Oral Acyclovir Therapy of Recurrent Herpes Simplex Virus Type 2 Infection of the Hand

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Acyclovir was evaluated as treatment of recurrent herpes simplex virus type 2 infection of the hand in a double-blind, placebo-controlled crossover study. In nine fully evaluable patients, oral acyclovir (2 g/day in three doses for 10 days) initiated during the earliest phase of a recurrence reduced the mean durations (± standard deviation) of clinical symptoms from 10.1 (±3.6) to 3.7 (±3.0) days (P = 0.008), signs from 11.1 (±3.7) to 6.2 (±3.3) days (P = 0.024), and viral positivity from 5.3 (±3.8) to 0.6 (±1.1) days (P = 0.011).

Effective treatments for most human herpes simplex virus (HSV) infections have been well documented (7, 9–12). However, recurrent HSV infection of the hand, which can be frequent, painful, and cosmetically unacceptable, has attracted little therapeutic attention (1–3, 5, 6, 8). After an earlier uncontrolled observation, we evaluated in this double-blind, placebo-controlled crossover study the effects of early intervention with oral acyclovir on the durations of symptoms, signs, and viral culture positivity of recurrent HSV type 2 (HSV-2) infection of the hand (4).

Fourteen patients (11 males and 3 females) with documented HSV-2 infection of the hand participated in a study that was approved by the University of Calgary Committee on Medical Ethics. All the patients were between 18 and 50 years old and had between 2 and 12 recurrent infections per year. They were otherwise in good health with no evidence of any underlying immunodeficiency. All the females were using a recognized form of contraception and were not pregnant at the time of treatment.

A double-blind, placebo-controlled crossover design was adopted in view of the limited number of eligible patients. Due to uncertainties about the bioavailability of acyclovir at the time of the study design, a high-dose regimen was selected. Active drug or placebo (provided by Burroughs Wellcome, Kirkland, Quebec, Canada) was randomized to either cycle A or B by a computer program. The patients were given written instructions and a bottle of 100 tablets (cycle A). They were advised to take four tablets when prodromal symptoms which they felt likely to result in HSV infection of the hand were first noticed, followed by two doses each of three tablets in a 24-h period. A total of 10 tablets per day in three doses was given for a total of 10 days. The patients were reviewed within 24 h of initiating therapy and then daily until the episode resolved. After the first course of therapy, the patients returned the cycle A bottle and were given a second bottle (cycle B) with identical instructions.

The presence and severity of symptoms (pain, swelling, tingling, tenderness, and discomfort) and both local and systemic signs of infection (erythema, papule, vesicle, pustule, scab, lymphangitis, and lymphadenopathy) were recorded at each visit. Symptoms were classified on the initial visit by the patient as being mild, moderate, or severe and then were assessed daily on a comparative basis (worse, same, better, or gone). The episode was classified as being resolved when both the symptoms and signs had disappeared. Whenever a papule, vesicle, pustule, or scab was present, samples for viral culture were taken. After the skin was cleaned with alcohol, a 25-gauge needle was used to release fluid, and the lesions were swabbed with a Dacron-tipped applicator. The samples were placed in standard viral transport medium, refrigerated at 4°C, and planted on HeLa and/or human embryonic lung cells within 72 h. At each visit, the patients were questioned about any side effects. No adverse effects were recognized during either phase of the study.

Descriptive statistics of central tendency (mean values) were calculated by using the MINITAB statistical program. Comparisons between acyclovir and placebo therapy were analyzed by using within-patient paired t tests.

Before participating in the first arm of the protocol, one female (no. 11) and one male (no. 5) withdrew because of a family relocation and a job transfer, respectively. One patient (no. 14) failed to develop any recurrences that could be monitored during the 1 year of observation prior to the termination of the study. One patient (no. 8) completed cycle A (acyclovir) and was lost to follow-up for cycle B. During cycle A, the patient’s durations of symptoms and signs were 5 and 3 days, respectively, and no virus was isolated. One patient (no. 2) completed cycle A (acyclovir) and withdrew since she wished to become pregnant. During cycle A, the patient’s durations of symptoms and signs were 1 and 4 days, respectively, and no virus was isolated. Nine patients completed both arms of the study.

All the patients were instructed to initiate therapy as soon as a prodrome suggestive of an attack was noted. Despite describing long prodromal phases in the past, most patients initiated therapy at a time very close to the appearance of clinical signs (9 h for placebo versus 4 h for acyclovir; P = 0.14). A reluctance to initiate therapy for a 10-day clinical trial without being absolutely certain the symptoms would progress into clinical signs or no immediate access to the drug supply were commonly cited as excuses for this delay.

The results of the study are shown in Table 1. The mean duration of symptoms for the entire episode from initial prodrome to complete resolution of symptoms was 10.1 days in the placebo-treated group, compared with 3.7 days in the acyclovir-treated group (P = 0.008). The time to first subjective improvement in symptoms was reduced from 4.3 to

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TABLE 1. Durations of symptoms, signs, and viral culture positivity during placebo and acyclovir treatment courses

<table>
<thead>
<tr>
<th>Patient</th>
<th>Symptoms</th>
<th>Signs</th>
<th>Viral positivity</th>
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<tr>
<td></td>
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<td>Acyclovir</td>
<td>Placebo</td>
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</table>

Mean: 10.1, SD: 3.6, 3.7, 11.1, 3.0, 3.7, 6.2, 3.3, 5.3, 3.8, 0.6, 1.1

P value* 0.008, 0.024, 0.011

* Paired t comparison.

1.2 days (P = 0.003). For almost all patients, the duration of symptoms and time to symptomatic improvement were shorter during the acyclovir treatment than during the placebo treatment.

The mean duration of objective signs in the placebo-treated group was 11.1 days, compared with 6.2 days in the acyclovir-treated group (P = 0.024). In every case, the duration of signs was shorter when the patients were receiving acyclovir therapy.

The mean difference in durations of viral shedding between the two study groups was statistically significant (5.3 versus 0.6 days; P = 0.011). Specimens from seven of the nine patients receiving therapy with oral acyclovir were not positive in viral culture. For two patients (12 and 6), viral cultures were positive at the initial and second visits only. In patient 13 during the placebo-treated episode, HSV was present from visits 1 to 9 and 11 to 15, representing what appeared clinically to be two recurrences in rapid succession.

In this study, a total daily dose of 2 g of oral acyclovir was found to be effective in reducing the durations of symptoms, signs, and viral positivity when initiated during the early sign of a recurrence of HSV-2 infection of the hand. However, the dosage of acyclovir, duration of therapy, and timing of intervention can likely be further optimized to give results equal or even superior to those described above. Other studies have suggested that lower doses of acyclovir are effective in the early treatment of recurrences of HSV-2 infections at other sites (10). The 10-day course of therapy was chosen to be longer than the anticipated duration of a recurrence. Since acyclovir shortened the duration of an episode to around 5 days, a 10-day course of therapy appears to be excessive in most situations. It is also possible that earlier intervention during the prodromal phase of a recurrence may achieve greater clinical effects.

Although the vast majority of recurrent HSV infections of the hand are HSV-2, HSV-1 infection of the hand is occasionally recurrent (3). Studies of recurrent HSV-1 infections of the lips suggest that they, too, respond to such treatment (9). Unfortunately, due to the relative rarity of patients with such infections, controlled studies of HSV-1 infection of the hand may be impractical.

In summary, oral acyclovir administered during the early stages of recurrent HSV-2 infection of the hand had a beneficial effect on the durations of symptoms, signs, and viral positivity.

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REFERENCES