Genitourin Med 1986;**62**:186-8

Efficacy of combined treatment with oral and topical acyclovir in first episode genital herpes

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SUMMARY Fifty patients presenting with first episode genital herpes were randomly allocated to seven day treatment with either oral acyclovir plus 5% acyclovir cream or oral acyclovir plus matching placebo cream. Combined treatment with oral and topical acyclovir was associated with a shorter duration of itching in women alone ($p=0{\cdot}04$) but gave no clinical relief of other symptoms, the time to healing of lesions, or the subsequent recurrence rate. Concomitant topical treatment with 5% acyclovir cream confers no advantages on patients who receive oral acyclovir.

Introduction

Acyclovir provides clinically effective antiviral treatment of first episode genital herpes when administered intravenously,[1] orally,[2-3] or topically.[4] The results of two recent studies in Sheffield have suggested that the antiviral effect of oral acyclovir is clearly superior to that of topical acyclovir cream.[5 6]

In the study published here the objective was to assess whether the concomitant use of acyclovir cream and oral acyclovir in patients suffering from first episode genital herpes conferred any more antiviral or clinical benefit than a placebo cream and oral acyclovir.

Patients and methods

STUDY POPULATION

Men and women aged 16 years or more who presented within six days of the onset of symptoms of first episode genital herpes to the department of genitourinary medicine, Royal Hallamshire Hospital, Sheffield, were eligible to enter the study. Patients were excluded if they had used other antiviral or immune stimulation treatment within the preceding seven days, if they had underlying immune deficiency, hepatic or renal disease, or were women who were not using a valid form of contraception. All entrants to the study gave informed consent.

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Accepted for publication 12 September 1985

The efficacy of each treatment was assessed by comparing the groups for the duration of viral shedding, duration of symptoms, and the times to healing of lesions. Each variable was analysed separately by fitting Cox's proportional hazards model with adjustments made for differences in response between male and female patients and between users and non-users of co-trimoxazole.

STUDY DESIGN

All patients were treated with oral acyclovir 200 mg four times daily for seven days. In addition they were given topical treatment with either 5% acyclovir cream or a matching placebo cream to be applied five times daily for seven days. The treatment was dispensed in a double blind fashion with separate stratification for the sex of the patient. Patients in both treatment groups were given identical advice regarding additional symptomatic treatment. Concomitant co-trimoxazole treatment was given to those patients considered to have secondarily infected lesions at presentation.

PATIENT ASSESSMENTS, LABORATORY STUDIES, AND TOXICITY SCREENING

These were identical to those described in detail in previous studies.[6 7]

FOLLOW UP FOR RECURRENCE

After their lesions had completely healed, patients were asked to report back to the clinic in the event of any subsequent recurrence and were seen routinely three and six months after entry.

TABLE I *Comparison of treatment groups at presentation*

	Patients treated with oral acyclovir and:	
	Acyclovir cream (n=24)	*Placebo cream (n=25)*
Number of men	7	7
Number of women	17	18
Mean age (years)	21·5	20·7
Mean duration of symptoms (days)	4·4	4·0
Mean duration of lesions (days)	3·3	3·2
No (%) with HSV-1 isolates	12(50)	16(64)
No (%) culture positive	23(96)	24(96)
No (%) with true primary (antibody negative) infection	20(83)	23(92)
No (%) also treated with co-trimoxazole	12(50)	10(40)

HSV-1 = herpes simplex virus type 1.

STATISTICAL ANALYSIS

The treatment groups were compared for their demographic and clinical data at entry to the study. Possible differences between the groups in the numbers of each sex, proportions infected with herpes simplex virus type 1, and proportions with true primary infections, were assessed using the Fisher's Exact test. Differences in the severity of symptoms were assessed using the Pearson χ^2 test; in the mean age of patients using the *t* test; in the duration of symptoms and signs before presentation using the log rank test.

Results

Of 50 patients who entered the study one defaulted before completing the protocol and was excluded from the analysis. Of the 49 patients completing treatment, 24 received acyclovir cream and 25 received placebo cream. Three, two receiving acyclovir cream and one receiving placebo cream, did not complete follow up.

Table I compares the treatment groups at entry to the study. The differences for any of the assessed demographic or clinical variables were not significant.

Table II shows the efficacy of each treatment for women only and for men and women combined. The mean (SD) duration of viral shedding, of a variety of symptoms, and of the times to healing of lesions are given. Small numbers prevented satisfactory analysis of the results for men only.

The only variable showing a statistically significant difference between the treatment groups was the shorter duration of itching in women treated with combined topical and oral acyclovir (p=0·04). All other variables gave non-significant results and no evidence of any trends.

There was no significant difference between the treatment groups in the proportion who developed one or more recurrences during the subsequent six month follow up period or in the times to first recurrence.

Of the 46 patients who completed follow up, 11 (50%) out of 22 who received acyclovir cream compared with 10 (42%) out of 24 treated with placebo

TABLE II *Efficacy of treatment with oral acyclovir and either acyclovir or placebo cream*

	Women			*Men and women*		
	Acyclovir (n=17)	*Placebo (n=18)*	*p Value*	*Acyclovir (n=24)*	*Placebo (n=25)*	*p Value*
Mean (SD) duration (days) of viral shedding:						
External lesions	2·6(0·4)	2·8(0·3)	NS	2·6(0·3)	2·0(0·3)	NS
Urethra or cervix	1·7(0·4)	1·8(0·3)	NS	2·1(0·4)	1·7(0·3)	NS
Mean (SD) duration days of symptoms:						
Itching	1·2(0·4)	2·7(0·6)	0·04	1·2(0·3)	2·2(0·5)	0·08
Pain	4·1(0·6)	3·6(0·4)	NS	4·0(0·6)	3·6(0·3)	NS
Dysuria	3·1(0·5)	3·0(0·4)	NS	3·1(0·5)	2·7(0·3)	NS
Discharge	3·3(0·9)	2·9(0·5)	NS	2·7(0·7)	2·6(0·4)	NS
All symptoms	5·4(0·8)	4·9(0·5)	NS	5·1(0·7)	4·7(0·4)	NS
Mean (SD) time (days) to healing:						
Original external lesions	6·0(0·6)	6·3(0·6)	NS	6·4(0·6)	6·5(0·6)	NS
All lesions	6·6(0·7)	6·7(0·5)	NS	6·9(0·6)	6·7(0·5)	NS

cream had a recurrence within six months of their first episode.

No adverse effects were reported by patients in any of the treatment groups, and values for haematological variables and biochemical data remained within their normal ranges after treatment.

Discussion

The durations of viral shedding and clinical manifestations observed in this study were similar to those observed in acyclovir treatment patients in a previous placebo controlled study.[6] The only variable that showed a significant difference between the treatment groups was the shorter duration of itching in women given concomitant acyclovir cream than in those given placebo cream. Itching was invariably the complaint of shortest duration among our patients, and there was no evidence of benefit from concomitant topical acyclovir treatment on the other more severe and disabling symptoms that occur in first episode genital herpes. As topical treatment with acyclovir does not give any additional benefits on the duration of viral shedding, the time to healing of lesions and the subsequent recurrence rate, it is not justified in patients who receive oral acyclovir to treat first episode genital herpes.

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