Antiviral Chemotherapy

New Directions for Clinical Application and Research

Volume 2

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Editors

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PREFACE

Since the first edition of this monograph in 1986, antiviral chemotherapy has become a major concern to both scientists and clinicians. The explosion of the AIDS epidemic in the United States and the rest of the world has created a demand for new and old drugs to treat opportunistic viral infections such as cytomegalovirus, as well as novel antiretrovirals active against the Human Immunodeficiency Virus. This book is the edited proceedings of the second triennial conference on Antiviral Chemotherapy, held in San Francisco, November 3-5, 1988. The contributors are all authorities in their respective areas, and much unpublished data was included in their reviews. This text should serve as a current reference on antiviral therapy for some time.

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MUCOCUTANEOUS HERPES SIMPLEX VIRUS INFECTIONS: PROPHYLAXIS AND TREATMENT

Gregory J. Mertz, M.D.

INTRODUCTION

Effective treatment for mucocutaneous herpes simplex virus (HSV) infections first became available in the United States in 1982 through 1985 with the licensure of topical, intravenous, and oral acyclovir (1). Licensure occurred at a time of increasing incidence and prevalence of genital herpes infections in the normal host (2). Additionally, development of more aggressive chemotherapy for malignancy, increased utilization of bone marrow, renal, cardiac, and liver transplants, and the AIDS epidemic have all increased the number of immunocompromised patients experiencing mucocutaneous HSV episodes (3). Thus, guidelines for prophylaxis and treatment of mucocutaneous HSV infections should be of interest to both primary care physicians and subspecialists.

Development of antiviral drugs for HSV

At present, only acyclovir is licensed for the therapy of mucocutaneous HSV infections in the Unites States. While many other types of antivirals have been evaluated including surface active agents such as topical ether or betadine (4,5) and immune modulators such as BCG and smallpox vaccines, isoprinosine and levamisol (6-12), none have proven to have useful activity. Interferon has shown promise in adequately controlled clinical trials, but to date the clinical benefit demonstrated in these trials has been very modest (12-15). One clinical trial suggested that 2-deoxy-D-glucose was effective (16), but concerns about the study design, lack of subsequent clinical studies, and lack of efficacy in animal models have created doubt about the initial claims of clinical efficacy (17).

Nutritional supplementation with lysine has been a popular alternative form of therapy, but no adequately performed studies have documented clinical efficacy of lysine treatment (18,19). A variety of nucleoside analogues have been evaluated, including idoxuridine (IDU), IDU in DMSO, adenine arabinoside (vidarabine), phosphonoformate (foscarnet) and acyclovir (20-27). Only the latter two have been found to be effective in animal models and in humans, although there is conflicting data regarding the efficacy of topical foscarnet treatment of recurrent genital herpes infections in the normal adult (26, S. Sacks, personal communication). At present it appears more likely that clinical trials in the U.S. will evaluate the efficacy of the intravenous foscarnet only for treatment of severe cytomegalovirus and acyclovir-resistant HSV infections in the immunocompromised host. As acyclovir is the only antiviral agent licensed in the U.S. for treatment of mucocutaneous HSV infections, the remainder of this chapter will focus on the use of acyclovir.

Acyclovir - mechanism of action and pharmacokinetics

Acyclovir is an acyclic analogue of guanine which owes much of its safety and specificity to the relative inability of uninfected cells to phosphorylate acyclovir. In HSV-infected cells, thymidine kinase specified by HSV phosphorylates acyclovir to acyclovir monophosphate. Further phosphorylation is accomplished by cellular kinases (1,28).

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The active antiviral form, acyclovir triphosphate, is a competitive inhibitor of deoxyguanosine triphosphate. In addition, it inactivates HSV DNA polymerase through formation of a complex with the DNA polymerase and the DNA template and acts as a chain terminator, because acyclovir has no 3'-hydroxyl group for subsequent 5'-to 3'-phosphodiesterase linkages (1,28).

Peak serum concentrations of acyclovir are about 9 μg/ml (40 μM) after an intravenous dose of 5 mg/kg or 250 mg/m^2 versus about 0.2 to 0.7 μg/ml (0.9 to 3.2 μM) after 200 mg oral dose and 0.7 to 1.4 μg/ml (3.2 to 6.4 μM) after a 400 mg oral dose (29-31). Only about 20% of an oral dose is absorbed (30). In HSV-uninfected cells, toxicity occurs at 70 μg/ml (300 μM) to 700 μg/ml (3000 μM), whereas susceptible strains of HSV-1 and HSV-2 have mean 50% inhibiting levels of less than 1 μg/ml (4.6 μM) (32).

Following oral absorption or IV administration, 85 to 90% of the drug is excreted unchanged in the urine (33). Thus, dose adjustment is necessary in patients with renal failure (34).

MUCOCUTANEOUS HSV INFECTIONS IN THE NORMAL HOST

First-episode genital herpes

Untreated primary first episodes of genital herpes (those in persons without prior HSV-1 or -2 infection) tend to be more severe and prolonged as compared to untreated nonprimary first-episode genital herpes (first-episode genital herpes in a person with prior infection with HSV of the heterologous type) (35). Overall, HSV-2 causes 70-90% of primary and 99% of nonprimary first-episodes (35), although there is some geographic variation in these proportions.

Untreated primary episodes usually persist for several weeks and are characterized by bilateral, painful lesions, dysuria, and systemic symptoms such as fever and malaise (35-37). Symptoms of aseptic meningitis occur in up to 25% of patients, although most patients with meningitis are not ill enough to require hospitalization (35-37). Lesions typically progress through stages of vesiculation, ulceration, and crusting, and most patients develop crops of new lesions. Systemic symptoms and complications such as aseptic meningitis are uncommon in patients with nonprimary first episodes (35-37).

Diagnosis

Most authorities recommend viral culture with typing in patients suspected of having first-episode genital herpes (36,37). Although patients presenting with typical signs and symptoms generally can be diagnosed with confidence by an experienced clinician, less typical presentations must be differentiated from other infectious and noninfectious causes of genital ulcers. Furthermore, virus type is the most important predictor of the likelihood and frequency of subsequent episodes. Patients with primary HSV-2 infections are likely to have recurrent episodes and may have frequent episodes, whereas those with primary HSV-1 genital infections are less likely to have recurrent episodes and are unlikely to experience frequent recurrences (35,38).

Primary and nonprimary genital herpes cannot be reliably differentiated by clinical findings alone, although severe first episodes with complications such as aseptic meningitis are almost always primary episodes (35). Serologic studies of acute and convalescent sera are required to differentiate primary from non-primary

infection (39-41). Recently, Corey et al demonstrated that recurrence rates were lower in the second year following first-episode genital HSV-2 infections in patients with nonprimary compared with primary first episodes (42). Nonetheless, serologic differentiation of primary from nonprimary first episodes is generally not performed outside the research setting. In addition, currently available commercial serologic assays cannot reliably differentiate nonprimary first episodes from first-recognized episodes in persons with unrecognized acquisition in the past (40,41).

Management of first-episode genital herpes

Oral, intravenous, and topical acyclovir have all been shown to be effective for treatment of first-episode genital herpes in placebo-controlled trials, and all three are licensed for this indication by the U.S. Food and Drug Administration (FDA). Although the three preparations have not been directly compared in randomized, controlled trials, topical acyclovir therapy appears to be significantly less effective when compared to oral and intravenous acyclovir treatment (43-49). Yet when three independent, placebo-controlled trials performed at the same center were compared controlling for differences in placebo groups, both oral and intravenous acyclovir appeared to have greater virologic and clinical efficacy when compared to topical acyclovir (43). Unlike topical therapy, treatment with either oral or intravenous acyclovir shortened the duration of dysuria, demonstrated a trend in decreasing the duration of systemic symptoms, and markedly decreased the proportion of patients forming crops of new lesions on treatment (43-49) (Table 1).

Table 1: Signs and symptoms of first-episode primary genital herpes in acyclovir (ACV) - compared with placebo-treated patients.

	Treated Patients					
Median no. days after start of treatment	Topical ACV n=28	Placebo ointment n=23	I.V. ACV n=14	Placebo n=13	Oral ACV n=33	Placebo n=27
Local itching	4*	8	2§	8	4*	6
Local pain	5*	7	3*	7	5§	9
Dysuria	4	5	4*	7	3*	6
Vaginal discharge	6	7	4§	11	6	8
Percentages with systemic symptoms at 7 days of treatment	18%	30%	0	46%	9%	18%
Complete crusting of lesions	8*	13	6§	13	7§	13
Complete healing of lesions	11*	15	9§	21	13§	20
Percent forming new lesions after 48hr of therapy	(69%)	(74%)	20%§	69%	13%§	74%

* $p<0.05$ Mantel-Cox Test
§ $p<0.01$ Mantel-Cox Test

All comparisons are between patients who had described symptoms at time of enrollment into the study. (From Corey L, Benedetti J, Critchlow C, et al: Treatment of primary first-episode genital HSV infections with acyclovir: Results of topical, intravenous and oral therapy. J Antimicrob Chemother 12(b):79;1983, with permission).

Although the indications for treatment of recurrent genital herpes are controversial, treatment is clearly indicated in most patients with first-episode genital herpes. Treatment with oral or intravenous acyclovir initiated within the first week results in an eight to 11 day mean reduction in the duration of viral shedding, a four day mean reduction in pain, and a seven or more day mean reduction in time to healing of all lesions (43). Oral acyclovir is less expensive and more convenient to administer than intravenous acyclovir, and it has become the therapy of choice for first-episode genital herpes. Combination therapy with oral and topical acyclovir and oral acyclovir plus isoprinosine has been evaluated, and neither combination was found to be more effective than treatment with oral acyclovir alone (50,51).

As would be predicted from animal studies, neither oral nor intravenous acyclovir treatment following the onset of lesions in first episodes prevents subsequent episodes nor does it influence the frequency of recurrent episodes in the first year after treatment of the first episode (46,47,49,52). Bryson and her collaborators have suggested that treatment of first episodes with oral acyclovir may decrease the frequency of recurrences in the long term (those in the second year or more after the first episode) (52), but data collected by Mertz et al failed to support this finding (53). This issue remains unresolved.

When first-episode genital herpes is suspected, therapy with oral acyclovir should be initiated pending results of viral culture and tests for other agents considered in the differential diagnosis. In general, a dose of 200 mg orally five times daily is employed for 10 days. Both higher doses (eg. 400 mg) and longer duration of therapy have been evaluated (Y. Bryson, personal communication). Although these alternate regimens are well tolerated, there is no clear evidence at present that they result in enhanced virologic or clinical benefits in the normal host. If hospitalization is clinically warranted, intravenous acyclovir therapy can be initiated at a dose of 5 mg/kg/dose over one hour every eight hours. Most patients can be discharged within a few days, and a 10-day course of treatment can be completed with oral acyclovir. Treatment with topical acyclovir 5% ointment (six times daily) is generally not recommended if oral acyclovir therapy is available because of the virologic and clinical superiority of the latter treatment (43).

Recurrent genital herpes

An episode of recurrent genital herpes in normal adults is characterized by unilateral, localized lesions which progress through the same stages as lesions in first-episode disease but which heal in a mean of nine to 10 days (35). Unique to recurrent episodes is the prodrome, a symptom such as pain, itching, or tingling, which precedes the onset of lesions in about 50% of persons with recurrent genital herpes. Features common in first episodes such as cervical shedding of virus in women and new lesion formation are much less common, occurring in about 5% to 12% and 28% to 43% of recurrent episodes, respectively (35).

HSV-2 was isolated from 98% of persons with recurrent genital herpes followed at a research clinic in Seattle (35). If an immunologically normal patient with recurrent genital herpes has had a positive culture for HSV in the past, repeat cultures are rarely indicated unless used to evaluate recurrent symptoms not typical of genital herpes. However, virologic confirmation is encouraged in patients without a history of a positive culture.

Episodic treatment of recurrent genital herpes

Episodic therapy of recurrent genital herpes with the 5% ointment available in the U.S. has not been shown to be effective either when started by the patient at the prodrome or first sign of lesions or by the physician after the onset of lesions (46,55-56). The ointment is not licensed for this indication, and this form of treatment is not recommended.

Episodic treatment with oral acyclovir is clinically effective, particularly when therapy is initiated by the patient at the first sign of prodrome or lesions (57). Reichman et al demonstrated a statistically significant advantage in patient-initiated versus physician-initiated treatment in parameters such as the duration of viral shedding and time to crusting and healing (57) (Table 2). However, even when episodic therapy with oral acyclovir is patient-initiated, the benefit is not as dramatic as with treatment of first episodes, suppression of frequently recurrent genital herpes, or treatment or suppression of episodes in the immunocompromised host.

Table 2. Effect of orally administered acyclovir on the course of recurrent genital herpes.

	Part A (physician-initiated therapy)		Part A (Patient-initiated therapy)	
	Acyclovir	Placebo	Acyclovir	Placebo
Lesions present at first clinic visit:				
Duration of virus sheddfhg	2.0±0.1*¥	3.0±0.3	2.1±0.2¥	3.4±0.3
Time to crusting	2.1±0.2	2.3±0.2	2.4±0.2¶	3.2±0.3
Time to healing	6.3±0.3§	7.0±0.3	5.5±0.3£	6.5±0.5
All lesions				
Duration of virus shedding	2.1±0.2¥	3.1±0.3	2.1±0.2¥	3.9±0.3
Time to crusting	2.2±0.2£	2.7±0.2	2.4±0.2¥	3.9±0.3
Time to healing	6.3±0.3¶	7.4±0.3	5.7±0.3¥	7.2±0.5
Duration of itching	2.5±0.2	2.9±0.3	2.8±0.3§	3.6±0.3
Duration of pain	2.8±0.2	3.1±0.3	3.0±0.3§	3.4±0.3
Development of new lesions during therapy, %	16.0	24.5	7.3	21.7

* Days (mean±SEM), as measured from the first clinic visit.
¥ Duration significantly less than observed in placebo group (P≤.001) by logrank test.
¶ Duration significantly less than observed in placebo group (P≤.01) by logrank test.
§ Duration not significantly less than observed in placebo group (0.05≤p≤.10), by logrank test.
£ Duration significantly less than observed in placebo group (p≤0.5), by logrank test.

(From Reichman RC, Badger GJ, Mertz GJ, et al: Treatment of recurrent genital herpes simplex infections with oral acyclovir: a controlled trial. JAMA 251:2103;1984, with permission) Copyright 1984, American Medical Association.

When deciding whether to recommend episodic treatment to patients with recurrent HSV infection, the potential benefits, which include a mean reduction in the duration of viral shedding and healing of less than two days and a mean reduction in the duration of symptoms of less than a day (57), must be weighed against the cost and inconvenience of taking medication. This author generally discourages episodic therapy for patients with mild recurrences but considers

episodic therapy for patients who experience prodromes and describe frequent new lesion formation and lesions that last for more than a week to 10 days. Patients with frequent recurrences generally prefer suppressive to episodic treatment regardless of the severity or duration of episodes (58-59).

Neither significant adverse effects nor emergence of acyclovir-resistant HSV have been described in normal adults employing episodic treatment for periods of one or two years, and at present, there does not appear to be any rationale for recommending routine laboratory monitoring for drug toxicity or screening for drug resistance in this setting (58-59).

Suppressive acyclovir therapy

In contrast to the modest clinical benefit from episodic treatment in normal adults, daily suppression of episodes with oral acyclovir has been dramatically effective in patients with a history of frequently recurrent genital herpes. A variety of studies have documented the effectiveness of daily suppressive therapy for periods of three months to four years (58-70). Mertz et al have reported the results of a large, multicenter, trial comparing suppressive and episodic treatment for up to two years in almost 1200 patients with a mean frequency of over 12 recurrences per year prior to enrollment (58-59). Suppressive treatment during the first year of the trial was placebo-controlled, but episodic treatment employed open-labelled acyclovir. During year one, patients treated with daily acyclovir suppression (400 mg PO bid) had a mean frequency of only 1.8 recurrences per year compared with 11.4 per year in patients on placebo suppression plus episodic therapy of recurrences; 44% of patients on suppressive therapy remained free of recurrences for one year versus only 2% of those treated with placebo suppression (58, Figure 1). In the second year of the trial, patients could choose either form of treatment, and 89% chose suppressive over episodic treatment. In patients treated with suppressive treatment for two years without interruption, 45-50% were free of recurrences during each year of treatment, and 29% had no episodes for two consecutive years (59).

A variety of doses and dosing intervals have been evaluated, including 200 mg one to five times daily, 400 mg one or two or three times daily, and 800 mg once daily. The FDA currently recommends a dose of 200 mg tid. This dose appears highly effective as does 400 mg bid (58,59,62,65,70). A dose of 200 mg bid appears as or only slightly less effective as compared to 200 mg tid and 400 mg bid (58,59,60,62,70). The former dose should be considered in patients who are particularly concerned about cost. Higher or more frequent doses do not appear necessary for most immunologically normal patients. In patients with persistent recurrences despite standard suppressive doses of acyclovir, increasing the dose to 200 mg five times daily and 400 mg three or four times daily appeared to be effective (70). Both anecdotal experience and limited data from clinical trials suggest that a dose of 200 mg once daily is markedly less effective than the regimens described above and may be completely ineffective (62).

When oral acyclovir was licensed in 1985 and suppressive therapy was approved for up to six months, results of three to six month trials were available to the FDA. Since then, reports of several one year trials, a two year trial, and a small four year trial have been published. These reports indicate that long-term suppressive treatment is very safe and extremely well tolerated (58,59,62,65,70). Concerns about acyclovir resistance in HSV isolates recovered from normal adults

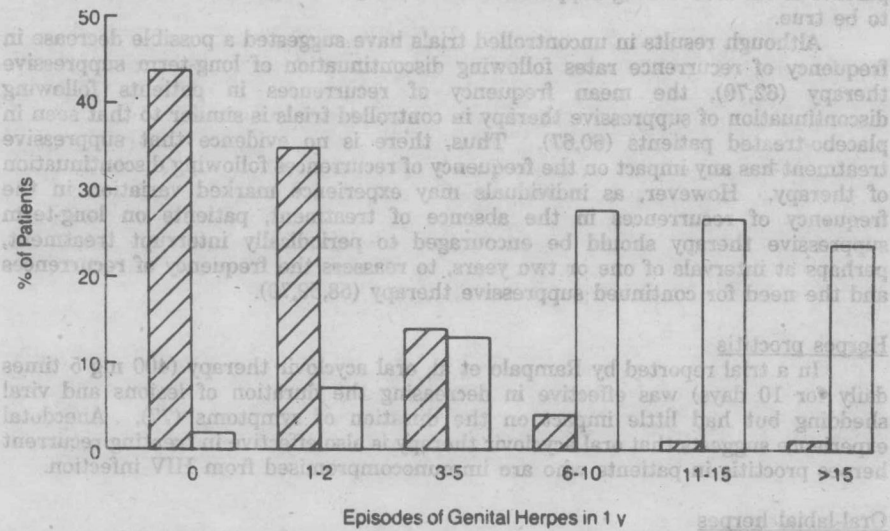

Figure 1: Frequency of genital herpes episodes in one year among 519 patients receiving continuous suppression (hatched bars) with 400 mg of acyclovir orally twice daily for one year and among 431 patients (open bars) receiving placebo (episodic treatment) for one year. All patients received open-labelled acyclovir for five days during investigator-confirmed episodes of genital herpes. (From Mertz GJ, Jones CC, Mills J, et al: Long-term acyclovir suppression of frequently recurring genital herpes simplex virus infection: A multicenter double-blind trial. JAMA 206:201;1988, with permission).

during suppressive therapy in one early trial (68) have not been supported by acyclovir susceptibility testing of isolates from larger, long-term trials (58,70,71). Sperm motility and morphology have been studied in a placebo-controlled trial in men using up to 1 gram per day of oral acyclovir for six months, and no adverse effect was found (72). As in the case of long-term episodic therapy, there does not appear to be any indication for routine laboratory monitoring for drug toxicity or screening of isolates for acyclovir resistance in normal adults during long-term suppressive oral acyclovir therapy at doses up to 1 gram/day (58,59,62,64,65,70).

Acyclovir chemosuppression may also be indicated in patients with infrequent recurrences if they are associated with severe complications such as erythema multiforme, eczema herpeticum, or herpetic whitlow leading to interruption of work (73-75). However, most patients do not derive adequate benefit to justify the cost and inconvenience of suppressive therapy unless they experience frequent recurrences (more than 6-8/year). Patients should be warned that viral shedding during episodes (58,59,68,70) and transmission to sexual partners (76) have been documented in normal adults during suppressive therapy. Furthermore, no studies have been performed to determine whether the risk of transmission to a sexual