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Recurrences after first episodes of genital herpes in patients treated with topical acyclovir cream

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Summary

The effect of topical acyclovir treatment of first episode genital herpes on the time to first recurrence in a group of 42 patients receiving either acyclovir or placebo was investigated. Topical acyclovir treatment had no effect on time to first recurrence in patients with either first episode HSV-1 or HSV-2 infections. There was no significant difference in the time to first recurrence in patients with either true primary or initial genital infections. However, the time to first recurrence in patients with first episode HSV-2 was significantly shorter than in patients with first episode HSV-1. Acyclovir treatment appeared to have no effect on the development of neutralising antibody in patients with either virus type.

acyclovir; recurrence; genital herpes

Introduction

The considerable interest shown in genital herpes at the present time is due to several factors, including the 60% increase in incidence in the United Kingdom during the past 5 years (Communicable Disease Surveillance Centre, 1982), that first episodes may be severe enough to require hospital admission and recurrence may be frequent, causing both physical and psychological distress [1], and the strong association between genital herpes infections and cervical cancer [6]. Although many treatments [16] have been tested in the past, none has been shown to be of any clinical benefit [3]. However, recently the antiviral compound acyclovir has been shown to have low toxicity and a specific mode of action against herpesviruses, and to be effective

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topically and systemically in the treatment of both first and recurrent episodes of genital herpes [6,7,9,14,17,22].

The aim of the present study was to determine whether treatment of first episode genital herpes (HSV) infection with topical acyclovir cream had any effect on the time to subsequent clinical recurrences; and since both HSV-1 and HSV-2 are now established as important causes of genital infection in some populations [2], the effect of virus type on recurrence was also investigated. In addition, the effect of acyclovir treatment on the antibody response to virus infection was studied. The effect of topical acyclovir cream on first episode genital herpes in this group of patients has already been reported [9].

Materials and Methods

Patients

42 patients who enrolled in a double-blind placebo-controlled trial of 5% acyclovir cream were followed after treatment and first clinical recurrences noted. The patients were followed up for varying lengths of time after treatment ranging from 7 to 733 days. 34 of the patients were followed up for more than 100 days.

Virus typing

Initial virus isolates were typed by restriction enzyme analysis and a modified ELISA technique [2,23].

Antibody response

Acute phase sera were collected 5 days after first appearance of symptoms and convalescent sera 2–4 weeks later. The neutralising antibody titres of these sera were determined by the microneutralisation test described by Nahmias et al. [15] using HSV-1 strain 71-15 and HSV-2 strain Curtis Thigh. Patients with reciprocal antibody titres of <10 against both virus types in the acute serum were classified as true primary infections. Patients with reciprocal antibody titres >10 against either virus type in the acute serum were classified as initial infections.

Statistical analysis

The incidence of HSV-1 in males and females was compared using the χ^2 test with Yate's modification. Since patients were followed up for varying lengths of time recurrence rates were studied using survivorship analysis. This allowed data from all patients to be used and adjusted for differences in length of follow up. Life tables were then compared using Mantel–Haenszel χ^2 statistics [13].

Results

Virus typing

The distribution of patients with first episode HSV-1 and HSV-2 infections into

TABLE 1

Incidence of HSV-1 and HSV-2 in patients treated with acyclovir or placebo

	Acyclovir		Placebo	
	HSV-1	HSV-2	HSV-1	HSV-2
Males	1	9	1	7
Females	8	5	5	6

One patient infected with HSV-1 and one patient infected with HSV-2 both treated with placebo were excluded from the analysis of time to first recurrence because they were followed up for less than 7 days after completing treatment.

acyclovir and placebo-treated groups is shown in Table 1. There was an approximately equal distribution of patients with type-1 or type-2 infections into either acyclovir or placebo-treated groups. HSV-1 was isolated from 13/24 (54%) of female patients and from 2/18 (11%) males: this difference was significant ($\chi^2 = 7.61$, $P<0.005$). 17 out of 24 female patients (71%) had true primary infections compared to 5 out of 18 males (28%). Thus there was a significant difference in the incidence of true primary infections between males and females ($\chi^2 = 5.2$, $P<0.0125$).

Time to recurrence

The time to first recurrence in all patients with first episode type-1 infections with acyclovir or placebo is shown in Fig. 1. During the follow up period 33% of patients with HSV-1 infections treated with acyclovir and 20% of patients treated with placebo

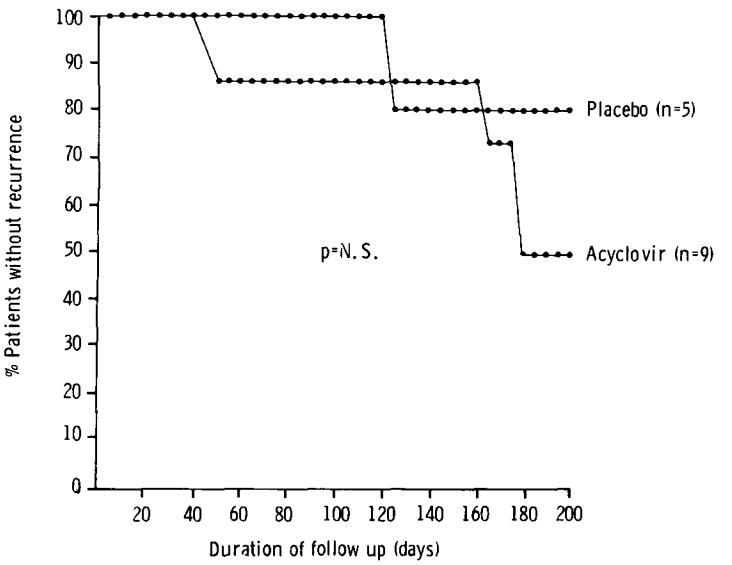

Fig. 1. Time to first clinical recurrence in all patients with first episode HSV-1 treated with acyclovir or placebo.

TABLE 2

Recurrences and duration of follow up in patients treated with acyclovir or placebo

Virus type	No. with recurrence (total %)		Mean duration of follow up in days ± S.D. (range)	
	Acyclovir	Placebo	Acyclovir	Placebo
HSV-1	3/9 (33)	1/5 (20)	280 ± 156 (110–544)	319 ± 103 (155–413)
HSV-2	9/13 (69)	7/13 (54)	237 ± 222 (55–582)	322 ± 154 (7–733)

experienced at least one clinical recurrence (Table 2). There was no significant difference in time to first clinical recurrence between patients receiving acyclovir or placebo. Similarly there was no significant difference in time to first recurrence when patients with first episode HSV-2 treated with acyclovir were compared to patients treated with placebo (Fig. 2). During the follow up 69% of patients with HSV-2 infections receiving acyclovir and 54% receiving placebo had at least one clinical recurrence (Table 2). However, the time to first recurrence for patients with first episode HSV-2 was significantly less than the time to first recurrence in patients with first episode HSV-1 ($\chi^2 = 4.02$, $P < 0.025$; Fig. 3). In patients with HSV-1 infections 29% experienced at least one clinical recurrence compared to 62% of patients with first episode HSV-2 during follow up (Table 3).

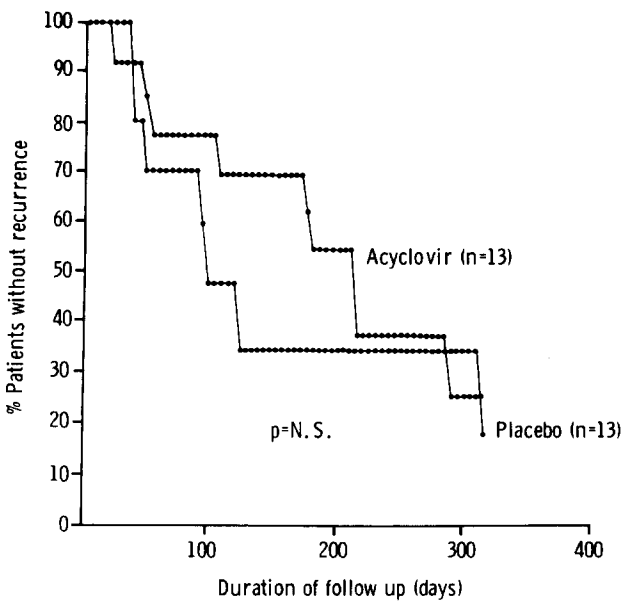

Fig. 2. Time to first clinical recurrence in all patients with first episode HSV-2 treated with acyclovir or placebo.

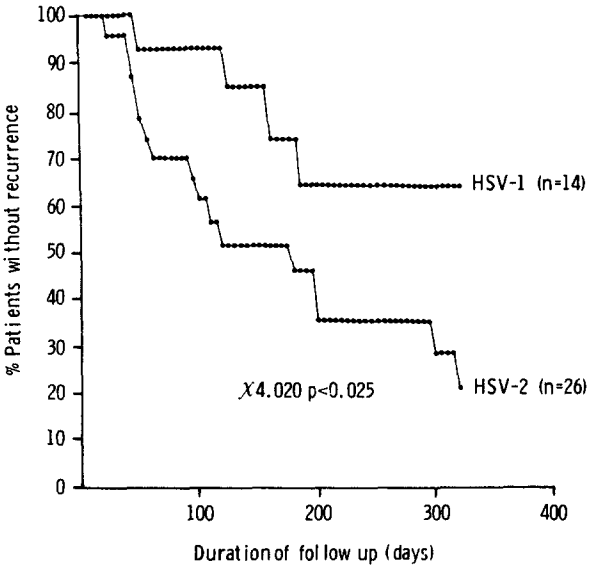

Fig. 3. Time to first clinical recurrence in all patients with first episode HSV-1 or HSV-2 infections.

TABLE 3

Recurrences and duration of follow up in patients with first episode HSV-1 or HSV-2 infections

Virus type	No. with recurrence (total %)	Mean duration of follow up in days ± S.D. (range)
HSV-1	4/14 (29)	309 ± 136 (110–544)
HSV-2	16/26 (62)	261 ± 187 (7–733)

When the time to first clinical recurrence in patients with true primary infections was compared to time to first recurrence for initial infections there was no significant difference (data not shown): during follow up 22% of patients with primary HSV-1 and 40% of patients with initial HSV-1 infections had at least one clinical recurrence and in patients from whom HSV-2 was isolated 67% with primary and 57% with initial infections experienced a recurrence (Table 4).

Antibody response

The neutralising antibody titres against the homologous virus for patients with HSV-1 or HSV-2 infections treated with acyclovir or placebo are shown in Table 5. There was a smaller rise in antibody titre in patients with first episode HSV-2 who received acyclovir (1.9-fold rise) compared to patients who received placebo (3.2-fold rise). However, the patient numbers were small and so no statistical analysis of the results could be made.

TABLE 4

Recurrences and duration of follow-up in patients with primary or initial infections

Virus type	No. with recurrence (total %)		Mean duration of follow-up in days ± S.D. (range)	
	Primary	Initial	Primary	Initial
HSV-1	2/9 (22)	2/5 (40)	298 ± 150 (110–544)	263 ± 113 (160–400)
HSV-2	8/12 (67)	8/14 (57)	348 ± 215 (17–733)	222 ± 156 (7–507)

TABLE 5

Geometric mean titres of neutralising antibody against homologous virus in patients treated with acyclovir or placebo

Treatment	Patients infected with HSV-1 Geometric mean titre against HSV-1 (No. sera tested)		Patients infected with HSV-2 Geometric mean titre against HSV-2 (No. sera tested)	
	Acute	Convalescent	Acute	Convalescent
Acyclovir	13.0 (8)	35.9 (6)	23.3 (13)	43.6 (7)
Placebo	10.4 (6)	31.3 (3)	12.3 (12)	39.5 (8)

Discussion

In the group of patients studied treatment of first episodes of genital herpes with topical acyclovir cream had no effect on the time to first clinical recurrence with either HSV-1 or HSV-2 infections. This confirms the report by Corey et al. [6], who found that acyclovir treatment was effective in reducing the duration of virus excretion and symptoms in first episode infections but that there was no decrease in the frequency of recurrences or the time to first recurrence. This was not unexpected since acyclovir treatment was initiated up to 5 days after first appearance of the lesions and it is probable that latent infection of the sacral ganglia had already occurred: indeed Stanberry et al. [21] have reported that latent infection of ganglia precedes development of external lesions in guinea pigs with experimental genital HSV-2 infections. In addition, virus was isolated from the cervix or urethra of most patients [9] and as acyclovir cream was not applied to these lesions it is possible that latent infection was established from these untreated lesions. However, there was a reduction in the duration of virus excretion from internal lesions in patients treated with acyclovir compared to patients receiving placebo suggesting that there may have been some local absorption of acyclovir [9]. The effects of acyclovir treatment on latent infections in animals are not clear. Some studies found a reduction in latency only if treatment was begun 24–48 h after virus inoculation with treatment after the establish-

ment of latency having no effect on latent virus [4,8,10–12,18], but there is one report of a significant reduction in nervous system infection during latency when treatment was started 3 weeks after a primary infection [19]. Thus, although acyclovir cream has a valuable role in the treatment of first episode genital infections [6,7,9,17,22], treatment does not appear to influence subsequent recurrences.

In the particular group of patients studied HSV-2 infections were significantly more common in males. Serological analysis suggested that this was influenced by the incidence of antibody to HSV-1 in the acute phase serum which was much greater in males than in females. The data for recurrences was also analysed separately for female patients alone since Reeves et al. [20] found that males tend to have more frequent recurrences than females and results similar to those for all patients together were obtained (data not shown). In addition, as the frequency of males and females in the acyclovir and placebo groups was similar this factor was of minor importance in determining the effect of acyclovir treatment on time to first recurrence. The results of the present study confirm the observations of Reeves et al. [20] concerning the influence of virus type and lack of influence of acute phase antibody on time to first recurrence.

Although the number of patients was too small for statistical analysis of the serological data, acyclovir treatment appeared to have no effect on convalescent antibody titres which were similar in acyclovir and placebo-treated patients. However, there was a trend towards a smaller rise in neutralising antibody titres in patients treated with acyclovir. This may have been due to a reduction of the antigenic load in patients who received acyclovir but confirmation of this observation requires a larger group of patients for analysis.

Acknowledgements

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