CLINICAL RESEARCH

Failure of acyclovir cream in treatment of recurrent herpes labialis

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Abstract

A double blind, randomised, crossover placebo controlled trial of 5% acyclovir cream, applied topically five times a day for five days, was carried out in 45 patients with recurrent herpes labialis. These patients had a total of 72 episodes, 34 of which were treated with the 5% acyclovir cream and 38 with placebo cream. Treatment was begun by the patients as soon as possible after the onset of prodromal symptoms.

There was no significant clinical benefit from treatment with acyclovir cream compared with placebo cream. The median healing times were nine days with acyclovir cream, 10 days with placebo cream, and 13 days when no treatment was given. The possibility that the 40% propylene glycol cream base alone has a therapeutic effect must therefore be considered.

Introduction

Recurrent perioral herpes simplex infections are common. Studies in North America have shown that they occur in 20% or more of young adults.^{1 2} These infections are usually caused by herpes simplex virus type 1. Many subjects suffer one to three recurrences a year and some as many as 12 or more in a year.

These infections are a particular problem when they occur in

hospital staff. Because of the risks to, for example, newborn infants, immunocompromised patients, and patients with atopic eczema non-genital herpes simplex infection is one of the commonest causes of lost working time in hospital staff who have contact with patients. An Australian study of hospital staff showed that in one year 119 (34%) of 347 staff members in direct contact with patients reported 165 infections of non-genital herpes simplex virus. Herpetic infections accounted for 17% of all sick leave taken by staff members in contact with patients, and the time lost was more than double that due to all other illnesses or injuries.³ A reliable treatment that could abort or shorten attacks would have obvious economic benefits as well as reducing the risk to patients.

A large range of antiviral and other treatments has been tried, and until recently none of them had been shown to have any clinical benefit in placebo controlled trials. Recent reports, however, have claimed success in the treatment of recurrent herpes labialis and recurrent genital herpes using topical preparations of the antiviral agent acyclovir.⁴⁻¹⁰ Topical acyclovir has been used in an ointment base consisting of macrogol (polyethylene glycol) and in a cream base containing propylene glycol, and it has been suggested that the cream preparation is more effective than the ointment.^{5 7 11}

We report on a trial of 5% acyclovir cream in patients with recurrent herpes labialis in which treatment was begun by the patients as soon as possible after the onset of prodromal symptoms.

Patients and methods

Patients entered into the study had a history of at least three recurrences of herpes labialis a year. All were aged 18 or more and gave informed consent.

The diagnosis of herpes simplex was confirmed in the patients seen at St Thomas's Hospital by electron microscopy and culture at the start of a first untreated episode. These patients were seen throughout this untreated episode, during which they also kept diary cards. Further specimens were obtained at the start of each treated episode. In the patients seen at the London and Basildon hospitals, the diagnosis was confirmed clinically before they were entered into the study, though specimens were not obtained.

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All patients were allocated randomly under double blind conditions to receive either a 10 g tube of 5% acyclovir in 40% propylene glycol cream or a matching placebo consisting of 40% propylene glycol cream. They were instructed to start applying the cream as soon as possible after the onset of the first prodromal symptom of their next attack and to continue treatment five times a day for five days. They were seen in the clinic as soon as possible after the start of the attack, and subsequently attempts were made to see them daily for assessments. All patients were seen at least three times during each attack. The presence of pain, itching, and other symptoms and the site, size, and stage of the lesions were recorded at each visit until complete healing had occurred. Any possible adverse effects were recorded. In addition, each patient recorded details of the symptoms including severity, the appearance of the lesions, and the number of applications of cream on a diary card that was filled in daily. After the first treated episode each patient was given, again under double blind conditions, either acyclovir cream or placebo cream, whichever they had not received previously. When the second episode occurred the patients began treatment, and assessments were made as before.

The Cox proportional hazards regression model was used to compare treatment groups.

Virological diagnosis was made by negative staining of vesicular fluid before examination by electron microscopy as well as culture in human embryonic lung fibroblastic cell cultures. The sensitivity to acyclovir of available virus isolates was assayed at the Wellcome Research Laboratories, Beckenham, Kent, using the method of Collins *et al.*¹²

Results

Although 72 patients were entered into the trial, data from only 45 were evaluated as 24 patients, having received the drug, failed to return for any assessment and a further three were excluded for inadequate compliance. The criteria for inclusion were documented recurrences during the study period, the start of treatment within 24 hours of the onset of an attack, regular attendance for assessment, and the completion of the diary cards for each attack. Of the patients who were included in the analysis, 24 were entered at St Thomas's Hospital, 16 at The London Hospital, and five at Basildon Hospital.

Twenty seven patients completed both treatment episodes, and a further 18 completed only the first episode. Thus 72 treated episodes were included in the analysis of efficacy. Thirty two of the 45 patients included in the trial analysis were hospital staff.

Table I compares the details of patients in the two groups. No significant differences in these variables were found between the groups.

Variables used to assess efficacy were healing time of lesions present on the first visit (original lesions); healing time of original lesion and fresh lesions developing during the attack; time to first crust on the

original lesions; time to first loss of crust from original lesions; and duration of all symptoms. Analysis of the criteria used to assess efficacy showed that no significant differences existed between the acyclovir and placebo preparations (table II). The median healing time of lesions was 13 days in the group of patients not receiving treatment, whereas it was 10 days in the group treated with placebo and nine days in the group treated with acyclovir.

Minor adverse effects were reported by nine patients. In eight of these flaking of the skin occurred in the area of application, and the ninth patient complained of a stinging sensation.

The presence of herpes simplex virus was confirmed at the beginning of the untreated episode in all of the 24 patients from St Thomas's Hospital by electron microscopy or culture, or both. All viral isolates obtained before treatment were sensitive to acyclovir.

Discussion

Our study showed that 5% acyclovir cream had no significant therapeutic advantage over placebo cream in patients with recurrent herpes labialis. The untreated episodes studied in 24 of our patients, however, lasted longer than the episodes treated with either acyclovir or placebo cream. As all the other conditions were similar, including the collection of specimens for isolation of virus in the patients seen at St Thomas's Hospital, this finding suggests that the 40% propylene glycol cream base may have a beneficial effect. This may explain the advantage of acyclovir cream over acyclovir ointment reported in previous studies.^{5-7,11} Eight of our patients reported flaking of the skin as an adverse effect. This has also been noted in two previous trials of acyclovir cream for herpes labialis.^{5,8} Perhaps this tendency to dryness may explain the therapeutic effect of the cream base. Van Vloten *et al* observed a reduction in time to complete healing in episodes treated with placebo,⁸ and as many of their subjects had previously been in a group treated with acyclovir they explained this on the basis of "a possible carry over effect of acyclovir treatment"—that is, after treatment with acyclovir the next attack may be shorter. This seems simply to reflect our finding that the cream base may be beneficial.

Even though strenuous efforts were made to maintain contact with patients, 24 of the 72 patients originally entered into the trial failed to return for assessment of any treated episode, and a further 18 completed only the first treatment episode. Many patients also dropped out of a previous trial of acyclovir cream.⁵ It may reflect poor motivation of the patients but may also be because recurrences are fewer than their histories suggest. Trials of treatment for herpes labialis are difficult to organise because so many patients are needed with whom regular contact must be maintained and so much time is required to complete a study. Perhaps parallel studies rather than the cross-over design would overcome these difficulties.

Acyclovir cream is now readily available. So far there have been only two placebo controlled trials reporting beneficial effects of treating herpes labialis with acyclovir cream.^{5,8} As we have failed to show any therapeutic efficacy with this preparation and its widespread use may encourage the development of strains of herpes simplex virus that are resistant to acyclovir, we are reluctant to advocate its use in herpes labialis. As other workers claim to have shown some therapeutic efficacy, however, we suggest that further large scale, double blind placebo controlled parallel trials should be carried out.

We thank Drs Jane Yeo and Paul Fiddian for their advice, Mr D A Jones and Ms C Burke for their statistical advice, and Dr P Collins for testing virus strains for sensitivity to acyclovir (Wellcome Research Laboratories).

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TABLE I—Details of patients and episodes

	Acyclovir cream (n = 34)	Placebo cream (n = 38)
No of men	5	9
No of women	29	29
Mean age (years)	33.7	31.1
Mean age at onset of disease (years)	16.8	15.5
Mean No of recurrences/year	5.6	5.2
Mean duration of lesions (days)	9.7	9.8
Mean No of lesions	1.6	1.5
Stage of infection when treatment initiated:		
Prodromal	3	4
Erythematous	2	3
Papular	14	16
Vesicular	14	12
Mean time from when lesion first noted to first treatment (hours)	4.9	4.4

TABLE II—Comparison of treatment with acyclovir cream and placebo cream

	Acyclovir cream	Placebo cream	p Values
Median healing time of original lesions (days)	9	10	0.82
Median healing time of original and fresh lesions (days)	9	10	0.80
Median time to first crust (days)	2	2	0.64
Median time to first loss of crust (days)	5	5	0.56
Median duration of all symptoms (days)	5	6	0.33

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(Accepted 4 April 1985)

Relation of gene expression (allotypes) of the fourth component of complement to insulin dependent diabetes and its microangiopathic complications

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Abstract

About a quarter of insulin dependent diabetics have low concentrations of the fourth component of complement (C4), and a low concentration of C4 is associated with diabetic microangiopathy. The variability of the expression of the C4 gene was compared in insulin dependent diabetics with and without microangiopathy and controls. Of the two genes coding for C4, the A gene (C4A) was not expressed—that is, C4A null—in 16 (13%) of the 126 insulin dependent diabetics compared with none of the 93 controls ($p < 0.001$), and all these 16 subjects had low concentrations of C4. Lack of expression of the other C4 gene (C4B) was not associated with insulin dependent diabetes, but a rare variant, C4B3, was significantly increased in the diabetics (21/126; 17%) compared with the controls (none) ($p < 0.001$). The prevalence of C4B3 was also increased in the diabetics with complications when compared with those without (14/50 (28%) v 7/76 (9%), $p < 0.01$).

Low plasma C4 concentrations in insulin dependent diabetics are at least partly due to variation in the expression of the C4 gene. The association of the rare C4B3 variant with microangiopathy suggests a genetic component of its aetiology.

Introduction

Environmental (possibly viral) and genetic factors appear to have a role in the pathogenesis of insulin dependent diabetes.¹⁻³

We previously reported that about a quarter of insulin dependent diabetics have low plasma concentrations of the fourth component of complement (C4).^{4,5} Low C4 concentrations are found irrespective of age or duration of disease⁴ and are associated with diabetic microangiopathy.⁵ Studies of identical twins⁴ and families⁵ suggest that the characteristic of low concentrations of C4 is inherited. As C4 is important in viral neutralisation⁶ and the clearance of immune complexes⁷ it might have a role in the pathogenesis of insulin dependent diabetes and its microvascular complications.

The genes that code for C4 are on the short arm of chromosome 6 in the HLA region, this region being concerned with cellular and humoral immune responses.⁸ Two genes, C4A and C4B, each contribute to about half of the total serum C4 concentration. Both are highly polymorphic: 13 different variants (allotypes) have been described for the A protein and 22 for the B protein. In addition, non-expressed (null) genes have been described at each locus, which lead to lower serum concentrations of C4.⁹ The prevalence of null alleles is increased in insulin dependent diabetics,¹⁰ as are other rare C4 allotypes.^{10,11} We studied the prevalence of C4 allotypes in normal controls and in insulin dependent diabetics with and without microangiopathy.

Subjects and methods

We studied 126 white insulin dependent diabetics routinely attending two diabetic clinics in the West Midlands. Insulin dependence was defined on the basis of initial acuteness of presentation, a tendency to ketosis, requirement for insulin from diagnosis, and age at onset. Of the 126 insulin dependent diabetics, 76 had no evidence of microangiopathic complications and 50 had retinopathy with or without persistent proteinuria. Retinopathy was diagnosed by ophthalmoscopic features through dilated pupils and in most cases was confirmed by fluorescein angiography. Twenty nine subjects had severe complications (proliferative retinopathy with or without proteinuria or background retinopathy and proteinuria).

The mean (SD) age of the diabetics with complications was 36 (11) years (range 18-63) and of those without complications 28 (11) years (range 14-57). The respective durations of diabetes were 20 (9) years (range 7-35) and 12 (9) years (range 1-38).

Ninety three healthy non-diabetic white university undergraduates attending the local blood transfusion centre were studied as a control group (most were aged 18-22). None had a family history of diabetes.

Plasma C4 concentration was measured by radial immunodiffusion, and values ≤ 0.23 g/l were defined as low, as previously described.⁵ Phenotyping of C4 was performed by agarose gel electrophoresis of neuraminidase treated edetic acid plasma with immunofixation.¹²

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