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Oral Acyclovir Suppression of Recurrent Genital Herpes: A Double-blind, Placebo-controlled, Crossover Study

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A randomised, double-blind, placebo-controlled, crossover study was conducted in 31 male patients with a history of frequently recurrent genital herpes who received consecutively 200 mg acycovir and matching placebo by mouth four times a day for 12 weeks each. During acyclovir therapy recurrences were completely prevented in 24 (77%) and were reduced in both frequency and duration in the remainder compared with those occurring during treatment with placebo. The incidence and nature of adverse events reported during each treatment period was virtually identical. No long-term effects on recurrence rates were discernible but chronic suppressive therapy can be considered to offer the means of controlling the severe forms of disease experienced by some patients. *Key words: Acyclovir; Herpes simplex.* (Received June 21, 1984.)

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Double-blind, placebo-controlled trials have demonstrated that oral acyclovir (Zovirax®, Wellcome) will reduce the duration of recurrent episodes of genital herpes (1, 2). Greater clinical benefit from orally administered drug can be obtained by the use of early patient-initiated therapy during the prodromal period of an attack (3). For patients with severe and/or frequent attacks such benefit may not be considered sufficient.

It was therefore decided to attempt complete suppression of recurrent genital herpes in frequent sufferers using regular daily therapy with oral acyclovir. A dose of 200 mg four times a day was chosen since this had previously been shown to be effective in the prophylaxis of herpes simplex infections in cardiac transplant recipients (4). Since the majority of patients attending the study centre clinics with recurrent genital herpes in previous trials (1, 2) were male the current study was limited to male patients. We report the results of this double-blind, placebo-controlled trial of oral acyclovir in the suppression of recurrent genital herpes.

PATIENTS AND METHODS

Male patients with a history of culture-proven recurrent genital herpes attending special clinics at the Municipal Health Centre, Oslo and the University Central Hospital, Helsinki were invited to partici-

pate in the study. Patients experiencing at least 8 recurrences per year, who were not receiving other antiviral therapy, were aged over 18 years and gave their informed consent were included. Local hospital ethical committees approved the protocol.

Treatment was randomly allocated under double-blind conditions. Therapy consisted of a 200 mg tablet of acyclovir by mouth four times daily, or matching placebo tablets, for 12 weeks. Patients were then given the alternative medication for a further 12 weeks. Clinical assessments were performed at the onset of the study, every 4 weeks during the trial and where possible during any recurrence that occurred. Patients were required to keep a daily record to monitor compliance and report the occurence of specific signs and symptoms of a recurrence. When symptoms occurred without the development of any signs then the episodes were termed completely abortive. If erythema alone was seen in association with symptoms then the lesions were classified as partially abortive. Episodes with lesions developing normally were defined as recurrences. Swabs from the urethra, or any lesions present at the time, were taken for viral culture each time the patient attended the clinic. Specimens were sent to the virus laboratories in transport medium and inoculated into cell cultures. Isolates were identified by cytopathic effect and confirmed by an indirect immunofluorescence test. Routine haematological and biochemical screening tests were carried out in all patients at the start of the study and then at monthly intervals during the treatment periods.

RESULTS

A total of 31 patients were analysed for presenting details according to the study centre (Table I). The only significant difference between the groups was a higher proportion of patients from the Oslo centre with herpes simplex affecting other sites. A separate analysis of the first and second treatment periods indicated no important differences between the treatment effects apart from an increase in the apparent breakthrough infections during the second, acyclovir treated, episodes of the Oslo patients. The lack of any carryover effect thus allowed combination of the results and for convenience the separate analysis data have been omitted.

The numbers of patients in each treatment group experiencing recurrences or abortive episodes were compared. One patient receiving placebo was withdrawn after 9 days, before having had a recurrence. Otherwise all patients treated with placebo had at least one recurrence (90%) or abortive episode only (10%). All the Oslo patients had recurrences whilst receiving placebo. Overall only about half the patients had recurrences (23%) or abortive episodes only (26%) whilst receiving acyclovir. More of the acyclovir recipients who had recurrences came from the Oslo centre (6 vs. 1) whilst more of the Helsinki centre patients (6 vs. 2) had abortive episodes.

Significant differences between the acyclovir and placebo-treated groups were detected

Table I. *Details of patients at presentation according to centre*

	Oslo ($n=18$)	Helsinki ($n=13$)	
Age in years[a] (SE)	32.3 (1.78)	29.5 (1.13)	
Years since initial attack[a]	2.5	2.1	
No. of recurrences per year[b]	11	11	
Duration of recurrences in days[b]	10	8	
Usual severity of pain (0–3)[a]	1.4	1.7	
Days since last recurrence[a]	6	11	
Herpes simplex at other sites (%)	50	8	$p<0.05$
Genital herpes in partner (%)	22	23	

[a] Mean values.
[b] Median values.

for all parameters analysed relating to onset of first recurrence/episode, mean number of recurrences/all episodes, and percentage of treatment period affected, whether overall results or separate centres were considered (Table II and Fig. 1). On average patients experienced their first recurrence by two weeks and had more than 2.5 recurrences lasting approximately 20 days whilst receiving 84 days of placebo therapy. During acyclovir treatment the average overall recurrence rate was 0.5, lasting 3 of the 84 days. If all episodes are considered (i.e. recurrences and abortive episodes) then there were three times as many during placebo treatment (3.9 vs. 1.3) and they lasted about 27 days as compared with only 6 days on acyclovir.

For patients having episodes during both treatment periods the mean duration of these in days have been calculated and compared. Overall the average duration of episodes was significantly reduced by more than one third (from 6.6 to 4.2 days; $p<0.05$) and the duration of abortive episodes by a similar amount. Only six patients had proper recurrences during both parts of the study which provided a rather small group for analysis. Even so the differences in healing times approached significance (9.2 vs. 5.2 days; $p=0.07$).

None of the 53 random viral cultures taken during acyclovir therapy were positive for herpes simplex compared with 23 of the 67 (34%) taken during placebo treatment and 19 of the 53 (36%) taken before or after the treatment periods. If only those cultures taken whilst active lesions were present are considered the values are for acyclovir 0 of 3 (0%), placebo 23 of 31 (74%) and no treatment 19 of 28 (68%). The small number of samples obtained from lesions in acyclovir recipients reflects the relative infrequency of recurrences and their short duration.

There were few adverse events reported during therapy and these were equivalent for the two treatment groups (37% placebo; 31% acyclovir). In all about one quarter of the patients had a single abnormal haematological or biochemical parameter, usually on only one occasion. One patient had an abnormally low white cell and platelet count at the end of their course of acyclovir therapy and was then withdrawn from the study. Prior to treatment the values had been low but not abnormal and after treatment was stopped they returned to normal ranges. The other laboratory findings were unremarkable. Two patients

Table II. *Results, overall and for each centre*

PCB = placebo, ACV = acyclovir

	Overall		Oslo		Helsinki	
	PCB $n=31$	ACV $n=31$	PCB $n=18$	ACV $n=18$	PCB $n=13$	ACV $n=13$
Median days to first						
Recurrence	14	>84***	11	>77**	21	>84**
Episode (any)	9	>63***	9	>77***	7	49*
Mean no. of episodes						
Recurrences	2.6	0.5***	2.9	0.7***	2.2	0.2**
All episodes	3.9	1.3***	4.1	1.3***	3.6	1.3**
Mean percentage of treatment period[a] with						
Recurrences	23.7	3.3***	30.2	5.3***	14.7	0.6**
All episodes	31.8	7.4***	38.2	8.7***	23.1	5.6***

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.

[a] An approximate total duration can be calculated by taking % of 84 days.

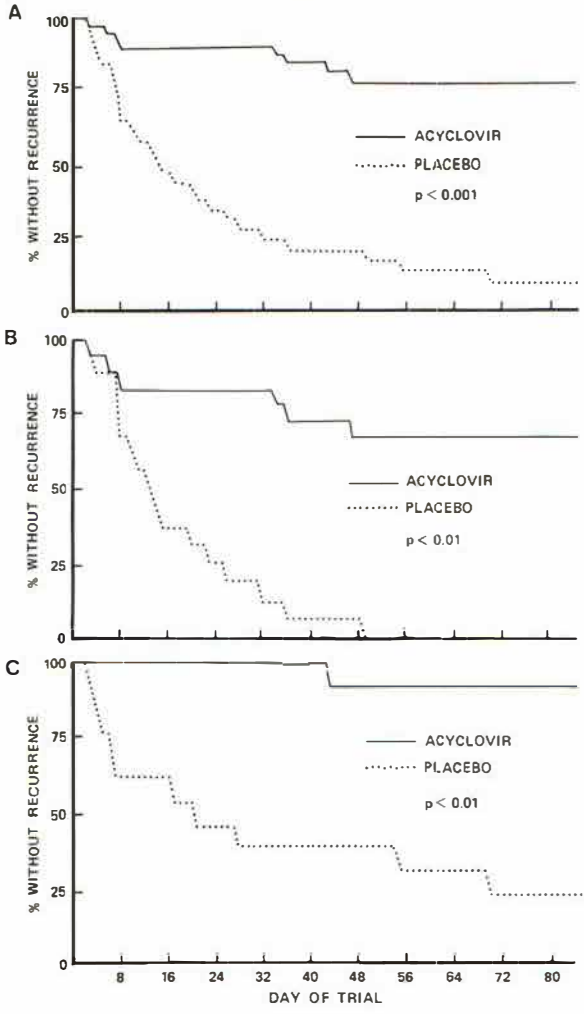

Fig. 1. Time in days to first recurrence of genital herpes in (A) all patients, (B) Oslo patients and (C) Helsinki patients whilst receiving acyclovir or placebo.

in each group, including one during both treatment periods, complained of uncomplicated headaches at one of their monthly follow-up visits. Another two patients receiving acyclovir had headaches in association with fever suggestive of an acute viral illness.

DISCUSSION

In this study 77% of patients with recurrent genital herpes did not experience a clinical recurrence during therapy with acyclovir whilst only 10% receiving placebo did not. For those patients who experienced recurrences during active suppressive treatment these were fewer in number and of shorter duration than those occurring during placebo therapy. Abortive episodes occurred in slightly more placebo-treated patients, 16 vs. 12 (data not presented), and there were more abortive episodes in total during placebo therapy, 41 vs. 26. Of these only 14 episodes (5 placebo, 9 acyclovir) were completely abortive and 53 (36 placebo, 17 acyclovir) partially abortive. Acyclovir therapy, therefore, also appeared to reduce the incidence of partially abortive episodes. Suppression of clinical recurrences does not lead to an increase in abortive episodes.

When acyclovir-treated patients experienced recurrences or abortive episodes then these lasted for a shorter time than those occurring during placebo treatment. The average duration of lesions overall was 6.6 days on placebo and 4.2 days on acyclovir. These results are comparable with those reported for patient-initiated therapy (3) indicating that once an episode has begun it may be impossible to reduce the duration of mild infections by more than about two days. There may thus be only two alternatives that can be offered to patients with recurrent herpes simplex infections, namely complete suppression of recurrences or a moderate treatment effect on established episodes with only a limited "therapeutic window" available for the former.

The rather limited data included in this study relating to isolation of herpes simplex indicate that any breakthrough infections that occur are effectively treated by the dose of acyclovir employed. Failure to detect viral shedding in any of the patients receiving acyclovir is an encouraging sign that emergence of resistance is not a frequently or rapidly occurring event during suppressive therapy. Virus strains isolated from most of the Helsinki patients after completing the acyclovir treatment have been tested for sensitivity to acyclovir in vitro and been found to fall within the normal range (K. Ewart, personal communication).

Continuous therapy with acyclovir for a period of 12 weeks was well tolerated but did not lead to a permanent reduction in recurrences that could be detected in these patients. Nevertheless chronic suppressive therapy may offer the best hope of palliation for frequent sufferers, so it is necessary to determine whether longer periods of treatment are equally well tolerated.

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