1 patient who received aciclovir as an intravenous bolus.[27] There have been several other reports of reversible nephrotoxicity associated with aciclovir when administered at high intravenous doses.[53,54] Aciclovir is eliminated through the kidney and is poorly soluble in urine. Its crystallisation in the renal tubules leads to nephrotoxicity, which is reversible upon discontinuation of the drug. When high dose aciclovir has been used in patients with poor renal function, central nervous system symptoms such as stupor, psychiatric effects and coma have been noted.[55-57] Dosage adjustment in patients with renal impairment and/or elderly patients is important as well as maintaining adequate hydration during intravenous therapy. Rarely, reversible and mild blood dyscrasias have been reported in children and neonates.[20,58,59]

Aciclovir has also been found to be particularly well tolerated during long term use. When used orally for the prevention of genital HSV recurrences over 5 years (n = 389)[38] the most common adverse effects were the same as those reported previously, plus vaginal candidiasis in women. The study showed that the incidence of adverse effects appeared to decrease with time.

Immunocompromised patients tend to have coexisting medical problems. Nevertheless, aciclovir therapy (either acute or suppressive) has not caused other toxic effects beyond reversible nephrotoxicity. While aciclovir is not approved for use in pregnancy, oral therapy is recommended for first episode treatment of genital herpes or disseminated disease in pregnant women.[21] There has been reasonable experience using aciclovir during pregnancy and no teratogenic effects have been registered.[10] The Aciclovir in Pregnancy Registry was established to evaluate the outcomes of pregnancies with exposure to aciclovir. From June 1, 1984 through July 31, 1998, 1017 reports of live births after aciclovir use during pregnancy were gathered (562 exposures were in the first trimester). 28 of 1017 (2.8%) neonates had birth defects, which is similar to the rate in the general population. Based on the available data, the findings do not support an increased risk for birth defects among infants born to mothers exposed to aciclovir during pregnancy.[60] In the US the Food and Drug Administration (FDA) has designated the oral and intravenous formulations of aciclovir as pregnancy category B. This signifies that either animal studies do not indicate a risk to the fetus and there are no controlled human studies, or that animal studies do show an adverse effect on the fetus but well controlled studies in pregnant women have failed to demonstrate a risk to the fetus. In contrast, the FDA has labelled the topical formulation of aciclovir as pregnancy category C, which signifies that either studies have shown that the drug exerts animal teratogenic or em-

bryocidal effects, but there are no controlled studies in women, or that no studies are available in either animals or women. As always, the benefit of treatment must be weighed against the potential risk.

6. Risk *vs* Benefit Analysis

Aciclovir has been proven effective in decreasing clinical symptoms and therefore improves quality of life by decreasing pain, anxiety, depression, and sexual dysfunction associated with HSV lesions.[6] It assists immunocompetent patients with frequently recurrent disease by effectively decreasing the number of recurrences. In immunocompromised hosts, aciclovir hastens recovery from painful mucocutaneous infections and is very effective in suppression of recurrent infections.

Aciclovir use has been proven to be particularly well tolerated. Thus, when therapy is warranted, aciclovir can be used in any patient population regardless of age or disease. The dosage of aciclovir must be adjusted based on renal function, and routine safety and tolerance assessments need to be made as appropriate.

Although aciclovir has been shown to be very effective for acute HSV infections, it has low oral bioavailability (15 to 30%) and a 200mg tablet must be given 5 times daily. Alternative regimens of 400mg thrice daily and 800mg twice daily have also been recommended for the treatment of initial and recurrent HSV disease.[21] Newer drugs, valaciclovir and famciclovir, have enhanced oral bioavailability and also provide convenient dosage regimens (2 to 3 times daily). However, aciclovir is available as a less expensive generic product (table III). Aciclovir is also the only drug available in multiple formulations making it more convenient for patients who have special medication needs (e.g. suspension for paediatric patients).

The emergence of drug-resistant viral strains is a concern for antiviral therapy in general. Though very rarely reported in immunocompetent persons,[40] aciclovir resistance is encountered in the immunocompromised population. The incidence of aciclovir-resistant HSV was investigated in clinical specimens collected from a tertiary care centre over a 1-year period.[61] The definition of *in vitro* HSV-resistance was an IC_{50} (50% inhibitory concentration) of >9 μmol/L for aciclovir. No immunocompetent patients harboured culturable resistant virus whereas 5% of the immunocompromised patients did [most commonly, marrow transplant recipients (14% of total) and patients with symptomatic HIV infection (7% of total)]. The average duration of aciclovir treatment in these patients was 46 days. Hence, highly immunosuppressed patients who were treated long term had the highest risk of aciclovir-resistance.

The most prevalent mechanism of aciclovir-resistance for HSV is a deficiency in thymidine kinase, which prevents intracellular phosphorylation.[4] A study involving HIV positive patients with aciclovir-resistant HSV showed foscarnet to be effective (unlike aciclovir, foscarnet does not require phosphorylation by thymidine kinase).[4] Besides a lack of, or mutated thymidine kinase, an altered DNA polymerase can confer aciclovir resistance. However, studies involving long term use of aciclovir in immunocompetent patients have not shown this pattern of resistance.[38,39]

Table III. Cost of therapy (prices based on average US wholesale price in 1999)

Drug (dosage form)	Dosage and duration of therapy	Cost for course ($US)
Penciclovir (1% cream)[a]	Application of a thin film over the affected area q2h while awake for 4 days	22.38
Aciclovir (capsule)	200mg PO 5 times daily for 5 days	28.50
Aciclovir (tablet)[b]	400mg PO tid for 5 days	9.45
Aciclovir (IV)	5 mg/kg IV q8h for 7 days	875.00[c] 148.00[b,c]
Famciclovir (tablet)	250mg PO bid for 5 days	31.80
Valaciclovir (caplet)	500mg PO bid for 5 days	30.09

a Available as a 2g tube.

b Generic product.

c Based on a 70kg person.

bid = twice daily; **IV** = intravenous; **PO** = orally; **q2h** = every 2 hours; **tid** = 3 times daily.

7. Future

New treatment strategies employing aciclovir are under investigation. For example, aciclovir continues to be evaluated for suppression of genital HSV infection during pregnancy. The safety to mother and neonate, and a clear reduction in caesarean deliveries (and the associated costs and complications), remains to be established.[9,10,35] Another area of interest is the use of aciclovir to decrease the asymptomatic shedding of genital HSV thereby decreasing transmission between discordant couples and possibly from mother to fetus.[14] Further research in this area is ongoing.

In addition, investigators are examining whether famciclovir is able to alter the course of HSV disease; early studies in animals have shown that the drug may reduce the chance of reactivation of latent virus when initiated early in primary infection.[62] Lastly, new antiviral drug discovery programmes are active; the development of inhibitors of herpes virus protease is one example.

References

1. Skoldenberg B. Genital herpes: past, present and future. Antiviral Chem Chemother 1997; 8 (1 Suppl.): 43
2. Whitley RJ, Kimberlin DW, Roizman B. Herpes simplex viruses. Clin Infect Dis 1998; 26: 541-55
3. Rooney JF, Straus SE, Mannix ML, et al. Oral acyclovir to suppress frequently recurrent herpes labialis. Ann Intern Med 1993; 118 (4): 268-72
4. Snoeck R, Andrei G, Gerard M. et al. Successful treatment of progressive mucocutaneous infection due to acyclovir and foscarnet-resistant herpes simplex virus with (s)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC). Clin Inf Dis 1994; 18: 570-8
5. Montgomerie JZ, Becroft DM, Croxson MC, et al. Herpes simplex virus infection after renal transplantation. Lancet 1969; II: 867-71
6. Carney O, Ross E, Ikkos G, et al. The effect of suppressive oral acyclovir on the psychological morbidity associated with recurrent genital herpes. Genitourin Med 1993; 69: 457-9
7. Barton SE. All patients with recurrent genital herpes should be offered suppressive therapy with acyclovir. J Med Virol 1996; 6: 65-6
8. Brown ZA, Selke S, Zeh J, et al. The acquisition of herpes simplex virus during pregnancy. N Engl J Med 1997; 337: 509-15
9. Scott LL, Sanchez PJ, Jackson GL, et al. Acyclovir suppression to prevent cesarean delivery after first-episode genital herpes. Obstetrics & Gynecology 1996; 87 (1): 69-73
10. Smith JR, Cowan FM, Munday P. The management of herpes simplex virus infection in pregnancy. Br J Obstet Gynaecol 1998; 105: 255-60
11. Corey L. Herpes simplex virus infections during the decade since the licensure of acyclovir. J Med Virol 1993; Suppl. 1: 7-12
12. Crooks RJ, Murray A. Valaciclovir-a review of a promising new antiherpes agent. Antiviral Chemistry & Chemotherapy 1994; 5 Suppl. 1: 31-37
13. Sacks SL, Wilson BR. Genital herpes: management issues for the next century. Antiviral Chem Chemother 1997; 8 Suppl. 1: 45-50
14. Wald A, Zeh J, Barnum G, et al. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. Ann Intern Med 1996; 124 (1 Pt 1): 8-15
15. McKenna D, Murphy G. Mucocutaneous herpes simplex infections. Irish Med J 1995; 88 (6): 202-03
16. Momin F, Chandrasekar PH. Antimicrobial prophylaxis in bone marrow transplantation. Ann Intern Med 1995; 123: 205-15
17. Schlech WF, Meagher N, Cohen AD, et al. A randomized double-blind placebo controlled trial of oral acyclovir in renal allograft recipients. Can J Infect Dis 1993; 4 (2): 84-8
18. Scoular A, Barton S. Therapy for genital herpes in immunocompromised patients: a national survey. Genitourin Med 1997; 73: 391-3
19. Wald A, Corey L, Cone R, et al. Frequent genital herpes simplex virus shedding in immunocompetent women. J Clin Invest 1997; 99(5): 1092-7
20. Balfour HH. Antiviral Drugs. N Engl J Med 1999; 340 (16): 1255-67
21. 1998 Guidelines for treatment of sexually transmitted diseases. MMWR Morb Mortal Wkly Rep 1998; 47 (RR-1): 18-24
22. Amir J, Harel L, Smetana Z, et al. Treatment of herpes simplex gingivostomatitis with aciclovir in children: a randomised double blind placebo controlled study. BMJ 1997; 314: 1800-3
23. Spruance SL, Hamill ML, Hoge WS, et al. Acyclovir prevents reactivation of herpes simplex labialis in skiers. JAMA 1988; 260 (11): 1597-9
24. Raborn GW, Martel AY, Grace MGA, et al. Oral acyclovir in prevention of herpes labialis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998; 85: 55-9
25. Shaw M, King M, Best JM, et al. Failure of acyclovir cream in treatment of recurrent herpes labialis. BMJ 1985; 291: 7-9
26. Fiddian AP, Ludmilaivanyi. Topical acyclovir in the management of recurrent herpes labialis. Br J Dermatol 1983; 109: 321-6
27. Mindel A, Adler MW, Sutherland S, et al. Intravenous acyclovir treatment for primary genital herpes. Lancet 1982; I (8274): 697-700
28. Thin RN, Nabarro JM, Parker JD, et al. Topical acyclovir in the treatment of initial genital herpes. Br J Vener Dis 1983; 59: 116-9
29. Corey L, Nahmias AJ, Guinan M, et al. Trial of topical acyclovir in genital herpes simplex virus infections. N Engl J Med 1982; 306 (220): 1313-9
30. Mertz GJ, Critchlow CW, Benedetti J. et al. Double-blind placebo-controlled trial of oral acyclovir in first-episode genital herpes simplex virus infection. JAMA 1984; 252 (9): 1147-51
31. Bryson YJ, Dillion M, Lovett M, et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir. N Engl J Med 1983; 308 (16): 916-21
32. Reichman RC, Badger GJ, Guinan ME, et al. Topically administered acyclovir in the treatment of recurrent herpes simplex genitalis: a controlled trial. J Inf Dis 1983; 147 (2): 336-40
33. Reichman RC, Badger GJ, Mertz GJ, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir. JAMA 1984; 251 (16): 2103-07

34. Nilsen AE, Aasen T, Halsos AM, et al. Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. Lancet 1982; II (8298): 571-3
35. Brocklehurst P, Kinghorn G, Carney O, et al. A randomised placebo controlled trial of suppressive acyclovir in late pregnancy in women with recurrent genital herpes infection. Br J Obstet Gynaecol 1998; 105: 275-80
36. Thin RN, Jeffries DJ, Taylor PK, et al. Recurrent genital herpes suppressed by oral acyclovir: a multicentre double blind trial. J Antimicrob Chemother 1985; 16: 219-26
37. Mertz GJ, Jones CC, Mills J, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection. JAMA 1988; 260 (2): 201-6
38. Goldberg LH, Kaufman R, Kurtz TO, et al. Long-term suppression of recurrent genital herpes with acyclovir. Arch Dermatol 1993; 129: 582-7
39. Douglas JM, Critchlow C, Benedetti J, et al. A double-blind study of oral acyclovir for suppression of recurrences of genital herpes simplex virus infection. N Engl J Med 1984; 310 (24): 1551-6
40. Straus SE, Takiff HE, Seidlin M, et al. Suppression of frequently recurring genital herpes: a placebo-controlled double-blind trial of oral acyclovir. N Engl J Med 1984; 310 (24): 1545-50
41. Shepp DH, Newton BA, Dandliker PS, et al. Oral acyclovir therapy for mucocutaneous herpes simplex virus infections in immunocompromised marrow transplant recipients. Ann of Intern Med 1985; 102: 783-5
42. Meyers JD, Wade JC, Mitchell CD, et al. Multicenter collaborative trial of intravenous acyclovir for treatment of mucocutaneous herpes simplex virus infection in the immunocompromised host. Am J Med 1982; 73: Suppl 1A: 229-35
43. Wade JC, Newton B, McLaren C, et al. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation. Ann Intern Med 1982; 96 (3): 265-9
44. Whitley RJ, Levin M, Barton N, et al. Infections caused by herpes simplex virus in the immunocompromised host: natural history and topical acyclovir therapy. J Inf Dis 1984; 150 (3): 323-9
45. Saral R, Ambinder RF, Burns WH, et al. Acyclovir prophylaxis against herpes simplex virus infection in patients with leukemia. Ann Intern Med 1983; 99: 773-6
46. Prentice HG, Hann IM. Prophylatic studies against herpes infections in severely immunocompromised patients with acyclovir. J Infect 1983; 6 Suppl. I: 17-21
47. Pettersson E, Hovi T, Ahonen J, et al. Prophylactic oral acyclovir after renal transplantation. Transplantation 1985; 39 (3): 279-81
48. Anderson H, Scarffe JH, Sutton RNP, et al. Oral acyclovir prophylaxis against herpes simplex virus in non-Hodgkin lymphoma and acute lymphoblastic leukaemia patients receiving remission induction chemotherapy. Br J Cancer 1984; 50: 45-49
49. Saral R, Burns WH, Laskin OL, et al. Acyclovir prophylaxis of herpes-simplex virus infections. N Engl J Med 1981; 305 (2): 63-7
50. Seale L, Jones CJ, Kathpalia S, et al. Prevention of herpesvirus infections in renal allograft recipients by low-dose acyclovir. JAMA 1985; 254 (24): 3435-3438
51. Straus SE, Smith HA, Brickman C, et al. Acyclovir for chronic mucocutaneous herpes simplex virus infection in immunosuppressed patients. Ann Intern Med 1982; 96: 270-7
52. Stein DS, Graham NMH, Park LP, et al. The effect of the interaction of acyclovir with zidovudine on progression to AIDS and survival: analysis of data in the multicenter AIDS cohort study. Ann Intern Med 1994; 121: 100-8
53. Sawyer MH, Webb DE, Balow JE, et al. Acyclovir-induced renal failure. Am J Med 1988; 84: 1067-71
54. Becker BN, Fall P, Hall C, et al. Rapidly progressive acute renal failure due to acyclovir. Am J Kidney Dis 1993; 22 (4): 611-5
55. Spiegal DM, Lau K. Acute renal failure and coma secondary to acyclovir therapy. JAMA 1986; 255 (14): 1882-3
56. Tomson CR, Goodship THJ, Rodger RSC. Psychiatric side-effects of acyclovir in patients with chronic renal failure. Lancet 1985; II (8451): 385-6
57. Bataille P, Devos P, Noel JL, et al. Psychiatric side-effects with acyclovir [letter]. Lancet 1985; II (8457): 724
58. Grella M, Ofosu JR, Klein BL. Prolonged oral acyclovir administration associated with neutropenia and thrombocytopenia. Am J Emer Med 1998; 16 (4): 396-8
59. Kimberlin D, Powell D, Gruber W, et al. Administration of oral acyclovir suppressive therapy after neonatal herpes simplex virus disease limited to the skin, eyes and mouth: results of a phase I/II trial. Pediatr Infect Dis J 1996; 15: 247-54
60. GlaxoWellcome. Acyclovir pregnancy registry and valacyclovir pregnancy registry interim report. GlaxoWellcome Inc. Worldwide Epidemiology; 1984 Jun 1-1988 Jul 31.
61. Englund JA, Zimmerman ME, Swierkosz EM, et al. Herpes simplex virus resistant to acyclovir. Ann Intern Med 1990; 112: 416-22
62. Field HJ, Thackray AM. Can herpes simplex virus latency be prevented using conventional nucleoside analogue chemotherapy? Antiviral Chem Chemother 1997; 8 Suppl. 1: 59-66

Correspondence and offprints: Dr *Courtney V. Fletcher*, Department of Experimental and Clinical Pharmacology, University of Minnesota, 7-151 WDH, 308 Harvard St. S.E., Minneapolis, MN 55455, USA.
E-mail: Fletc001@tc.umn.edu