Foscarnet Therapy for Severe Acyclovir-Resistant Herpes Simplex Virus Type-2 Infections in Patients with the Acquired Immunodeficiency Syndrome (AIDS)

An Uncontrolled Trial

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Study Objective: To determine whether trisodium phosphonoformate (foscarnet) is efficacious in treating severe mucocutaneous disease due to acyclovir-resistant herpes simplex virus type-2 (HSV-2) infection in patients with the acquired immunodeficiency syndrome (AIDS).

Design: Open-labeled drug administration to patients with AIDS and severe ulcerative disease due to acyclovir-resistant HSV-2 infection.

Setting: Medical floors of acute care hospital.

Patients: Four patients with AIDS who developed progressive ulcerative mucocutaneous lesions of the genitals, perineum, perianal region, or finger due to acyclovir-resistant, thymidine-kinase (TK)-negative strains of HSV-2.

Intervention: Foscarnet, 60 mg/kg body weight intravenously every 8 hours (with reduced dosage for renal impairment), for 12 to 50 days.

Measurement and Main Results: All patients receiving foscarnet had dramatic improvement in their clinical findings with marked clearing of mucocutaneous lesions and eradication of HSV from mucosal surfaces.

Conclusion: Foscarnet may be an effective treatment for severe mucocutaneous disease due to acyclovir-resistant, TK-negative strains of HSV-2.


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Herpes simplex virus (HSV) infections are frequent in both normal and immunocompromised persons. Recurrent HSV infections in the immunocompetent host are usually self-limiting, but patients with the acquired immunodeficiency syndrome (AIDS) often have persistent ulcerative mucocutaneous lesions due to this virus (1). In patients with AIDS, HSV infections usually heal rapidly with systemic acyclovir therapy. We have identified 12 patients with AIDS in whom acyclovir therapy failed because of the development of acyclovir-resistant strains (2). All of the strains studied were resistant to acyclovir due to a lack of viral thymidine kinase activity; however, they have remained susceptible to foscarnet and vidarabine, two antiviral agents that do not require viral thymidine kinase for activation (3). Four of these patients with severe infection due to herpes simplex virus type-2 (HSV-2) that was acyclovir resistant were successfully treated with trisodium phosphonoformate (foscarnet), a drug being investigated because of its activity against cytomegalovirus and human immunodeficiency virus infections.

Patients and Methods

Acyclovir resistance was suspected in the four patients because of persistent ulcerative mucocutaneous HSV disease that did not resolve with systemic acyclovir treatment. The patients were all homosexual men with chronic, ulcerative HSV infections who also had AIDS as defined by the Centers for Disease Control surveillance criteria. Virus isolates recovered from these patients were tested for susceptibility to antiviral drugs using the plaque reduction assay as previously described (4). Control acyclovir-susceptible and -resistant strains were included in each test. The concentration of drug that inhibited the plaque number by 50% (ID$_{50}$) when compared to the wells without drug was calculated by the method of least mean squares. The biochemical characteristic and animal virulence of the virus strains are reported separately (2).

Foscarnet (Astra Clinical Research, Westboro, Massachusetts) was administered intravenously through either a peripheral or central venous catheter. All patients initially received induction therapy of 60 mg/kg body weight of the drug every 8 hours for 14-21 days. Two patients also received maintenance foscarnet therapy (42 to 60 mg/kg / d) 5 to 7 d/wk. Each infusion was given over 2 hours.

Results

Patient 1

A 28-year-old man was diagnosed as having AIDS after developing Kaposi sarcoma on the hard palate in October 1986. He had had recurrent perianal HSV infection since 1982 and had been treated with daily oral acyclovir as suppressive therapy since 1985. He self-adjusted his dose of medication during this time and received between 400 and 4000 mg of acyclovir per day. In April 1987 he started zidovudine therapy and discontinued acyclovir therapy. Within 2 weeks of stopping oral acyclovir, however, he developed ulcerations of both the perianal region and the third finger of his left hand. Oral acyclovir therapy, 400 mg 5 times daily, was restarted, and although the hand lesion resolved with therapy the perianal lesions persisted. The patient was maintained on daily acyclovir, 2.4 g/d, but
the hand lesion recurred in October 1987. Therapy with oral zidovudine and acyclovir was continued (with the oral acyclovir dosage gradually increased to 4.8 g/d), but no further clinical response was noted.

In January 1988 cultures of the ulcerative hand lesion (Figure 1A) yielded HSV-2. In-vitro susceptibility tests showed resistance to acyclovir (ID$_{50}$ = 54.3 \(\mu\)g/mL), but the virus remained susceptible to foscarnet (ID$_{50}$ = 33.3 \(\mu\)g/mL). Both zidovudine and acyclovir were withdrawn, and the patient was begun on foscarnet 60 mg/kg every 8 hours. After 14 days of treatment the finger lesion and perianal fissure healed completely and virus cultures were negative (Figure 1B). The patient was treated with 100 mg of zidovudine and 400 mg of acyclovir every 4 hours. Although the finger lesion did not recur, a 5-mm perirectal ulcer developed 7 weeks after discontinuation of foscarnet therapy. Cultures of this ulcer yielded acyclovir-resistant HSV.

Patient 2

A 33-year-old bisexual man presented in June 1987 with a 5-\(\times\)3-\(\times\) cm perianal ulceration. Cultures showed HSV-2, and treatment with 200 mg of acyclovir 5 times daily was begun. The ulceration did not improve after several months of acyclovir therapy, despite a gradual increase to 1600 mg of acyclovir per day. In February 1988 the patient developed Pneumocystis carinii pneumonia and was treated with trimethoprim-sulfamethoxazole. The perirectal lesion persisted, and a repeat culture in March 1988 yielded HSV-2 that was resistant to acyclovir (ID$_{50}$ = 54.0 \(\mu\)g/mL) but susceptible to foscarnet (ID$_{50}$ = 14.0 \(\mu\)g/mL). Acyclovir was withdrawn and the patient was treated with foscarnet, 60 mg/kg, every 8 hours. After a 14-day induction period the lesion was reepithelializing and cultures were negative. During the initial treatment course (2 weeks) his 24-hour creatinine clearance fell from 1.47 to 0.97 mL/s. Foscarnet was continued as maintenance therapy with daily dosages ranging between 42 and 60 mg/kg . d. Dosage adjustments were required during this time because his 24-hour creatinine clearance decreased further to 0.60 mL/s. The patient received foscarnet for a total of 50 days, at which time his lesion had completely healed. He was released from the hospital on 400 mg of acyclovir three times daily. Two weeks after completion of fos-
carnet therapy his 24-hour creatinine clearance had increased to 0.85 mL/s.

Patient 3

One month after successful treatment of *P. carinii* pneumonia, a 42-year-old homosexual man developed ulcerative lesions of his right buccal mucosa and lower lip. Cultures in January 1987 yielded both herpes simplex virus type-1 (HSV-1) and HSV-2. Topical and oral acyclovir therapy was started, but the lesions increased in size. In March 1987, 1200 mg of oral zidovudine per day was added to a regimen of 1000 mg of oral acyclovir per day. The facial lesions persisted, and by December 1987 extensive mucocutaneous ulcerations extended along the upper lip, lower lip, buccal mucosa, gingival mucosa, and cheek. The largest single lesion (along the right cheek) was 7.6 cm × 6.3 cm. The patient was hospitalized in December 1987 and received intravenous acyclovir, 15 mg/kg · d, for 14 days. Although some improvement in the appearance of the lesions was noted, they increased in size once intravenous therapy was discontinued and oral acyclovir therapy, 2000 mg/d, was restarted. In January 1988 intravenous acyclovir, 15 mg/kg · d, was administered on an outpatient basis, but the lesions continued to increase in size. Cultures yielded HSV-2 that was resistant to acyclovir (ID$_{50}$ = 46.7 µg/mL) but susceptible to foscarnet (ID$_{50}$ = 25.9 µg/mL). The patient was rehospitalized and treated with foscarnet, 60 mg/kg every 8 hours for 21 days. The lesions decreased during therapy and repeated cultures were negative. The patient was released from the hospital and has been maintained on, 50 mg/kg, foscarnet administered 5 to 7 days per week. The lesions have healed completely and cultures have remained negative.

Patient 4

A 29-year-old homosexual man with a history of recurrent perianal HSV infection developed *P. carinii* pneumonia in February 1987. Before this time his HSV recurrent infections had responded well to short treatment courses of oral acyclovir. In November 1987, however, he developed recurrent perianal herpes infection that did not respond to oral acyclovir. Oral acyclovir, 400 mg 5 times daily, was administered continually from November 1987 through March 1988, but the lesions increased in size and number. Cultures in March 1988 yielded HSV-2, and in-vitro susceptibility testing showed that the isolate was resistant to acyclovir (ID$_{50}$ = 18.3 µg/mL) and susceptible to foscarnet (ID$_{50}$ = 14.8 µg/mL). Acyclovir therapy was discontinued, but new herpetic lesions involving the perirectal area, penis, and scrotum developed during the next 2 months (Figure 1C). The largest perirectal lesion at this time was 5 × 3 cm. In May 1988 cultures were still positive for acyclovir-resistant HSV-2, and the patient was treated with foscarnet, 60 mg/kg every 8 hours. After 12 days of therapy the penile and scrotal lesions had resolved completely (Figure 1D), the large perianal lesion was markedly decreased in size, and all cultures were negative. Foscarnet therapy was discontinued at this time and the patient was discharged on acyclovir, 400 mg three times daily.

Discussion

Four patients with AIDS who developed severe mucocutaneous HSV-2 infections due to acyclovir-resistant virus responded to intravenous foscarnet therapy. The virus strains isolated from these patients were shown to be resistant to acyclovir by in-vitro susceptibility testing, and the lesions failed to heal with systemic acyclovir therapy; however, the ID$_{50}$ values for foscarnet were within the range that was achievable in the serum of patients receiving the drug.

Acyclovir-resistant strains of HSV have been previously reported in both normal (7-9) and immunocompromised patients (2, 10-15). The clinical significance of recovering drug-resistant virus from patients with normal immune function is unclear; however, patients with defects in cellular immunity may develop progressive mucocutaneous disease because of these strains despite acyclovir therapy (2, 10-15). Although foscarnet has been shown to have good in-vitro activity against HSV in animal models, clinical experience with the drug in humans with HSV infection is limited (16). Vinekier and colleagues (15) have reported a beneficial clinical response to intravenous foscarnet in a single immunocompromised patient with severe HSV infection due to acyclovir-resistant virus.

Although the four patients reported here responded very well to foscarnet therapy, this was not a controlled trial and a longer period of follow-up will be necessary to determine the natural history of acyclovir resistance in patients with AIDS. It is likely that natural selection of acyclovir-resistant HSV variants occurs with acyclovir therapy in the large pool of virus that is found in extensive mucosal lesions. Because latent virus should remain susceptible to acyclovir, recurrences developing after complete healing of the lesions should be due to acyclovir-susceptible virus. It is possible, however, that the acyclovir-resistant virus strains that develop in mucocutaneous lesions are capable of infecting paraspinous ganglia and establishing latency, possibly resulting in recurrences due to acyclovir-resistant virus. In one of our patients (Patient 1), a recurrence that developed after foscarnet therapy and complete healing of the lesions was due to acyclovir-resistant virus.

Most clinical isolates of HSV that are acyclovir resistant have markedly decreased thymidine kinase activity (TK- mutants). These virus strains are resistant to acyclovir because drug phosphorylation by viral thymidine kinase no longer occurs (3, 17). These TK- HSV variants remain susceptible in vitro to antiviral agents that do not require viral thymidine kinase for activation. Vidarabine, a nucleoside analog, is phosphorylated by host-cell enzymes. Foscarnet is an active inhibitor of HSV DNA polymerase in its native form and does not require phosphorylation for antiviral activity (3, 17). Both of these antiviral agents are not affected by the loss of thymidine kinase (3). Thus
far, all acyclovir-resistant HSV strains recovered from patients with AIDS have been TK- variants and have remained susceptible to both foscarnet and vidarabine (2). Strains of HSV that are resistant to acyclovir by virtue of alterations in the substrate specificity of the thymidine kinase or the viral DNA polymerase, however, may develop concurrent resistance to either foscarnet or vidarabine (3).

Oral absorption of foscarnet is poor, and intravenous therapy is required to achieve adequate serum levels (5). Intermittent administration of foscarnet, 60 mg/kg body weight every 8 hours (infused over 2 hours) produces peak and trough serum drug concentrations of 530 and 100 μM, respectively (6). Excretion of the drug occurs solely by renal mechanisms, with a serum half-life ranging between 0.7 and 4.8 hours (6, 16). Progressive impairment of renal function can occur with prolonged use of the drug, and dosage adjustments are required in patients with renal dysfunction (5, 16).

In view of the increasing numbers of patients with AIDS it is likely that acyclovir-resistant HSV infections will become more prevalent. These case reports, which show a beneficial effect of foscarnet therapy, are encouraging but they do not establish efficacy. Further clinical trials evaluating the use of foscarnet in persons with AIDS and acyclovir-resistant HSV infection are warranted, and the in-vitro susceptibility data suggest that both foscarnet and vidarabine should be studied.

Addendum

Since submission of this manuscript, an additional patient with AIDS and infection due to acyclovir-resistant herpes simplex virus who responded to foscarnet therapy has been described (18).

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