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MINIREVIEW

Acyclovir Prophylaxis for Herpes Simplex Virus Infection

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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 disease that are localized to cutaneous or mucosal surfaces and last from 4 to 10 days. Immunocompromised (IC) patients develop HSV episodes that may last more than 30 days, produce extensive necrotic lesions, and disseminate viscerally.

A series of clinical investigations over the last 6 years have shown the acyclic guanosine derivative acyclovir (ACV) to be effective in both shortening the course and suppressing the occurrence of symptomatic HSV type 1 (HSV-1) and HSV-2 infections in both normal and IC patients. This review discusses the use of chronic suppressive and prophylactic ACV, outlines indications for its use, and provides guidelines for treatment regimens.

SUPPRESSIVE ACV IN IC PATIENTS

Reactivation of HSV infection is a major cause of morbidity in IC patients (62, 64); seropositive recipients of bone marrow and organ transplants, patients with hematologic malignancies undergoing induction chemotherapy, patients with acquired immunodeficiency syndrome (AIDS), malnourished patients, patients with extensive burns, and individuals with primary immunodeficiency syndromes develop more frequent and severe outbreaks of HSV (19, 62, 64). A total of 50 to 80% of seropositive bone marrow or renal transplant recipients or acute leukemics undergoing induction chemotherapy experience reactivation of HSV, usually during the first 30 days after transplant (45, 46, 48). These episodes usually cause prolonged pain (mean duration, 13 days) and may occasionally disseminate mucocutaneously or viscerally (33).

Several studies have demonstrated the efficacy of ACV in the treatment of established HSV infection in IC patients (9, 33, 37, 50, 62, 64). In general, the clinical effects have included a 60 to 80% reduction in the time virus can be isolated from lesions (viral shedding), a 30 to 60% reduction in local symptoms, such as pain, and a 25 to 65% decrease in the time to complete healing of lesions. Most studies of therapy of mucocutaneous HSV infection in IC patients have used intravenous (i.v.) ACV at a dose of 250 mg/m^2 every 8 h or an oral formulation of 400 mg (two 200-mg capsules) five times per day. Some benefit has also been achieved with topical application of the 5% ointment six times per day. Although most of the patients in controlled trials have had bone marrow, renal, or heart transplants or hematologic malignancies, anecdotal reports indicate that ACV is also effective in treating HSV recurrences in patients with AIDS, common variable immunodeficiency, and heart-lung transplants (6, 52, 55).

There are, however, disadvantages associated with the treatment of established disease. First, despite the fact that ACV speeds the healing of lesions, patients still require an average of 2 weeks of treatment for the resolution of lesions (33). Further, IC patients often experience prompt recurrences when ACV therapy is stopped (62). Finally, prolonged pain and extensive lesions may occur because of delays in diagnosis due to the difficulty in distinguishing HSV mucositis from oral candida or mucositis associated with cytotoxic drugs. Thus, the administration of prophylactic ACV to suppress recurrent HSV infection has been proposed to obviate the problems encountered with intermittent therapy.

Several trials, including a variety of dosage regimens, have demonstrated that i.v. and oral ACV use decreases the number and duration of herpetic recurrences during the time drug is administered in bone marrow and renal transplant recipients and leukemics undergoing induction chemotherapy (2, 20, 42, 45, 46, 48). In most of the studies, from 0 to 10% of patients receiving ACV developed HSV recurrences while on therapy (defined as either excretion of HSV or development of lesions), compared with a 60 to 80% recurrence rate in placebo-treated patients. About half of the breakthrough recurrences in patients with ACV therapy are episodes of asymptomatic viral shedding rather than clinical lesions. Effective dosage regimens include i.v. doses of 250 mg/m^2 every 8 to 12 h and oral capsules of 200 mg four times per day to 400 mg five times per day for bone marrow transplant recipients and leukemics and 200 mg two to three times per day for renal transplant patients (2, 20, 42, 45, 46, 48, 61). Anecdotal reports indicate that ACV at 200 mg per os (p.o.) two to five times per day is effective in preventing recurrences for as long as 6 months in patients with common variable immunodeficiency syndrome (55). A once-daily dose of 250 mg/m^2 i.v. was not effective in suppressing recurrences in bone-marrow transplant patients, indicating that relatively constant levels of ACV are necessary to achieve a therapeutic effect in that population (49). Direct comparisons of i.v. versus oral regimens have not been made, although symptomatic breakthroughs appear to be more common with oral ACV, apparently related to the inability of sick patients to take medication at the prescribed dosage regimens (61).

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TOXICITY ASSOCIATED WITH SUPPRESSIVE THERAPY

ACV has not affected renal function in renal transplant recipients (48) or engraftment in bone marrow transplant patients (20, 46, 61). Although an early report demonstrated suppression of in vitro T-cell proliferation by ACV (26), subsequent in vitro studies (28, 54) and clinical studies in IC hosts have not demonstrated an intrinsic immunosuppressive effect of ACV. One study demonstrated that among marrow transplant recipients receiving methotrexate for graft-versus-host-disease prophylaxis, patients treated with ACV had significantly faster engraftment than patients receiving placebo (61). Additionally, a trend toward decreased incidence and severity of graft-versus-host disease was observed in ACV- as compared with placebo-treated patients (20). Neurologic sequelae have been reported in IC patients with the use of high-dose i.v. ACV (500 mg/m^2). These effects have been very infrequently reported with the lower i.v. doses used for prophylactic therapy and rarely with oral medication. Transient elevations of transaminases have been noted in 5 to 10% of ACV recipients, but the relationship of these elevations to ACV use has not been established (16). In our experience, such transient elevations have usually been associated with other drugs or with other viral pathogens, and rechallenge of the patient with ACV has not resulted in liver function abnormalities.

EMERGENCE OF RESISTANCE

In vitro resistance to ACV can result from thymidine kinase (TK)-deficient, TK-altered, or DNA polymerase-resistant strains of HSV. Clinically, TK deficiency is the most common mechanism of resistance of HSV to ACV (10, 47). Although animal studies have suggested that TK-deficient mutants are less virulent and less able to establish neural latency (18, 51), TK-deficient strains have been isolated from ACV-treated IC patients with active HSV infection (8, 51, 60). ACV-resistant strains of HSV have also been recovered from patients who have never been treated with ACV (15, 40). The clinical significance of ACV resistance is further confounded by the observation that TK-deficient mutants have been isolated from lesions from IC patients who have responded to treatment with ACV (8, 14, 62); no clear relationship has been established between response to prophylactic therapy and in vitro susceptibility testing of specific clinical isolates. The relationship between in vitro resistance to ACV and the subsequent development of breakthrough recurrences while on suppressive therapy is also unclear. Some studies have found breakthrough isolates resistant in vitro to ACV (42), whereas in others HSV isolates were susceptible (61).

Extrapolating from experiences with bacterial infections, it might be argued that the low levels of ACV in serum that are achieved with chronic oral therapy would provide the appropriate conditions for the selection of resistant viral strains. On the other hand, because the likelihood of mutation to resistance is proportional to the number of replicating viruses and the highest titers of virus are found in established lesions in compromised patients, prophylactic ACV might reduce the chances for emergence of ACV-resistant HSV strains (1). Most of the resistant isolates from IC patients have been from patients undergoing multiple courses of therapy for established infection. However, the major clinical use of ACV has also been with intermittent therapy. Further studies are warranted to determine whether chronic daily or frequent intermittent ACV use would be more likely to foster the emergence of ACV-resistant viral strains.

RECOMMENDATIONS REGARDING USE OF ACV IN IC PATIENTS

We believe that the frequent reactivation rate of ACV in IC patients, the delay in clinical recognition of disease, and the slow clinical response of established infection warrants the use of prophylactic, systemic ACV in selected IC patients. We recommend routine screening for HSV antibodies in patients undergoing bone marrow transplants or induction chemotherapy for hematologic malignancy (Fig. 1). Seropositive patients should receive ACV prophylaxis beginning the day of conditioning or induction and continuing for a period of about 6 weeks. Some investigators stop medication when the absolute neutrophil count is >500 or when marrow engraftment has occurred. Either ACV at 200 mg p.o. four times a day or ACV at 250 mg/m^2 i.v. every 8 h can be used. A similar approach can be advocated for seropositive patients undergoing renal, cardiac, or liver transplantation. For renal transplant patients, dosage modifications include an oral dose of 400 mg after the last hemodialysis before surgery and, after surgery, 200 mg p.o. three times a day if creatinine clearance is ≥30 ml/min and 200 mg p.o. twice a day if creatinine clearance is <30 ml/min.

HSV infections in patients with AIDS are common. Although i.v. and p.o. ACV have been used successfully to treat established outbreaks in AIDS patients, recurrences are common (3, 52). Patients with human immunodeficiency virus infections who have severe, progressive, nonhealing, or frequently recurring perianal, genital or oral-labial HSV lesions should be considered candidates for chronic suppressive therapy. Although there are no controlled studies to determine the most effective dosage regimens or long-term efficacy of ACV in patients with AIDS, a dose of 400 mg p.o. three to four times daily appears reasonable. Because chronic suppression of HSV outbreaks is one of the few effective measures that can be taken to improve the quality of life of patients with AIDS, continuation of ACV therapy indefinitely may be justified.

Anecdotal reports also indicate that chronic ACV appears effective in suppressing clinical recurrences of HSV in individuals permanently or temporarily immunosuppressed because of primary immunodeficiency syndromes or treatment of collagen vascular disease, solid tumors, or chronic lung disease with steroids or cytotoxic agents or both (55). ACV doses of 200 mg p.o. two to five times per day have been used with success. The duration of therapy should be guided by the persistence of severe disease.

SUPPRESSIVE ACV USE IN IMMUNOLOGICALLY NORMAL PATIENTS

HSV infection in immunologically normal individuals spans a broad clinical spectrum that includes asymptomatic infection; recurrent, localized orolabial or genital lesions; severe, frequently recurring disease; and outbreaks associated with systemic complications, such as erythema multiforme, eczema herpeticum, or recurrent aseptic meningitis.

ACV in topical, oral, and i.v. forms has been shown to be effective in treating first-episode primary and nonprimary genital HSV infections by decreasing the duration of lesions by 29, 35, and 57%, the duration of viral shedding by 55, 80,

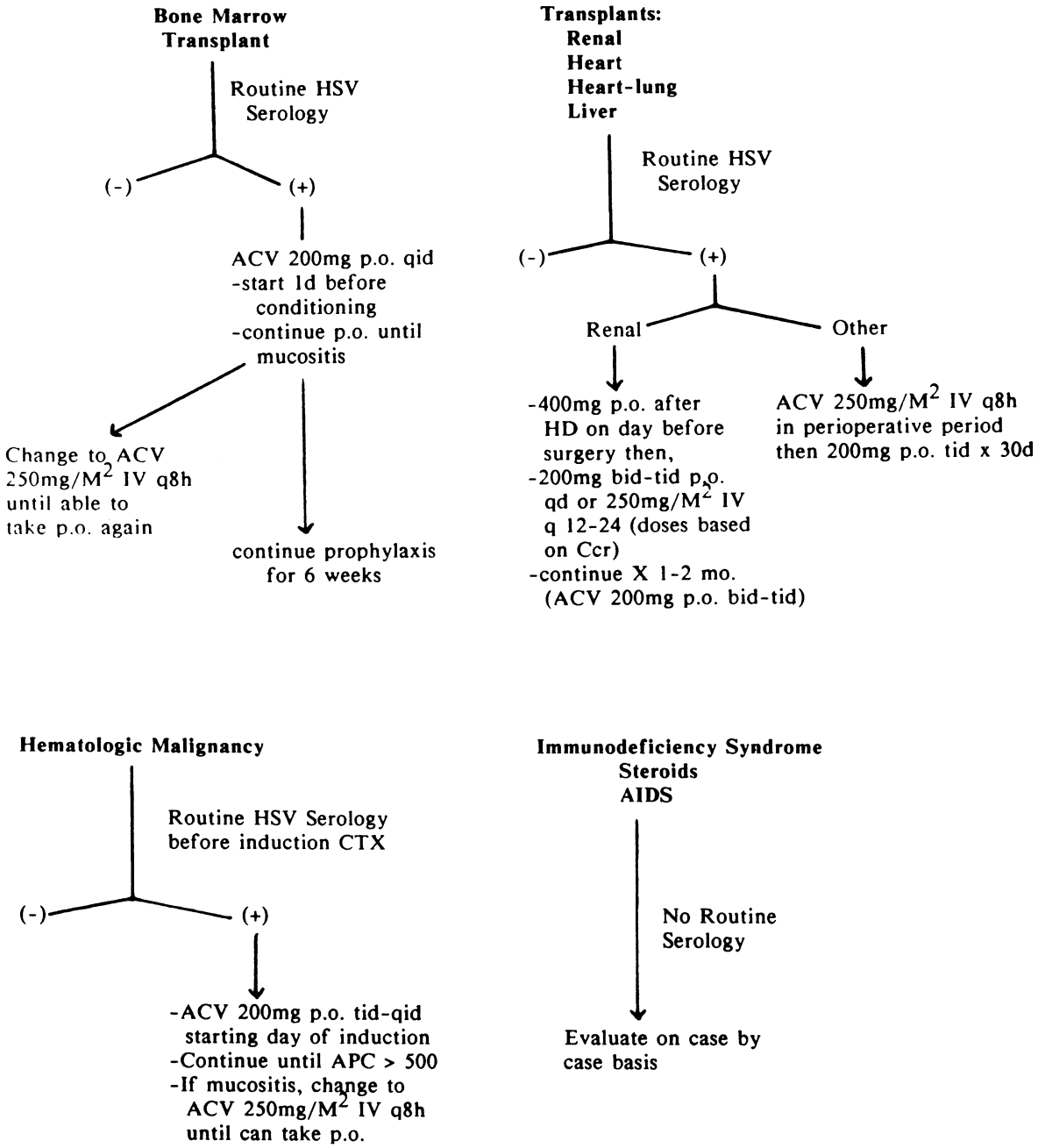

FIG. 1. Strategy for use of prophylactic ACV in IC patients. Abbreviations: qid, 4 times daily; q8h, every 8 h; HD, hemodialysis; bid, twice a day; tid, 3 times a day; qd, daily; Ccr, creatinine clearance; CTX, chemotherapy; APC, absolute poly count.

and 85%, and the duration of pain by 26, 44, and 57%, respectively (7, 11–13, 17, 34, 38, 58). In recurrent genital HSV, topical ACV shortens the period of viral shedding but does not significantly affect the duration of pain or time to healing (12, 17). Oral ACV does not produce significant reduction in symptoms of recurrent genital HSV episodes but does decrease the duration of viral shedding and slightly reduces the time to healing (38, 43).

Recurrence rates of genital herpes vary in individuals over time. Most patients who seek medical attention for symptomatic genital HSV report from five to eight recurrences per year (16, 24). Long-term natural history studies are not available to predict reliably whether and when recurrences decrease or change over time. At currently used dosages, there is no convincing evidence that treatment of first-episode genital HSV infection with ACV has an effect on the subsequent recurrence rate (6a, 7, 30, 31, 36).

Four studies (16, 22, 35, 57) involving 275 patients with frequently recurring genital herpes (4 to 12 episodes per year) who used ACV in doses of 200 mg two to five times daily for up to 4 months showed that 65 to 85% of patients became completely free of recurrences during treatment. Preliminary data suggest that a once-daily dose of 800 mg is also effective in suppressing recurrences (S. R. Mostow, J. L. Mayfield, and J. J. Marr, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 788, 1985).

More than 90% of persons with frequently recurring genital herpes have a significant reduction in the number of clinical recurrences while on suppressive therapy. Compared with untreated recurrences, breakthrough recurrences are associated with milder symptoms, shorter duration of viral shedding, and shorter duration of lesions. Definitive studies are not available on the effect chronic suppressive ACV has on the frequency of asymptomatic genital tract excretion of virus and how this may impact on subsequent risk of transmission of disease. Published reports and our own experience indicate that occasional cases of transmission occur during therapy, usually due to sexual activity at the time of a mild breakthrough recurrence (44; L. Corey, personal observations).

TOXICITY OF SUPPRESSIVE ACV

Because frequently recurring genital herpes may plague a patient for years, many patients may desire to take oral ACV continuously for prolonged periods, raising the issue of long-term safety. Preclinical animal studies of ACV showed no drug-related toxicity, carcinogenesis, effect on fertility, or abnormal fetal development. Although ACV has been shown to have mutagenic potential in 2 of 11 in vitro systems, the implications of these results for humans treated with chronic suppressive therapy for long periods are unknown (59).

Side effects of daily suppressive oral ACV are uncommon. Data from a recent multicenter trial of over 1,000 patients taking doses of two 200-mg capsules three times daily for 1 year showed no significant clinical or laboratory toxicity (J. L. Drucker, L. G. Davis, and the Herpes Collaborative Group, Abstr. 2nd World Congr. Sex. Transm. Dis., 1986). A recent study also showed no effect on sperm motility or morphology in men with recurrent genital herpes who were treated with two or five capsules daily for 6 months (L. Corey and A. Paulsen, unpublished data).

HSV RESISTANCE IN IMMUNOCOMPETENT PATIENTS

As with IC patients, the relationship between in vitro resistance to ACV and duration of chronic suppressive therapy in immunocompetent patients remains unclear. Comparison of the in vitro 50% inhibitory dose values of 183 HSV-2 strains isolated before, during, and after chronic suppressive therapy has shown no differences between ACV- and placebo-treated patients (39). The six HSV-2 isolates from breakthrough recurrences in this study were all susceptible to ACV. In another study, three HSV-2 isolates from patients who had breakthrough recurrences were found to be highly resistant to ACV (57). However, subsequent HSV-2 isolates from these same patients were susceptible to ACV. About 6% of HSV-2 isolates from persons never receiving ACV have exhibited in vitro ACV resistance (50% inhibitory dose, >3 μg/ml) (29). These persons may respond less well to standard dosages of ACV (J. M. Douglas, M. Thouless, O. Schmidt, and L. Corey, Clin. Res. **32**:42A, 1984). Continued surveillance of HSV strains associated with breakthrough recurrences is necessary to assess the frequency of appearance of resistance, mechanisms of resistance, and virulence of resistant strains in terms of infectivity and latency.

CLINICAL INDICATIONS FOR SUPPRESSIVE ACV IN IMMUNOLOGICALLY NORMAL INDIVIDUALS

ACV appears safe and effective when used continuously for up to 1 year. Because of unknown long-term effects and the possibility of inadvertent use in early pregnancy, the drug should not be used indiscriminately.

Absolute indications for the use of intermittent-versus-chronic-suppressive ACV therapy based on the number of outbreaks are difficult to construct. Patients with frequently recurring genital herpes who have considerable physical discomfort, emotional upset, and potential for transmission of infection to sexual partners are candidates for chronic suppressive therapy. Persons with six or more recurrences per year derive the greatest cost benefit from such an approach. Persons who have three to four genital recurrences per year are best managed with supportive care and acute intermittent oral therapy. Similarly, persons with frequent recurrences who are minimally symptomatic and not at risk of transmitting infection to an uninfected partner may also be best served by supportive or intermittent therapy. The cost of chronic therapy ($1.50 to $2.50/day) may affect this decision. Studies indicate it takes 5 to 7 days of therapy before clinical effects can be seen. Intermittent use, e.g., weekend therapy, has been associated with subsequent clinical recurrences and transmission of disease (44, 56), indicating that ACV must be administered on a daily basis.

OTHER CLINICAL SETTINGS FOR SUPPRESSIVE ACV

Chronic suppressive therapy should also be considered for those individuals whose HSV recurrences are associated with serious (and occasionally life-threatening) systemic complications, such as erythema multiforme (4, 5, 21), recurrent aseptic meningitis (53), and eczema herpeticum (27, 63).

Herpetic whitlow is an occupational hazard of medical and dental personnel which, like other HSV infections, causes painful recurrences that are infectious and may interfere with patient care. Daily oral ACV has been reported to be successful in suppressing frequently recurring herpetic whitlow and should be considered when this condition interrupts job performance (25).

Short-term prophylaxis is also useful in the perioperative period. Dermabrasion of the face is a predictable trigger of orolabial HSV in seropositive patients, and, when reactivated, the HSV may spread to abraded areas, resulting in delayed healing and scarring. Similarly, surgeries involving the trigeminal ganglion or lumbar disks may reactivate HSV (23, 41). Although HSV recurrences resulting from these procedures may not be medically serious, they pose an inconvenience, a potential source of nosocomial infection, and an additional source of pain in the postoperative period that might be prevented by a short perioperative course of ACV. Short-term prophylaxis has also been used to decrease sun-associated oral-labial HSV, such as in skiers (S. Spruance, M. Hamill, W. Hoge, G. Davis, and J. Mills, 26th ICAAC, abstr. no. 1182, 1986).

One theoretical use for short-term suppressive therapy is in pregnant women with recurrent genital HSV; ACV administration late in the third trimester might prevent outbreaks near the time of delivery and avoid the need for cesarean section. The incidence of HSV infection in neonates born to women with HSV-2 antibody is low (about 1 in 2,000 births), so routine use of ACV in seropositive women to prevent neonatal HSV infection is unlikely to be cost-effective. However, among women with frequently recurring genital HSV who have a high rate (20 to 50%) of cesarean section, effective prophylaxis would be desirable. Although ACV is not teratogenic in animals, until studies defining its

pharmacology and safety in pregnancy are available, the use of suppressive oral ACV late in pregnancy cannot be advocated. A national registry for reporting cases of women who inadvertently receive ACV in pregnancy has been established by the Centers for Disease Control and the manufacturer of ACV, the Burroughs Wellcome Co. No teratogenic effects have been identified in children born to women thus far reported.

Short-term ACV might also be useful as a "morning-after pill" to protect seronegative individuals from primary infection after contact with a sexual partner who has an active lesion or who develops prodromal symptoms or a lesion during or soon after sexual contact (32). No data are available to determine whether this is an effective strategy. If ACV increases the frequency of asymptomatic primary infection, this strategy may be more harmful than useful.

TREATMENT GUIDELINES FOR ACV PROPHYLAXIS

Doses of oral ACV from 400 to 1,000 mg/day have been effective in immunocompetent persons. A dosage of 600 mg/day in three doses is a reasonable starting point, although some patients may be adequately suppressed on 400 mg/day and some may require 800 mg/day. We treat patients for periods of 6 to 9 months. The rationale for limiting therapy to these time periods stems from data that demonstrate a marked variation in the natural history of recurrent genital HSV infection. At least 25% of individuals experience a 50% increase or decrease in their recurrence rate over a period of 8 months (16). Patients may present to their physicians when they are having a flurry of recurrences that may be a temporary change from their usual baseline recurrence rate. Therefore, we recommend stopping ACV after 6 to 9 months and allowing patients to experience two to three recurrences to determine whether the underlying recurrence rate is still severe enough to warrant continued prophylaxis. If it is, the prophylaxis can be reinitiated. "Drug holidays" may be less frequent or eliminated in patients with severe or life-threatening complications associated with HSV outbreaks.

For short-term prophylaxis, such as in the perioperative period, prophylaxis can be started 48 to 72 h before the procedure to achieve therapeutic levels in blood and then be continued postoperatively for 5 to 7 days. For dermabrasion, prophylaxis may need to be continued until re-epithelialization has occurred.

The only major contraindication to the use of oral ACV is pregnancy. Women should have a negative pregnancy test before prophylaxis is started, and they must use an effective form of birth control through the period of therapy. Laboratory monitoring for subclinical toxicity has not been required. In some studies, slight increases in hemoglobin concentration and mean corpuscular volume have been noted in some patients treated with long-term ACV (57). We monitor liver and renal function on a monthly basis in patients with a history of liver or renal disease.

It should be remembered that the administration of ACV does not guarantee freedom from transmission of disease. HSV may be transmitted during breakthrough recurrences. In addition, because most HSV infections are transmitted by individuals who are asymptomatic and, therefore, untreated, ACV is expected to have little if any impact on the epidemiology of genital HSV infection (32).

SUMMARY

ACV is an effective agent for the treatment and prophylaxis of HSV infections in both IC and immunologically normal individuals. The drug is well tolerated in both populations and is not significantly associated with clinical or laboratory toxicities. Because of the great potential benefit and low risk, organ transplant recipients and patients with hematologic malignancies undergoing induction chemotherapy should be screened routinely for HSV antibodies; seropositive individuals should receive prophylactic ACV during the period of most profound immunosuppression. Immunologically normal individuals with frequently recurring genital HSV or serious complications associated with outbreaks are candidates for long-term suppression with ACV.

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