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A Randomized, Double-Blind, Comparative Trial Comparing High- and Standard-Dose Oral Acyclovir for First-Episode Genital Herpes Infections

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Orally administered acyclovir ameliorates the clinical course and decreases the duration of viral shedding in patients with first-episode genital herpes infections. We investigated in a randomized, double-blind, comparative trial whether a higher (4 g) than standard (1 g) daily dose of oral acyclovir results in greater clinical benefit and influences the time to first recurrence. A total of 139 patients with first-episode genital herpes were randomized to receive orally 4 or 1 g of acyclovir daily. A total of 52 subjects were excluded from the efficacy analysis because most had recurrent disease. Of 87 eligible subjects, 28 (32%) had primary herpes simplex virus type 1 (HSV-1) infections, 48 (55%) had primary HSV-2 infections, and 11 (13%) had nonprimary HSV-2 infections. We did not find any statistically significant differences in the duration of symptoms or viral shedding between the two dose groups, nor did the median time to first recurrence differ between the two groups. Initiation of therapy with either dose within the first 3 days of the appearance of symptoms shortened the duration of the first episode. Adverse gastrointestinal effects developed in 8% of subjects receiving the higher dose, whereas no adverse reactions were observed among those receiving the standard dose ($P = 0.10$). We conclude that, in comparison with standard therapy, higher-dose oral acyclovir does not result in additional clinical benefit or modify the time to first recurrence. The present study may have implications for the development and efficacy of congeners of acyclovir which provide higher levels in blood than the standard dose of acyclovir.

Initial genital infection with herpes simplex virus (HSV) type 1 (HSV-1) or 2 (HSV-2) often results in severe local symptoms and systemic illness. Oral treatment with acyclovir (1 g daily) shortens the duration of viral shedding as well as local and constitutional symptoms (2, 10), but it does not appear to influence the rate of subsequent recurrences (3, 4, 10). Several prodrugs of acyclovir which provide higher levels of acyclovir in blood than the parent compound after oral administration have been developed. To determine whether higher doses of antiviral medication modify the natural history of genital herpes, we studied the effects of high-dose (4 g daily) and standard-dose (1 g daily) acyclovir administered orally on the clinical course of the first episode of genital herpes and the time to first recurrence.

MATERIALS AND METHODS

The study was conducted at the University of Washington Viral Disease Research Clinic at Harborview Medical Center, Seattle. The participants were healthy women and men with first-episode genital herpes who presented within 5 days of the onset of symptoms and who received no prior antiviral or immunomodulatory therapy. At the initial visit, a medical history was elicited and a physical examination was performed. Samples of genital lesions were taken for viral culture; additional samples from the cervix were taken from women and additional sample from the urethra were taken from men. The number and the stage (papule, vesicle, pustule, ulcer, crust, or healed) of the lesions were recorded. Subjects were randomized to one of the following three regimens: (i) acyclovir at 800 mg five times a day for 10 days and then 200 mg five times a day for each recurrence, (ii) acyclovir at 800 mg five times a day for 10 days and then placebo for each recurrence, or (iii) acyclovir at 200 mg five times a day for 10 days and then 200 mg five times a day for each recurrence. Subjects and investigators were blinded to the group assignments. Assessment of local and systemic symptoms, evaluation of the number and the stage of lesions, and samples for viral cultures were done in the clinic every other day until healing. Subjects were asked to return to the clinic if they developed a recurrence. At the time of entry into the study and on day 14, serum was collected and a complete blood count, serum chemistries, and urinalysis were performed; women had a negative pregnancy test prior to randomization. All episodes were confirmed by viral culture and by seroconversion to HSV positivity, as determined by Western blotting (immunoblotting) (1). The initial viral isolate from the genital lesion examined at the time of entry into the study was typed by using an HSV-specific monoclonal antibody. For analysis, patients were classified by their Western blot results and viral isolates into those with primary HSV-1, primary HSV-2, nonprimary HSV-2, and recurrent HSV-2 status (5).

For the present analysis of the duration of the first episode and the time to the first recurrence, subjects randomized to the two groups receiving high-dose acyclovir were combined (group 1) and compared with those receiving lower-dose acyclovir (group 2).

Demographic and clinical variables were compared by using the chi-square test and the Wilcoxon test. The log-rank test for censored data was used for the comparison of the duration of

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TABLE 1. Baseline demographic and clinical characteristics of study patients

Characteristic[a]	Group 1 (n = 59)	Group 2 (n = 28)
Gender (no. [%])[b]		
Male	21 (36)	4 (14)
Female	38 (64)	24 (86)
Race (no. [%])		
White	47 (80)	22 (79)
Other	12 (20)	6 (21)
Age (yr)[c]	22 (17–39)	22 (18–33)
Yr of education[c]	14 (11–18)	15 (11–18)
Age (yr) at first sexual intercourse[c]	18 (10–26)	18 (14–25)
No. of prior sexual partners[c]	7 (1–52)	8 (1–25)
No. (%) with history of prior sexually transmitted disease	21 (36)	9 (32)
Serologic status and viral type (no. [%])		
Primary HSV-1	20 (34)	8 (29)
Primary HSV-2	30 (51)	18 (64)
Nonprimary HSV-2	9 (15)	2 (7)
Constitutional symptoms (no. [%])[b]		
None	19 (32)	5 (18)
One	16 (27)	8 (29)
Two or more	24 (41)	15 (54)

[a] $P > 0.05$ for all comparisons, except as noted.
[b] $P = 0.04$.
[c] Valves are medians (ranges).

events and the time to first recurrence. All tests of significance were two-tailed. The study was approved by the University of Washington Human Subjects Review Committee, and all subjects gave written consent.

RESULTS

Study population. One hundred thirty-nine people were randomized into the study. Of those, 87 who met the eligibility criteria and who returned for at least one follow-up visit were included in the efficacy analysis. The remainder did not have culture-proven herpes (4 subjects), had serologic evidence of recurrent rather than first-episode disease, which was defined by the presence of HSV-2-specific antibodies in sera at the time of entry into the study (29 subjects), did not start taking the drug within the initial 5 days (9 subjects), or failed to return for a follow-up appointment (10 subjects). Demographic characteristics and sexual histories were comparable in both groups (Table 1). Women were present in a higher proportion in group 2 (those who received standard-dose acyclovir) than in group 1 (86 versus 64%; $P < 0.05$). Constitutional symptoms at the time of entry into the study, such as fever, photophobia, headache, and stiff neck, were also present significantly more frequently among subjects in group 2 than among subjects in group 1 ($P < 0.05$), because these symptoms tend to occur more often in women. Viral type and serologic status at the time of entry into the study, two factors which have been shown to influence subsequent recurrences, were similar in the groups receiving standard-dose and high-dose acyclovir. Overall, 28 (32%) of the 87 patients with first-episode disease had primary HSV-1 infections, 48 (55%) had primary HSV-2 infections, and 11 (13%) had nonprimary HSV-2 infections.

TABLE 2. Effect of dose on duration of first-episode genital herpes and time to first recurrence[a]

Characteristic	Group 1 (n = 59)	Group 2 (n = 28)
Duration of lesions from onset of:		
Symptoms	14 (11–18)	12 (11–15)
Therapy	11 (8–14)	10 (7–11)
Duration of:		
Pain	7 (5–10)	9 (7–12)
Itching	6 (2–11)	8 (3–13)
Viral shedding	3 (1–3)	3 (1–5)
Time to first recurrence	45 (20–128)	53 (11–196)

[a] Values are median duration (in days) and interquartile range (25th and 75th percentiles).

Comparison of acyclovir at 4 g daily and 1 g daily. We could detect no statistically significant differences in the duration of symptoms, viral isolation from lesions, or healing times between those who received high-dose acyclovir and those who received low-dose acyclovir. The median durations of lesions were 14 and 12 days from the time of onset and 11 and 10 days from the start of therapy in the high- and standard-dose acyclovir groups, respectively (Table 2). The median durations of reported pain in groups 1 and 2 were 8 and 9 days, respectively, and the median durations of itching were 7 and 8 days, respectively. HSV was recovered after the onset of therapy for a median of 3 days from the lesions of patients in both groups. We also detected no significant differences with respect to the duration of symptoms, lesions, or viral shedding between the two groups when the potential effects of viral type, patient gender, or constitutional symptoms were considered in the analysis.

The initiation of therapy within 3 days of the onset of symptoms influenced the subsequent treatment course in both the high- and standard-dose groups. Subjects who initiated therapy within 3 days of the onset of symptoms rather than later (4 to 5 days) experienced shorter episodes (12 versus 16 days in group 1 and 12 versus 15 days in group 2), but these differences did not reach statistical significance ($P = 0.19$).

Overall, 80% of patients subsequently had recurrences during the follow-up period. The median times to the first recurrence among subjects with HSV-2 infection were 25 and 31 days, respectively, in those receiving high- and standard-dose acyclovir. It is of interest that the median time (in days) to the first recurrence also did not differ statistically between those subjects who initiated therapy within 72 h of the appearance of lesions and those who did not ($P = 0.41$ for overall comparison of early versus late therapy, adjusted for dose).

We compared the occurrences of adverse effects in subjects who were randomized to receive higher- and standard-dose acyclovir. Since the subjects' serologic statuses appeared unlikely to influence the occurrence of toxicity, we analyzed all patients who were randomized and followed them, including the 42 patients whose specimens were culture negative or with recurrent genital herpes who were excluded from the efficacy analysis. Seven of 88 subjects receiving 4 g of acyclovir daily but none of 41 subjects receiving 1 g of acyclovir daily experienced adverse effects ($P = 0.10$). All seven patients with drug toxicity developed gastrointestinal intolerance; two patients also had headaches. No patient experiencing adverse effects required

interruption or discontinuation of the study medication, although one subject withdrew from the study because of headache, nausea, and vomiting after 3 days of treatment.

DISCUSSION

We investigated whether a higher dose of oral acyclovir would have a more pronounced antiviral effect in first-episode genital herpes and influence the time to the first recurrence. We found that the clinical course and the duration of viral shedding did not differ in subjects receiving oral acyclovir at 1 g daily and those receiving acyclovir at 4 g daily. Similarly, we could not influence the time to the first recurrence by increasing the dose of oral acyclovir or initiating therapy within 72 h of the onset of lesions.

Oral acyclovir has been shown to have an important clinical benefit in first-episode genital herpes, markedly shortening the duration of local and systemic symptoms, genital lesions, and viral shedding from lesions. Previous studies have suggested that intravenous acyclovir, which achieves levels in plasma five times greater than that from 800 mg given five times a day, may have an even more pronounced benefit (3). Because congeners of acyclovir that produce higher levels in blood and related compounds with longer intracellular half-lives are being developed, we sought to evaluate whether we could improve the therapeutic benefit of oral acyclovir with higher doses. Four grams daily, the dose used for the treatment of varicella zoster virus infection, results in levels in blood that are an average of two times greater than those from standard-dose acyclovir and twice the area under the concentration-time curve than that from standard-dose acyclovir (9). However, despite these pharmacologic differences, we could discern no measurable clinical benefit among immunocompetent patients with genital herpes. While our study was relatively large for treatment studies of culture and serologically proven genital herpes, our study still lacked sufficient statistical power because of the known variability of first-episode genital herpes. For example, the size of our sample provided less than 60% power to detect a difference of 3 days in the healing time of genital lesions between high- and low-dose acyclovir in patients. Thus, while it is possible that there may be a difference in the two treatment doses, it is unlikely to be large. Importantly, we did see a trend in both groups that the earlier initiation of therapy was associated with a faster resolution of infection, suggesting that it is the time of the initiation of therapy rather than total dose that most influences healing rates.

Animal models of HSV infection have suggested that, in addition to ameliorating the clinical course of herpes infections, administration of acyclovir concurrently with the initial viral challenge may prevent establishment of neuronal latency, and thus recurrences (6–8). One of the original hopes of our study was to evaluate whether a more prompt antiviral response reduces the subsequent recurrence rate of genital herpes, but the initiation of therapy within 72 h of the onset of lesions with even 4 g daily failed to demonstrate an effect on the time to subsequent recurrence in patients with genital HSV-2 infections. These data corroborate the animal model results and suggest that abrogation of ganglionic latency by postinoculation, acute-episode therapy with nucleoside analogs is very unlikely. This is probably related to the facts that genital lesions result from the centrifugal spread of virus from the dorsal nerve root ganglia and that viral replication in the nervous system occurs for days prior to clinical presentation (5). It is possible, however, that early therapy would reduce the ganglionic viral burden which may be manifest clinically by a reduced recurrence rate over time, in contrast to a single determination of the recurrence rate, as measured in our study.

We found that 4 g of oral acyclovir had more side effects than 1 g. The lack of improved efficacy and increased cost do not warrant the use of increased dosages of acyclovir for the treatment of immunocompetent patients with genital herpes.

In summary, our study was unable to demonstrate a clinical benefit of 4 g of oral acyclovir daily over that of 1 g of oral acyclovir daily in patients with first-episode genital herpes. The study illustrates our incomplete understanding of the clinical pharmacology and antiviral mechanisms of nucleoside analogs. However, it appears that in immunocompetent patients with genital herpes, congeners of acyclovir that provide levels in blood equal to those seen with 4 g daily are unlikely to provide an improved benefit. It appears that 1 g of oral acyclovir daily should be the standard dose for the treatment of first-episode genital herpes.

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