Topical treatment of recurrent genital herpes simplex virus infections with trisodium phosphonoformate (foscarnet): double blind, placebo controlled, multicentre study

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SUMMARY A double blind, placebo controlled trial was performed in nine sexually transmitted diseases (STD) clinics in the United Kingdom and the Netherlands to investigate the efficacy of trisodium phosphonoformate (foscarnet) cream in treating recurrent genital herpes simplex virus (HSV) infection. The study group comprised 145 male and 85 female patients. Men received 0.3% foscarnet cream and women 1% foscarnet cream for five days.

The difference in time to healing between patients receiving foscarnet or placebo was not significant. Fewer patients treated with foscarnet had positive viral cultures after treatment, but the difference was not significant. The development of new lesions, however, was significantly less common in patients given foscarnet. Though topical foscarnet is a safe drug, no appreciable efficacy in treating recurrent genital HSV infection could be shown.

Introduction

The herpes simplex viruses (HSV) are among the most common human pathogens. Their characteristic feature is a capacity to establish latency in the host after the initial infection and to reactivate periodically.

Genital herpes is most commonly due to HSV type 2.¹ Though this disease has been recognised for hundreds of years,² with many attempts at treatment,

the past 10 years have seen a dramatic increase in the numbers of reported cases. This has been accompanied by more reliable and readily available methods of diagnosis, the discovery of new antiviral drugs,³ and the formation of patient organisations to demand better care.

The most important new drug developed for the treatment of HSV infection is acyclovir. Though systemic acyclovir has been shown to be effective in treating primary genital HSV infection⁵ and in the prophylaxis of recurrent disease,⁶ there remains doubt about its efficacy when used topically for treating recurrent mucocutaneous HSV infections.^{7,8} In addition, the potential development of acyclovir resistant mutant viruses⁹ has led to a search for other antiviral

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drugs for treating HSV infections. Foscarnet is an antiviral agent that is active against all herpes viruses. The inhibitory effect of foscarnet on isolated HSV DNA polymerase, HSV multiplication in cell cultures and in HSV infected animals, as well as its pharmacokinetic profile and toxicity, have been extensively reviewed.¹⁰

In this study, foscarnet cream was investigated for its efficacy in treating recurrent genital HSV infections. A 3% cream had been found to be irritating to uncircumcised men with HSV lesions in the subpreputial area (Aoki FY, unpublished observation). A similar effect was noted, though less often, in men using the 1% cream. No irritation was reported, however, with the use of 0.3% cream.¹¹ No local intolerance was noted in women or circumcised men. The results of the earlier work suggested that 0.3% foscarnet cream reduced the period with ulcers and shortened the healing time in patients with recurrent genital HSV infection. The objective of the study published here was to evaluate the efficacy of topical foscarnet 0.3% cream in men and 1% cream in women as a treatment of recurrent genital herpes simplex infections.

Patients and methods

A double blind, placebo controlled, multicentre trial of parallel group design was undertaken. Six United Kingdom and three Dutch centres participated. Ethical committee approval for the study was obtained at all centres. Eligible patients were aged over 18 and had recurrent genital HSV infection affecting the penis or scrotum in men or the introitus or vulva in women. On admission to the study, patients had evidence of a recurrence in the prodromal, erythematous, papular, or vesicular stage. Patients with vesicles were included only if they were seen within six hours of detection of the lesions.

Patients were excluded if they had had a previous genital HSV recurrence, had received antiviral treatment within the preceding two weeks, had had immunostimulant treatment within the previous month, had had antiherpes immunotherapy within the past 12 months, or if they were immunodeficient. Furthermore, patients with other concomitant genital infection requiring treatment and patients with a history of allergy to any of the constituents of the cream (such as parabenes) were also excluded, as were pregnant and breast feeding women.

At the initial visit, patients to be included in the trial gave their written informed consent to participating in the study. At each clinic visit the genital area and the original lesion were examined and swabbed for viral HSV culture. The assessment of the original lesion was based on the following variables: area of erythema, stage of lesion (redness, swelling, blisters, sores, or

TABLE Scale for recording stage and severity of herpes simplex virus lesions

Stage	Severity
Redness	None, slight, distinct, or intense
Swelling	None, some, distinct, or severe
Blisters	None, one, few, or many
Sores	None, one, several, or deep
Scabs	None, one, several, or loose

scabs), and appearance of new lesions. Patients recorded the stage and severity of the lesions daily on a scale like that of the investigator (table). They also recorded pain and itching on a visual analogue scale.

Patients were randomly allocated either foscarnet cream (0.3% for men and 1% for women) or placebo (the vehicle only) in identically labelled 5 g tubes. Each tube was labelled with the patient's number. Treatment started immediately, and the patient was instructed about continuing treatment at home and about recording on a form details of symptoms, signs, and treatment. Treatment was administered every two hours on day 1, and then every four hours on days 2 to 5. The cream was applied topically in sufficient quantity to cover the lesion completely.

No concomitant antiviral treatment was permitted. If other drugs were taken they were recorded by the investigator. The patients revisited the clinic for assessment on days 3 to 5 and again on days 7 to 9. If the original lesion was not healed by this third visit another appointment was made after the lesion had healed. At the first and last visit the patient had a blood test to measure routine haematological and biochemical variables. At each visit the patient was asked general and specific questions about adverse events and local intolerance.

Statistical analysis of the data used the Kaplan-Meier product limit estimator to assess the time event functions. In addition, the log rank test was used to test the hypothesis that two such functions for foscarnet and placebo were equal.^{11 12} Conventional (two tailed) non-parametric statistical methods were used to analyse the remaining data.

Results

From March 1984 to April 1985, 253 patients (152 men, 101 women) entered the study. Seventeen patients did not fulfil the entry criteria; nine had extragenital lesions, four had had vesicles for more than six hours before treatment started, two had yeast infections, one was pregnant, and one was receiving steroid treatment. Four further patients did not return after the first visit and two had more than one lesion

assessed: these were excluded from analysis. Data relating to the remaining 230 patients were valid for efficacy evaluation. Data for men and women were analysed separately.

MEN

Of the 145 assessable men, 71 received foscarnet and 74 placebo. The groups were similar with regard to age, concomitant disease, current medication, medical history, and previous positive genital HSV culture. There was no appreciable difference in the lesion stage, location, size, severity of pain or itching, or virus isolation rate between the groups at the start of treatment. The duration and frequency of applications of cream did not differ between the two groups. The median time to healing (complete re-epithelialisation) of the original lesion was five days in both groups (fig 1). In the subgroup of patients with HSV culture positive lesions, however, the median time to healing was five days in those treated with foscarnet and six days in those receiving placebo ($p=0.44$). In a subgroup with small lesions at the start of treatment, the median time to healing was two days for foscarnet compared to five days for placebo ($p=0.002$), whereas in the subgroup with medium sized lesions at the start of treatment the median time to healing was shorter for placebo (four days) than for foscarnet (five days) ($p=0.08$).

The proportion of patients with a positive HSV culture from day 2 to healing was 26% in those receiving foscarnet and 43% in those receiving placebo ($p=0.07$). The percentage of lesions that aborted—that is, did not develop beyond the erythematous stage—was greater in those receiving placebo, though the difference was not significant.

New lesions, especially in untreated areas, developed appreciably less often in those receiving foscarnet compared with those receiving placebo ($p=0.05$). The proportion of patients who did not develop pain or itching during the episode was not

FIG 1 Time to healing of original lesion of 145 men.

FIG 2 Time to healing of original lesion of 85 women.

significantly reduced by treatment with foscarnet, except for pain in the group of patients with small lesions. In the same group, foscarnet treatment reduced the mean number of days with sores.

Three (4%) of the 71 men receiving foscarnet and eight (11%) of the 74 receiving placebo reported local intolerance. Adverse events were reported by eight (11%) receiving foscarnet and four (5%) receiving placebo.

WOMEN

Of the 85 assessable women, 44 received foscarnet and 41 placebo: both groups were similar at the start of treatment and were similar in presentation of the lesion. The groups were similar regarding duration and frequency of treatment and the pattern of concomitant medication, including contraceptive practice. The median time to healing was four days in both groups (fig 2). In women with positive HSV cultures at the start of treatment, the time to healing was five days in both groups ($p=0.29$). The proportion of patients with positive HSV cultures after treatment was started was 15% (6/41) in those receiving foscarnet compared with 30% (12/41) in those receiving placebo ($p=0.19$). Three patients treated with foscarnet were not tested. No lesions treated with placebo aborted, whereas 7% of lesions treated with foscarnet aborted. All these lesions were small, however, and none was HSV culture positive. More patients receiving placebo developed new lesions ($p=0.06$) and the mean duration of sores was shorter than in patients receiving foscarnet ($p=0.09$) when only large lesions were considered.

Seven patients (16%) receiving foscarnet and seven (17%) receiving placebo reported local intolerance. Adverse events were reported by six (14%) of those receiving foscarnet and five (12%) receiving placebo. None was serious.

ALL PATIENTS

We evaluated 22 haematological and biochemical variables. Of those who had normal values before treatment, 4% (5/116) receiving foscarnet and 3% (3/116) receiving placebo showed deviations from the normal range after treatment. The changes were not clinically significant.

Discussion

In this study there was no significant effect on the primary variable, time to healing, when topical foscarnet was compared with placebo. This lack of efficacy means that the preparation cannot be recommended for treating recurrent genital HSV infection. A significant reduction in the appearance of new lesions and a reduction in the virus isolation rate in the foscarnet treated patients, however, indicated that it had an antiviral action.

The poor effect of foscarnet cannot be explained by demographic or clinical differences between patients in the treatment and placebo treated groups. The effect of placebo in this study was surprising, as in a previous study the mean duration of lesions was 9-10 days in placebo treated patients, and 28% of women and 43% of men developed new lesions.¹ In our study only the initial lesion was evaluated, which could account for the difference. This protocol could make it more difficult to show an appreciable effect on time to healing, particularly if the drug acted principally by preventing new lesion development. Saline washing before viral sampling and simple hygiene measures in patients receiving foscarnet or placebo may have reduced the difference between the two groups and caused the apparent lack of efficacy of foscarnet.

Treatment of herpes lesions with topical acyclovir cream has been shown to be successful,⁶ but recent data have shed some doubt on the value of this form of treatment.⁷⁻⁸ Though topical antiviral treatments may reduce the duration of positive HSV cultures from treated lesions, clinical benefit may depend on treating all lesions, including those that are less accessible and not apparent at onset.¹³⁻¹⁵ In this study such lesions could not be treated. This may be one reason that an appreciable difference between foscarnet and placebo treatment was not shown.

In conclusion, topical foscarnet cream was a well tolerated drug in treating recurrent genital HSV infection, but its efficacy compared with placebo was not significant. Studies of its efficacy in the treatment of other viral diseases, however, will continue.¹⁶

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