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Double-blind comparison of weekend and daily regimens of oral acyclovir for suppression of recurrent genital herpes

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Summary

The potential utility of intermittent regimens of oral acyclovir for suppression of recurrent genital herpes depends on how long the suppressive effect of the drug persists during pauses in treatment. To study this question, we admitted 38 patients in a double-blind controlled trial comparing the results of daily acyclovir treatment (200 mg t.i.d.) with treatment on weekend days only (400 mg t.i.d. on Saturday and Sunday) for suppression of recurrent genital herpes. Of the 35 patients completing the study, significantly more failures occurred in the weekend group (13/17) than in the daily group (3/18, $P < 0.001$). Failures on the weekend regimen were more frequent as the week progressed ($P = 0.005$). The findings suggest a short-term persistence of suppression by acyclovir and hence that intermittent regimens with more closely spaced periods of treatment may be more effective than the regimen we studied. Most virus isolates studied, including all of those isolated from the patients during treatment, were sensitive to acyclovir.

genital herpes; acyclovir; intermittent therapy

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Introduction

Recurrent genital herpes simplex infections in normal and immune-deficient patients can be effectively suppressed by oral acyclovir treatment, 200 mg given 2–5 times daily [1,4,7,8]. After suppressive treatment is discontinued, recurrences resume in all patients. In a study of selected immune-deficient patients with very frequent recurrences, we reported that the time to herpetic recurrence after discontinuing suppressive therapy with a total daily oral acyclovir dose of 400 mg/day was shorter than after therapy with 1000 mg/day [7]. This suggested that the suppressive effects of acyclovir may persist for a few days beyond treatment and the duration of that persistent effect may be dose-dependent. We therefore attempted to determine whether the suppressive effect of a higher dose of acyclovir persists long enough to allow successful intermittent treatment, which would be more convenient, less expensive, and potentially less toxic. Patients were enrolled in a double-blind, controlled, crossover trial in which oral acyclovir treatment of 200 mg 3 times daily (daily regimen) was compared with 400 mg 3 times each on Saturday and Sunday only (weekend regimen). This regimen was chosen to provide an intensive brief period of virus suppression while allowing sufficient time between treatments to determine how long the suppressive effect can be expected to persist.

Methods

Study population

Healthy individuals between the ages of 18 and 50 years who had histories of culture-confirmed genital herpes with monthly or more frequent recurrences for at least one year and who agreed to use effective methods of birth control were eligible for entry into this study. Women were also required to be premenopausal and to have negative pregnancy tests.

Study design

At the initial visit, informed consent and a medical history were obtained from the patient, suspected lesions were examined, and an initial assignment to daily or weekend acyclovir treatment was made using a balanced randomization schedule with stratification by sex. All patients were provided with 25 200-mg acyclovir capsules and instructed to take one capsule 5 times daily for 5 days beginning the next Wednesday morning and ending Sunday evening. On Monday they were to begin treatment 3 times daily from specially designed pill packs, which consisted of capsules containing either 200 mg of acyclovir or a placebo compound that was identical in appearance and taste. Individually labeled packs containing medication for a single dose each were dispensed in perforated strips. Packs designated for Saturday or Sunday doses contained either two acyclovir capsules (weekend group) or one acyclovir and one placebo capsule (daily group). Packs designated for weekday doses contained either one placebo pill (weekend group) or one acyclovir pill (daily group). Clinic visits for routine assessment and medication refills were scheduled every 4 weeks. Additional

visits were arranged to evaluate suspected recurrences within 24 h of onset. The first phase of treatment was continued either until a recurrence was diagnosed or for 117 days (16 weeks and 5 days), whichever came first.

A recurrence was diagnosed clinically when a patient presented with typical symptoms and any number of vesicles, pustules, or ulcers. All suspicious sites were cultured. If the clinical impression of recurrent herpes simplex virus infection was less compelling but the viral culture was positive, the treatment was declared to be a failure from the time the culture was obtained.

On confirmation of a recurrence (either clinically or virologically) or on completion of the phase, the patients were immediately switched into the alternate study arm. The patients were then continued on the alternate blind treatment for 117 days or until the first recurrence, as before; however, in some cases treatment was discontinued because an early-stopping rule was invoked (see below). Following completion or discontinuation of protocol treatment, the patients were offered continued open treatment on acyclovir for a total of 8 months of therapy of some type.

Toxicity and compliance were monitored as in our previous study [8]. Serum acyclovir levels were determined blindly by radioimmunoassay [5].

Virus isolation

Viral cultures consisting of freshly aspirated or swabbed lesion material in 2 ml of veal-infusion broth were transported on ice to the laboratory, where they were inoculated (0.2 ml per tube) into two roller tubes containing human embryonic kidney cells and into two tubes of human diploid fibroblasts. The tubes were examined daily for 14 days for cytopathic changes characteristic of herpes simplex virus replication.

Statistical techniques

Relative frequencies were compared with use of Fisher's exact test, and arithmetic means with Student's *t*-test. Because the distributions of the duration of therapy and the recurrence times were asymmetrical in both treatment groups, medians were calculated to provide a more reliable estimate of the centering of the distributions and were compared by the test proposed by Mood. All of the distributions were estimated using the Kaplan-Meier method, and pairs of distributions were compared using the Gehan test. All statistical tests were two-tailed.

In addition, we included an early-stopping feature in the study design, i.e., it was provided that the study would terminate if at any time the accrued results could be shown to make the eventual inference to be drawn a foregone conclusion. An unblinded study statistician (D.A.) intermittently reviewed the study failures to determine whether the study could be terminated prior to completion of both phases of the crossover trial. The study would end when a significantly greater ($P<0.05$) mean duration of treatment was observed with one regimen as compared to the other.

In vitro sensitivity of viral isolates

The sensitivity of herpes simplex virus isolates to inhibition by acyclovir was measured in Vero cells by the dye uptake method [2,3]. Isolates requiring more than 10 μg/ml of acyclovir for 50% virus inhibition were considered resistant [3]. The dye

uptake method is less sensitive than the standard plaque reduction method, but the assays have been highly concordant in their abilities to identify resistant strains.

Results

38 patients were enrolled in this study, 26 of whom had participated in our earlier placebo-controlled acyclovir suppression trial [8]. The characteristics of the two treatment groups at the time of enrollment are summarized in Table 1. The groups were well matched for most historical, demographic, and clinical features and, except for being about 2 years older and having a higher proportion of patients with prior acyclovir use, they were not different from the group of patients who participated in the earlier trial.

35 patients continued their assigned treatments until complete or a recurrence was diagnosed. The data for three patients were excluded from the analysis of the results, but, in fact, their inclusion would not have altered the significant findings of this study. One male in the daily treatment group failed to refill his prescription. He ran out of pills and was dismissed on day 69 of the study, but had no signs or symptoms of recurrent infection to that point. Treatment was discontinued in two patients in the weekend group because of suspected drug toxicity. Hyperbilirubinemia was observed in one male during treatment (3.4 mg/dl) and therapy was discontinued. Gilbert's syndrome was diagnosed, and his bilirubin fluctuations were found later to be totally independent of acyclovir treatment. In retrospect, we had failed to notice an elevated bilirubin level from a pre-enrollment visit. One woman complained of diffuse myalgias and arthralgias and had an elevated erythrocyte sedimentation rate (30 mm/h). The symptoms persisted for several weeks despite termination of therapy and gradually disappeared during resumption of unblinded daily oral acyclovir treatment.

TABLE 1

Characteristics of the weekend and daily acyclovir treatment groups[a]

	Weekend	Daily
No. of patients	19	19
Sex (M/F)	10/9	10/9
Mean age in years (± S.E.M.)	34.2 ± 1.2	33.4 ± 1.6
No. with prior oral herpes	5	4
No. with prior acyclovir use	18	18
Mean no. of years since first episode of genital herpes (± S.E.M.)	4.5 ± 0.7	5.0 ± 0.6
Mean no. of recurrences/year (± S.E.M.)	17.7 ± 1.9	16.6 ± 2.1
Mean no. of days from last recurrence until onset of treatment (± S.E.M.)	15.8 ± 5.2	21.5 ± 4.9
No. of patients with lesions at onset of treatment	12	8

[a] None of the differences between treatment groups are significant ($P > 0.2$).

Effects of treatment

Eighteen weeks into the 32-week study, the early stopping rule was invoked, and all patients were switched to the open daily acyclovir phase to complete 8 months of treatment. The study was ended when it was found that of 11 patients known to have failed weekend treatment in the first study phase, at least 9 had subsequently been treated successfully over a longer period of time on daily acyclovir.

In the first phase, the relative frequency of recurrence was significantly lower for patients on daily therapy than on the weekend regimen ($P < 0.001$), and this finding was present to an equal extent for both men and women. Comparison of the mean duration of treatment on the two regimens showed that patients tended to remain free of recurrent infection for a significantly longer time on daily treatment (Table 2). Among patients on weekend therapy, recurrences were found to be significantly more frequent as the week progressed ($P = 0.005$) (Fig. 1). The mean lengths of treatment in the weekend or daily phases were significantly longer than the time to recurrence following completion of treatment for patients who had been in either phase initially (each $P < 0.001$, Gehan test). Times to recurrence following treatment for patients in the original weekend and daily groups were not significantly different from each other ($P > 0.20$, Wilcoxon's test).

Compliance and adverse reactions

The unique drug packaging system minimized dosage errors. Instructions for each dose appeared on the label of each individual pill pack, and the pill pack could be conveniently transported. In all, the weekend treatment patients reported only 10 missed pills, while the daily treatment patients reported a total of 77 missed pills (70 of which were accounted for by one patient who was removed from the study). Considering that daily treatment was more successful and therefore lasted longer, involving

TABLE 2

Results of treatment in the weekend and daily acyclovir groups

	Weekend	Daily	*P* value
No. of patients completing study	17	18	
Proportion of patients with recurrent herpes while on therapy[a]			
Male	7/9	1/9	0.008
Female	6/8	2/9	0.013
All	13/17	3/18	<0.001
Duration of treatment (days[b])			
Male	54.5 ± 11.8	109.0 ± 5.1	0.002
Female	72.7 ± 11.8	100.7 ± 11.4	0.06
All	63.1 ± 8.4	105.1 ± 5.9	<0.001

[a] Relative frequencies were compared by Fisher's exact test.

[b] Mean (± S.E.M.) number of days of treatment were compared using Student's *t*-test.

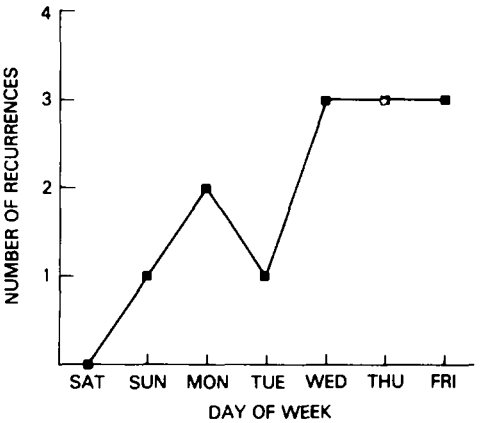

Fig. 1. The number of episodes according to the day of the week in which weekend treatment patients first experienced symptoms associated with a documented recurrence. There was a significant upward trend in the onset of such symptoms as the week progressed (Mann test, $P = 0.005$).

over 8200 scheduled pills, compliance was excellent. None of the treatment failures was known to be associated with compliance problems.

Serum for acyclovir levels was collected 5 min prior to and 2 h after the first morning dose on a Saturday for five patients on daily treatment and for three patients on weekend only treatment. Pretreatment levels for the weekend patients were less than 0.043 μg/ml, the lower limit of detection, and for the daily patients, 0.154 ± 0.029 μg/ml (mean ± S.E.M.). Post-treatment levels for weekend patients averaged 0.533 ± 0.084 μg/ml, higher than the 0.450 ± 0.033 μg/ml mean level of the daily patients, but with these few determinations, the differences were not statistically significant.

The number of individual reports of adverse symptoms is shown in Table 3. In addition to the previously mentioned problems that led to premature termination of therapy, there were several complaints of mild, particularly gastrointestinal, reactions. There were more such complaints among weekend patients, but the onsets of their problems were distributed throughout the week.

Average trends in the series of laboratory tests were estimated in each treatment group. Other than two patients with Gilbert's syndrome (one first diagnosed during

TABLE 3

Episodes of adverse symptoms reported by patients receiving weekend or daily acyclovir treatment

	Weekend	Daily
Dizziness/lightheadedness	2	0
Fatigue	0	1
Upset stomach/nausea	5	4
Loose stools	7	3
Arthralgias/myalgias	2	0

the study), there were no abnormalities of bilirubin. There were in fact no clinically important upward or downward trends of any test in either treatment group. We did not confirm our earlier observation of increasing mean corpuscular volume or corpuscular hemoglobin concentration during chronic suppressive acyclovir treatment [8].

In vitro sensitivity of viral isolates

In our earlier trial of acyclovir suppression, we recovered drug-resistant virus from three patients who experienced recurrences while on treatment. Because of that observation as well as the theoretical possibility that the likelihood of selecting for resistant strains could be even greater during intermittent treatment, we assessed the in vitro sensitivity of the 36 available virus strains recovered during symptomatic recurrences experienced prior to, during, or following acyclovir treatment in this trial.

Figure 2 shows that the isolates have a wide range of inherent sensitivity to acyclovir before treatment. However, there were no significant changes in viral sensitivity during or following treatment.

One patient shed virus with diminished sensitivity to acyclovir prior to and following the previous and present trials (mean ID_{50} of 5.0 μg/ml). He failed weekend, daily, and open treatments. His isolates are the subject of ongoing studies. The three patients from whom resistant isolates were recovered in our earlier trial participated in this study [8]. One successfully completed weekend treatment and had sensitive virus post treatment. The other two completed blind daily treatment. One had a recurrence

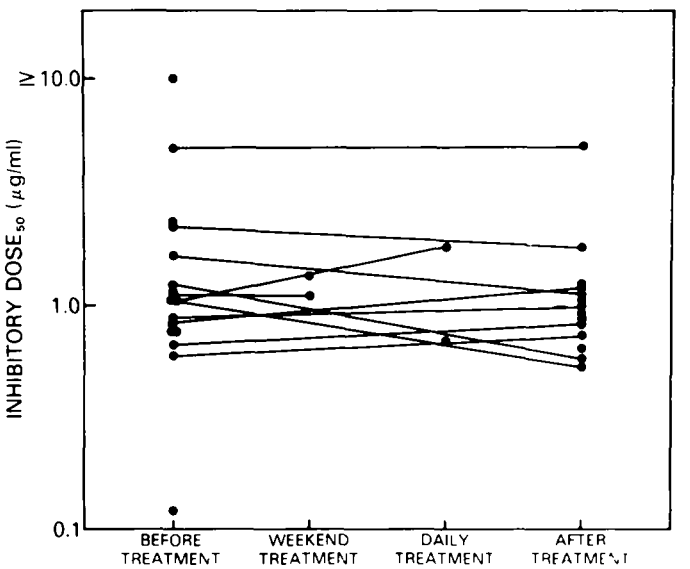

Fig. 2. In vitro sensitivity of herpes simplex virus isolates to acyclovir. The concentration of acyclovir required to inhibit by 50% the development of viral cytopathic effects in a dye-reduction assay (ID_{50}) is shown for isolates recovered from the treatment study patients. Isolates with ID_{50} values of ≥ 10 μg/ml are considered resistant. Comparisons of the sensitivities of earlier and later isolates are aided by lines connecting pairs of data points.

while on open daily treatment but the culture was negative. The other had sensitive virus recovered during his first post-treatment recurrence.

Discussion

Oral acyclovir in divided daily doses suppresses most expected episodes of genital herpes in patients who experience frequent recurrences [1,4,7,8]. The present study demonstrates that an intermittent regimen of oral acyclovir, involving high-dose treatment on weekend days only, is not clinically useful because it is significantly less effective than divided daily treatment for suppression of recurrent genital herpes (Fig. 2). However, weekend treatment appeared to be superior to no treatment at all. This assessment is based on the analyses of data regarding time to first recurrence after completion of treatment. Although there may be a small rebound following treatment [1], such that a recurrence could come sooner than expected, it would still appear that the time to recurrence among patients on weekend treatment is delayed.

Recurrences observed in the weekend group were significantly more frequent later in the week, with the first symptoms of outbreaks developing on Wednesday, Thursday, or Friday in 9 of 13 cases (Fig. 1). This suggests that the suppressive effect of the intermittent treatment may persist for about 2 days beyond the last dose. Since one can detect inhibitory levels of acyclovir in plasma for at most 16–18 h following a single 200–400-mg oral dose [6], the observed delay of 3–5 days in onset of the recurrence indicates either that inhibitory acyclovir derivatives persist within neuronal cells longer than in plasma or that clinically apparent reactivation of latent virus takes longer than one day following removal of an effective suppressant. Whichever the case, the present data indicate that an intermittent regimen with more frequent doses may afford more effective suppression, approaching that achieved with divided daily doses of acyclovir. Such intermittent regimens could be less costly or potentially less toxic than the present regimen (which is remarkably well tolerated in the short term), but the risk of selecting for resistant virus strains might be greater. From an analysis of a small number of isolates, there was no evidence that the patients in either group acquired or transmitted resistant strains during treatment (Fig. 2). On the contrary, all of the patients have been successfully suppressed in subsequent open daily acyclovir treatments.

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