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Section I. Chemotherapy

Efficacy of topical acyclovir cream in first and recurrent episodes of genital herpes

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Fifty-three patients with first episodes and 60 patients with prior culture proven recurrent genital herpes were enrolled in a single centre, double-blind, placebo-controlled trial of 5% acyclovir in an aqueous cream base versus matching placebo. For first episodes treated with topical acyclovir the median duration of pain (4 vs. 8 days, $P < 0.05$), time to healing of all lesions (8 vs. 14 days, $P < 0.001$), duration of viral shedding (4 vs. 11 days, $P = 0.001$) and duration of new lesion formation (0 vs. 2.5 days, $P < 0.001$) were reduced compared with placebo recipients. In patients with recurrent episodes who completed the study topical acyclovir significantly reduced the median duration of all symptoms (3 vs. 6 days, $P < 0.001$), the time to healing of all lesions (4 vs. 6 days, $P < 0.01$), and the formation of new lesions (5 vs. 29%, $P < 0.01$) compared with the controls. Greater clinical benefits were demonstrated in females than in males, particularly for first episodes, but the number of males was small. Topical acyclovir cream is well tolerated and an effective treatment for first and recurrent episodes of genital herpes.

acyclovir (Zovirax); genital herpes; herpes simplex virus

Introduction

Systemic acyclovir therapy has been shown to be effective in the treatment of first [6,9] and recurrent [8] episodes of genital herpes simplex virus (HSV) infection. Topical therapy with 5% acyclovir ('Zovirax', Wellcome) in an ointment base containing polyethylene glycol has also been demonstrated to have beneficial effects in first episodes of genital herpes but little effect in recurrent infections [3].

In an attempt to enhance cutaneous penetration and improve efficacy in recurrent HSV infections an alternative dermal formulation of acyclovir has been developed. This contains 5% acyclovir in a cream base containing 40% propylene glycol. Such a

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solvent will allow sufficient presentation of the drug in an aqueous phase to increase carriage through the skin but avoid the unpleasantness of solvents such as dimethyl sulphoxide. In an animal model for cutaneous HSV infections acyclovir cream was superior to acyclovir ointment [2]. Since there are potential difficulties in conducting multicentre trials it was decided to study the new preparation at a single centre.

We report the results of a double-blind, placebo-controlled trial of topical acyclovir cream in the treatment of first and recurrent episodes of genital herpes.

Patients and methods

Patients with clinically diagnosed first episodes or prior culture proven recurrent episodes of genital herpes presenting to the Department of Genitourinary Medicine, Sheffield, were entered into the study. Those with first episode (initial) genital herpes were included if they presented within 5 days of onset of symptoms of their attack. Patients with recurrent genital herpes were enrolled prospectively and given medication for self-iniation of therapy at the onset of the prodromal symptoms of their next recurrent episode. Patients aged < 16 yr, those who had received other antiviral agents within 14 days and those with other infections likely to make assessments inaccurate were excluded, as were women inadequately protected against pregnancy. All patients were routinely screened for other genital infections. Informed consent was obtained from all participants in the study. The local hospital ethical committee approved the study prior to its commencement.

Patients entering with first episodes were supplied with a 30-g tube containing 5% acyclovir in a cream base or the cream base alone. They were instructed to apply the cream to their external genital lesions only five times a day for up to 10 days or until 24 h after the external lesions had healed whichever was sooner. Those patients with recurrent genital herpes were given a 10-g tube containing acyclovir cream or matching placebo. They were carefully instructed to begin treatment of their next episode during the prodrome by applying cream to the site of the prodromal involvement, and to the area normally affected with lesions if different, five times a day for 5 days. In both groups the treatment was dispensed in a truly double-blind fashion, by random allocation with stratification for sex of the patient. Patients were given diary cards to complete after each application of cream so that some assessment of compliance could be performed.

Clinical assessments were carried out on admission to the study and at follow-up visits within 24 h of starting therapy and thereafter three times a week until lesions were completely healed. At each assessment swabs were taken from external lesions and, in addition, in patients with first episodes, from the cervix in females or urethra in males. Virus isolation was attempted in baby hamster kidney (BHK-21) or human embryo lung (2002) cells. Cultures were examined daily for 14 days for cytopathic effect. Representative isolates from patients with first episodes were typed by restriction enzyme analysis [1] and by a minor modification of an ELISA technique [15]. Sera from patients with first episodes were examined both at presentation and after 14–21 days for specific HSV antibodies using ELISA [8] and microneutralization

methods [7] with BHK-21 cells as indicators. Patients with antibody titres of < 10 by microneutralization against both HSV types 1 and 2 in the acute serum were defined as true primary infections.

Statistical analysis of the duration of symptoms, virus shedding and new lesion formation and time to first crust and healing of lesions was performed using a log-rank method of analysis [10]. For recurrent episodes the percentage of patients with positive cultures after day 0 were compared using Fisher's exact test.

Results

First episodes

At presentation there were no significant differences between the acyclovir and placebo treated groups in terms of demographic data, clinical severity, proportion of infections due to HSV type 1 or incidence of true primary infections (Table 1). Fifty-three patients were enrolled into the study but two patients in each treatment

TABLE 1

Patient details on entry

	First episodes		Recurrent episodes	
	Placebo n=24	Acyclovir n=29	Placebo n=21	Acyclovir n=20
No. females	16	20	9	6
No. males	8	9	12	14
Age (yr)	25.0	24.0	26.8	27.5
Duration of lesions (days)	3.2	3.7	0.5	0.3
Initial pain score[a]	2.0	2.0	-	-
Inguinal lymphadenopathy (%)	67	59	-	-
True primary [Ab-ve] (%)	46	48	0	0
Positive cultures (%)[b]	96	93	100	67
HSV type 1 (%)[c]	33	35	14	25
Infection in partner (%)	38	27	57	50
No. recurrences per year[d]	-	-	8	5
Average duration of recurrences (days)[d]	-	-	6.5	8
Frequency of prodrome (score)[a,e]	-	-	2.3	2.4

[a] Scoring system used: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

[b] For recurrent episodes therapy was initiated before cultures were taken.

[c] For first episodes the overall incidence was 34% (46% in females and 13% in males) and for recurrent episodes 20% (25% in females and 18% in males).

[d] Median values, otherwise mean values are given.

[e] Scoring system used: 0 = never, 1 = sometimes, 2 = half the time, 3 = often, 4 = always.

group failed to return for follow-up assessments and so have been excluded from the analysis of results.

Altogether 94% of patients had positive viral cultures from external lesions during the trial. Thirty-one (96%) of 36 women had HSV isolated from the cervix and 13 (87%) of 15 men had positive urethral swabs for HSV. The overall incidence of HSV-1 infections was 34%, but in females the incidence was 46% whereas in males it was 13%. Approximately half the patients in each treatment group had a prior HSV infection as evidenced by the presence of preexisting antibodies.

The results of the clinical and virological assessments are given in Table 2. When the data from all patients treated with acyclovir were combined there was a significantly reduced duration of pain, time to healing of original, external and all genital lesions, duration of new lesion formation and duration of viral shedding (from original, external and all genital lesions) compared with placebo-treated patients. Analysis of the data according to antibody status (primary or non-primary) or virus type (HSV-1 or 2) did not alter the overall outcome. The results for female patients alone are almost identical except that in addition the duration of dysuria showed trends in favour of acyclovir and in true primary females was significantly shorter. The overall effects in primary females were more marked but benefits were still seen in non-primary females alone. The virus type did not effect the outcome of treatment. For males alone the only parameter that achieved significance was the time to healing of the original, external genital lesions. The small number of males prevented analysis of subgroups. A graphic representation of the results is also shown (Fig. 1).

Recurrent episodes

Of the 60 patients recruited into this part of the study only 41 returned and then satisfactorily completed a treatment episode. The remaining 19 patients (10 acyclovir, 9 placebo) failed to return for follow-up assessments (11), did not experience a recurrence during the study period (4), had a recurrence but were unable to return (2) or failed to comply with the protocol (2). In contrast with the first episodes there was a preponderance of men in both the acyclovir and placebo-treated groups. The age, usual severity and frequency of recurrences in these patients were similar in the two treatment groups (Table 1). Although patients were requested to start treatment immediately after the onset of prodromal symptoms some delay occurred (mean 9.6 h) before therapy was initiated. At the time of onset of treatment the lesion in most cases had already progressed to papular or beyond. As therapy was initiated by the patient before the first swab for virus isolation was taken the proportion of acyclovir treated patients in whom HSV was cultured on day 0 (67%) was less than in the first episodes (93%).

In Table 3 the results of treatment in all patients, females and males are presented. In the whole group acyclovir treated patients had a significantly shorter duration of pain, itching and all symptoms combined. When divided according to sex the treatment groups are rather too small to draw definitive conclusions but still beneficial effects on symptoms were recorded. The median time to healing of all lesions in the whole group and males or females separately and time to first crust and healing of

TABLE 2

Results for first episodes of genital herpes

	All patients			Females			Males		
	PCB $n = 22$	ACV $n = 27$	P value	PCB $n = 16$	ACV $n = 20$	P value	PCB $n = 6$	ACV $n = 7$	P value
Duration of pain	8	4	<0.05	8	4	<0.01	5	4	NS
Duration of itching	9	9	NS	8	8.5	NS	10	9	NS
Duration of dysuria	4	4	NS	8	4	0.08[a]	1	3.5	NA
Duration of discharge	4	5	NS	7	5	NS	1	7.5	NA
Time to first crust	7	4	NS	8	4	NS	3	4	NA
Time to healing:									
original lesions	11	8	<0.01	9.5	8	<0.05	14	7	<0.05
all lesions	14	8	<0.001	14	8	0.001	14	9	NS
Time to last new lesions (no. with lesions)	2.5 (12)	0 (6)	<0.001	3.5 (10)	0 (4)	<0.001	0 (2)	0 (2)	NS
Duration of virus shedding:									
original, external lesions	7	3	<0.01	7	3	0.001	4	4	NS
all lesions, all sites	11	4	0.001	11	4	<0.001	10	6	NS

Results are given as median times in days.

[a] $P<0.05$ for true primary females alone.

NS = not significant; NA = not analysable (patient numbers too few, <5 per treatment group); PCB = placebo; ACV = acyclovir.

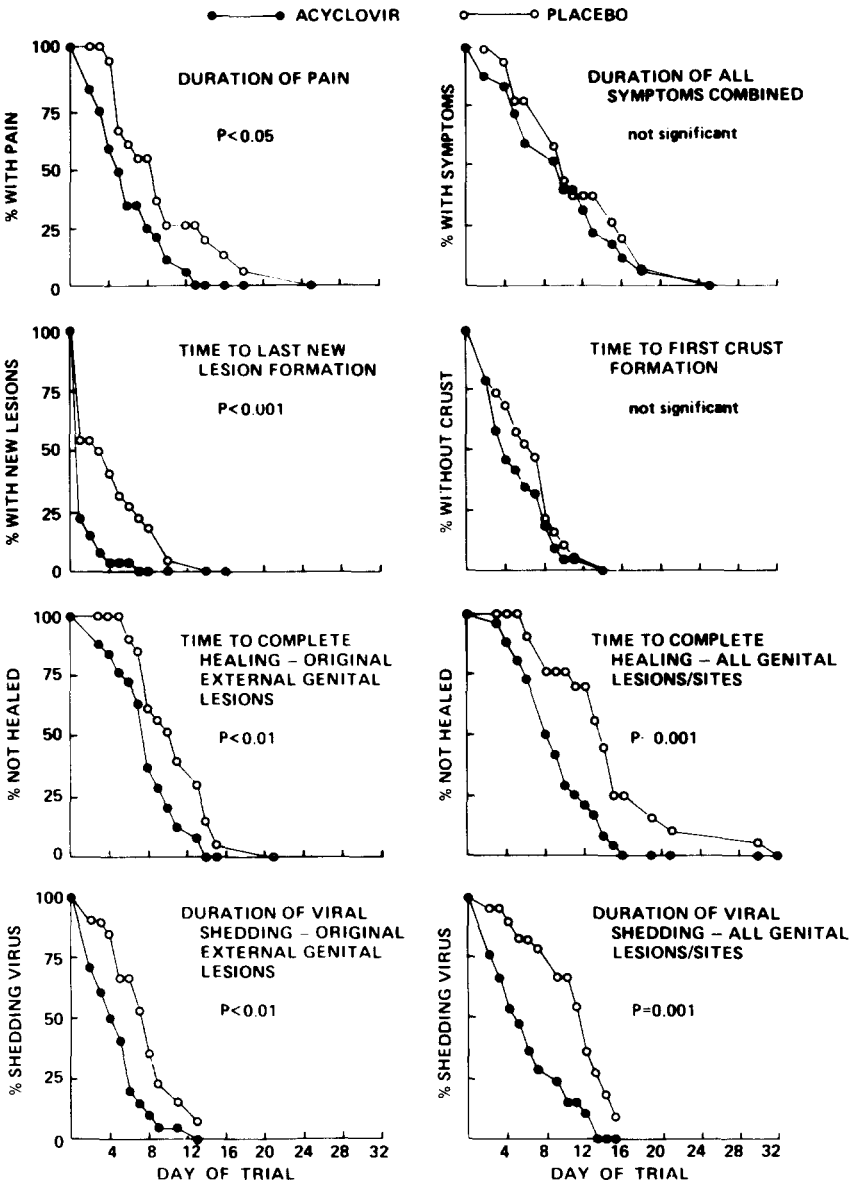

Fig. 1. Duration of various events for first episodes of genital herpes.

original external genital lesions in females alone were also significantly reduced in acyclovir treated patients. The formation of new lesions during the trial was dramatically reduced by acyclovir therapy. Insufficient data were available for a full statistical evaluation of the duration of viral shedding. However, the percentage of patients with positive cultures after day 0 was less for acyclovir recipients ($P < 0.05$ for the whole

TABLE 3

Results for recurrent episodes of genital herpes

	All patients			Females			Males		
	PCB $n = 21$	ACV $n = 20$	P value	PCB $n = 9$	ACV $n = 6$	P value	PCB $n = 12$	ACV $n = 14$	P value
Duration of pain	5	2	0.05	5.5	1	NA	4	3	NS
Duration of itching	8	5	0.001	6	3	NA	14	5	0.01
Duration of all symptoms	6	3	<0.001	6	2	<0.01	8	5	<0.05
Time for first crust	4	3	NS	5	3	<0.05	4	3.5	NS
Time to healing:									
original lesions	6	4	0.09	6	3	<0.05	5	6	NS
all lesions	6	4	<0.01	6	3	<0.01	6.5	6	<0.05
New lesion formation (%)	29	5	<0.01	22	0	NS	33	7	<0.05
Positive cultures after day 0 (%)	70	29	<0.05	67	33	NA	73	29	<0.05

Results are given as median times in days (apart from new lesion formation and positive cultures).
PCB = placebo; ACV = acyclovir; NS = not significant; NA = not analysable (patient numbers too small, <5 per treatment group).

group and males alone). The major parameters are also shown graphically (Fig. 2).

Side effects

The incidence of local adverse events was higher in patients with first episodes than in those with recurrent episodes (Table 4). There was no difference between the number of patients developing adverse events whilst receiving acyclovir or placebo therapy. Only one patient was withdrawn from therapy because of an adverse event and that patient was receiving placebo.

The few systemic adverse events reported during the study were all attributed to the disease; meningism (2 patients), micturition difficulty and paronychia during placebo therapy and micturition difficulty (2 patients) whilst on acyclovir. All these events occurred during first episodes.

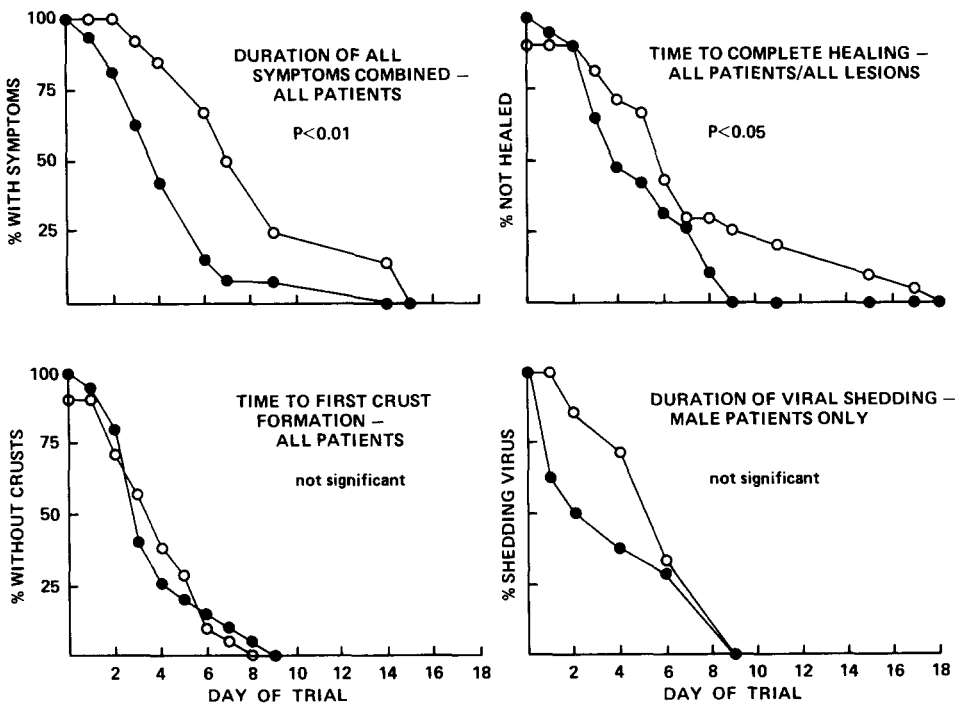

Fig. 2. Duration of various events for recurrent episodes of genital herpes (two patients in the placebo group had 'abortive' episodes and so are recorded as crusted and healed on day 0). ●——● = acyclovir; ○——○ = placebo.

TABLE 4

Local adverse events

	Placebo	Acyclovir
First episodes	(n – 22)	(n = 27)
Burning on application	3[a]	3
Rash	3	0
Itching	0	1
Recurrent episodes	(n = 21)	(n = 20)
Flaking of skin	1	1
Stinging	0	1
Total no. of adverse events	7	6
Patients with adverse events	6 (14%)	6 (13%)

[a] One patient was withdrawn from therapy.

Discussion

Both topical and oral acyclovir therapy have a potential advantage over intravenous treatment in allowing outpatient management of genital herpes. Previous studies of topical therapy with acyclovir ointment in first episodes have demonstrated virological and clinical benefit [3,14]. This study shows that acyclovir cream has a similar beneficial effect in first episodes of genital herpes. Treatment was associated with a significant shortening of the signs and symptoms of the external genital lesions. Typically, our patients had a high incidence of internal genital infection (cervix in females and urethra in males) as well as external disease. Like others we found that acyclovir applied only to the external lesions was associated with a significant reduction of virus shedding and duration of lesions at all sites including the internal ones (e.g. median duration of viral shedding from the cervix, 7.5 days versus 2 days, and urethra, 6 days versus 5 days). Perhaps even more notable was the lessening of new lesion formation in females. The high incidence of HSV-1 infections, especially among females, is believed to be related to the prevalence of orogenital sexual contact in Sheffield as previously reported by Barton et al. [1]. All patients with HSV-1 first episodes admitted to orogenital contact.

Women in general with first episodes appeared to fare better than men although the numbers were rather too small to make definite conclusions. One suggestion for this apparent discrepancy is that generally women have a greater surface area of external lesions which may result in better absorption of acyclovir. Certainly the results with oral acyclovir in male patients with first episodes are better than those reported here [9].

Previous studies of acyclovir ointment in recurrent genital herpes [3] or herpes labialis [13] in non-immunocompromised patients have demonstrated only modest benefits from therapy. Spruance et al., reported an antiviral effect without clinical

benefit even if the drug was applied within 8 h of onset of the lesions in herpes labialis [13]. Corey et al., in a large multicentre study of recurrent genital herpes treated within 48 h of onset of lesions found a reduced duration of viral shedding and a modest acceleration of external lesion healing in males only [3]. No clinical benefit on local symptoms was seen in either sex. More recently Reichman et al. reported an antiviral effect alone in males and no effect in females with recurrent genital herpes using the ointment formulation in a similar study [11]. Whilst it might be argued that in our study the use of very early self-medication could be the reason for the highly significant effects the results seem to support the superior efficacy of the cream formulation demonstrated in experimental cutaneous HSV infections in guinea pigs [2]. Early patient initiated therapy with acyclovir cream appears to be as effective as early oral therapy in recurrent genital herpes [12]. The same formulation of acyclovir cream has also been reported recently to have clinical benefits in herpes labialis [5] and the results in recurrent genital herpes have now been corroborated by similar findings in a larger multicentre study [4].

It was only possible to demonstrate an apparent effect on first crusting in females with recurrent infections. Since many lesions especially in females occur on moist, mucosal surfaces and therefore never crust, the time to first crusting is represented by the time to healing and so it is questioned whether this separate parameter is actually a useful one for evaluation of topical therapy in genital herpes. Although our data are still incomplete, so far we have found no evidence that topical therapy with acyclovir modifies the subsequent natural history of genital herpes after recovery from first or recurrent episodes.

Topical acyclovir in a cream base was associated with very few side effects and was effective treatment for both first and recurrent episodes of genital herpes. It may be considered as an alternative to oral acyclovir in the outpatient management of this increasingly common and distressing condition, although systemic therapy will usually be preferred for severe primary infections.

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References

1 Barton, I.G., Kinghorn, G.R., Najem, S., Al-Omar, L.S. and Potter, C.W. (1982) Incidence of herpes simplex virus types 1 and 2 isolated in patients with herpes genitalis in Sheffield. Br. J. Vener. Dis. 58, 44–47.

2 Collins, P. and Oliver, N.M. (1982) Acyclovir treatment of cutaneous herpes in guinea pigs and herpes encephalitis in mice. Am. J. Med. 73/1A, 96–99.

3 Corey, L., Nahmias, A.J., Guinan, M.E., Benedetti, J.K., Critchlow, C.W. and Holmes, K.K. (1982) A trial of topical acyclovir in genital herpes simplex virus infections. N. Engl. J. Med. 306, 1313–1319.

4 Fiddian, A.P., Kinghorn, G.R., Goldmeier, D., Rees, E., Rodin, P., Thin, R.N.T. and De Koning, G.A.J. (1983) Topical acyclovir in the treatment of genital herpes: a comparison with systemic therapy. J. Antimicrob. Chemother., in press.
5 Fiddian, A.P., Yeo, J.M., Stubbings, R. and Dean, D. (1983) Successful treatment of herpes labialis with topical acyclovir. Br. Med. J. 286, 1699–1701.
6 Mindel, A., Adler, M.W., Sutherland, S. and Fiddian, A.P. (1982) Intravenous acyclovir treatment for primary genital herpes. Lancet 1, 697–700.
7 Nahmias, A.J., Josey, W.E., Naib, Z.M., Luce, C.F. and Duffey, A. (1970) Antibodies to herpesvirus hominis types 1 and 2 in humans. I. Patients with genital herpetic infections. Am. J. Epidemiol. 91, 539–546.
8 Najem, S.N., Barton, I.G., Al-Olmer, L.S. and Potter, C.W. (1983) Antibody to herpesvirus hominis in patients with carcinoma of the cervix. Br. J. Exp. pathol., in press.
9 Nilsen, A.E., Aasen, T., Halsos, A.M., Kinge, B.R., Tjøtta, A.E.L., Wikström, K. and Fiddian, A.P. (1982) Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. Lancet 2, 571–573.
10 Peto, R., Pike, M.C., Armitage, P., et al. (1977) Design and analysis of randomised clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br. J. Cancer 35, 1–39.
11 Reichman, R.C., Badger, G.J., Guinan, M.E., Nahmias, A.J., Keeney, R.E., Davis, L.G., Ashikaga, T. and Dolin, R. (1983) Topically administered acyclovir in the treatment of recurrent herpes simplex genitalis: a controlled trial. J. Infect. Dis. 147, 336–340.
12 Salo, O.P., Lassus, A., Hovi, T., Fiddian, A.P. (1983) Double-blind, placebo-controlled, trial of oral acyclovir in recurrent genital herpes. Eur. J. Sex. Trans. Dis., in press.
13 Spruance, S.L., Schnipper, L.E., Overall, J.C., Jr., et al. (1982) Treatment of herpes simplex labialis with topical acyclovir in polyethylene glycol. J. Infect. Dis. 146, 85–90.
14 Thin, R.N., Nabarro, J.M., Parker, J.D. and Fiddian, A.P. (1983) Topical acyclovir in the treatment of initial genital herpes. Br. J. Ven. Dis. 59, 116–119.
15 Vestergaard, B.F. and Jensen, O. (1981) Diagnosis and typing of herpes simplex virus in clinical specimens by the Enzyme Linked Immunosorbent Assay (ELISA). In: The Human Herpesviruses: An Interdisciplinary Perspective, Nahmias, A.J., Dowdie, W.R., Schinazi, R.F., Eds. Elsevier, New York, pp. 391–394.