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Topical acyclovir in the treatment of genital herpes: a comparison with systemic therapy

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Controlled trials of acyclovir cream were conducted in the treatment of initial and recurrent genital herpes. For 54 patients with the first episode of genital infection (initial disease) treated with acyclovir the duration of viral shedding, formation of new lesions, times to crusting and healing and duration of symptoms were significantly reduced compared with the results obtained in 47 placebo recipients. When applied early in the course of recurrent episodes in 44 patients, acyclovir cream significantly reduced viral shedding, new lesion formation, time to healing and the duration of symptoms compared with the effects in 41 control patients. Topical therapy with acyclovir cream is well tolerated and compares quite favourably with systemic treatment, especially for recurrent genital herpes.

Introduction

Acyclovir has been reported in controlled trials to be effective systemically against initial genital herpes simplex infections whether given intravenously (Mindel *et al.*, 1982) or orally (Nilsen *et al.*, 1982). Five per cent acyclovir in a polyethylene glycol ointment base applied topically has also been shown to be effective for initial episodes of genital herpes by Corey *et al.* (1982) and Thin *et al.* (1983). For recurrent episodes, Nilsen *et al.* (1982) and Salo *et al.* (1983) demonstrated that orally administered acyclovir shortened the duration of the infection but Corey *et al.* (1982) reported that acyclovir ointment had little clinical benefit in this disease.

An alternative topical formulation, 5% acyclovir cream (an aqueous preparation in propylene glycol) has been developed which Collins & Oliver (1982) have shown to be superior to acyclovir ointment in the treatment of cutaneous herpes simplex infection in guinea pigs. This formulation has now been subjected to evaluation of efficacy and tolerance in man. We report in detail the results of two multicentre, double-blind, placebo-controlled studies of topical acyclovir cream in the treatment of initial and recurrent episodes of genital herpes. The results will then be discussed in comparison with those obtained from similar trials of systemic therapy.

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Methods

Patients

Consecutive patients presenting with first episodes of genital herpes and patients with a history of recurrent genital herpes were recruited into the studies at the various S.T.D. clinics of the participating centres. Male patients and females adequately protected from pregnancy, aged 16 years or more, who had not received other specific antiviral therapy in the preceding 14 days and not having other infections that might interfere with the assessments, were included. Patients with initial genital herpes were eligible providing they presented within 5 days of onset of their lesions. Those patients experiencing two or more recurrences per year were given therapy for early self-medication of a subsequent recurrence and required to start treatment within 24 h of onset, but preferably immediately after the prodrome began. Local hospital ethical committees approved the studies and informed consent was obtained from all patients before their enrolment.

Study design

For initial episodes treatment consisted of a 30 g tube of acyclovir cream (5% acyclovir in an aqueous cream base containing propylene glycol) or matching placebo (the aqueous cream base alone). Male and female patients were randomly allocated separately to the treatment groups under double-blind conditions. They were instructed to apply the cream liberally five times a day for up to 10 days or until healing had occurred, whichever was earlier. A history was taken and a full clinical examination was performed at presentation. Further clinical assessments were made three times a week until complete healing occurred. Symptoms and signs were scored subjectively at each visit from 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Lesions were classified as erythema only, papules, vesicles/pustules, ulcers/erosions, crusts and healed. They were grouped as original external lesions, internal lesions and new lesions. Swabs were taken at each assessment from representative lesions for viral culture. Virus isolation was performed in the relevant laboratories using standard methods. Acute and convalescent sera were obtained for examination of HSV complement-fixing antibody.

For prospective treatment of recurrent episodes patients were randomly assigned to receive either 5% acyclovir cream or matching placebo on a double-blind basis. They were instructed to begin treatment as soon as possible after the onset of prodromal symptoms or the appearance of any objective evidence of their next recurrence. Treatment was continued five times a day for 5 days. Patients were seen as soon as possible after the start of therapy and then at regular intervals (at least twice weekly)

Table I Baseline assessment data for patients with initial genital herpes

	Placebo $n = 51$	Acyclovir $n = 56$
No. females	31	35
No. males	20	21
Mean age (years)	24·5	25·5
Mean duration of lesions (days)	3·2	3·4
Pain score at entry (mean)	2·2	1·9
Positive culture at entry (%)	90	82
Infection in partner (%)	31	32

Table II. Results for all patients and culture positive patients with initial genital herpes treated with acyclovir (ACV) or placebo

	Median duration (days)					
	All patients			Culture positive patients		
	Placebo $n = 47$	ACV $n = 54$	1-tailed P-value	Placebo $n = 46$	ACV $n = 46$	1-tailed P-value
Viral shedding						
Original external lesions	6	3	< 0·001	6	3	< 0·001
All sites	9	3	< 0·001	9	3	< 0·001
Crusting time	7	4	< 0·05	7	4	< 0·05
Healing time						
Original external lesions	10	7	< 0·001	11	7	< 0·001
All sites	13	8	< 0·001	13	8	< 0·001
Pain	5	3	< 0·05	5	4	< 0·05
Itching	8	6·5	> 0·1	8	6·5	< 0·1
Dysuria	4	4	< 0·1	4	4	< 0·1
Discharge	4	4	> 0·1	4	4	< 0·1
Combined symptoms	8	5	0·01	9	6	< 0·1
New lesion formation %*	55	35	< 0·05	57	37	< 0·05

* Percentage of patients with new lesions during treatment.

until complete healing had occurred. Clinical assessments included recording the presence of symptoms and their severity and the stage of the lesions as described above. Particular attention was also paid to the development of new lesions. Swabs were taken for viral culture at each visit until healing was complete. Since therapy was begun before the first specimen was obtained it was appreciated that virological confirmation could not be obtained for all patients.

Analysis

The data were double entered into a specifically designed computer system (CLINDATA) as described by Ravenscroft & Smith (1981). After error checking, the data base was passed to the statistician who compared the treatment groups for initial

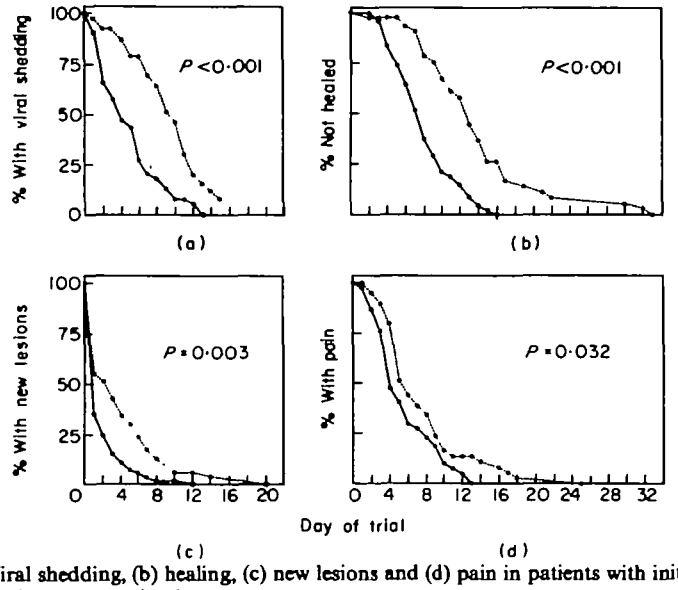

Figure 1. (a) Viral shedding, (b) healing, (c) new lesions and (d) pain in patients with initial genital herpes. ●——●, Acyclovir; ●---●, placebo.

assessment parameters using Student's *t*-test, a Mann-Whitney U-test and a chi-squared test. Efficacy analyses were performed using a long-rank method with a one-tailed test and Fisher's exact test.

Results

Initial genital herpes

A total of 107 patients with first episodes of genital herpes were entered into the study at four centres and their baseline data were compared (Table I). Forty-nine per cent of the study population were contributed by a single centre and half of these were classified as true primary infections. Serological data from the remaining centres were incomplete. No differences were found between the treatment groups at the 5% level of significance. Four patients in the placebo group and two in the acyclovir group failed to return to the clinic for any follow-up visits and so have had to be excluded from the analysis of the results.

Table III. Results for male and female patients with initial genital herpes

	Median duration (days)					
	Females			Males		
	Placebo $n = 31$	ACV $n = 35$	1-tailed P-value	Placebo $n = 16$	ACV $n = 19$	1-tailed P-value
Viral shedding						
Original external lesions	7	3	< 0·001	6	3	< 0·1
All sites	10	4	< 0·001	7	3	< 0·1
Crusting time	8	4	< 0·01	4	4	> 0·1
Healing time						
Original external lesions	10	7	< 0·001	11	6·5	< 0·001
All sites	13	8	< 0·001	11	8	< 0·01
Pain	6	3	< 0·01	4	3	> 0·1
Itching	7·5	6·5	> 0·1	9·5	2	> 0·1
Dysuria	8	3	< 0·01	1	4·5	> 0·1†
Discharge	6·5	4	< 0·1	1	7·5	—‡
Combined symptoms	9	6	< 0·05	6	3·5	> 0·1
New lesion formation %*	65	37	< 0·05	38	32	> 0·1

* Percentage of patients with new lesions during treatment

† 8 male patients had dysuria.

‡ 2 male patients had discharge; statistical analysis impossible.

Table IV. Baseline assessment data for patients with recurrent genital herpes

	Placebo $n = 41$	Acyclovir $n = 44$
No. males	22	30
No. females	19	14
Mean age (years)	28·5	29·9
Median no. recurrences/year	8	5
Average duration recurrences (days)	6·5	8
Usual severity score of symptoms	1·6	1·3
Frequency of prodrome (%)	75	65
Positive culture on day 0 (%)	73	63
Infection in partner (%)	53	40

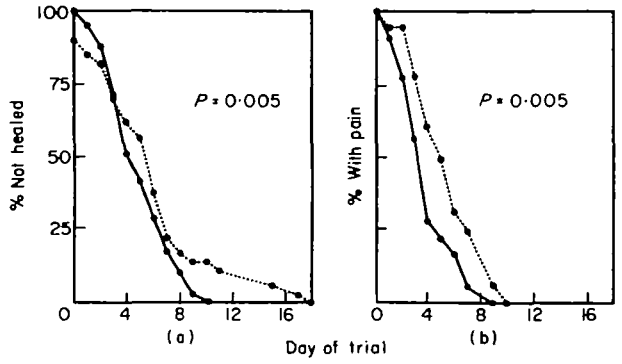

Figure 2. (a) Healing and (b) pain in patients with recurrent genital herpes. ●——●, Acyclovir; ● - - - ●, placebo.

Acyclovir significantly reduced the duration of viral shedding from original external genital lesions and from all lesions at all sites, the formation of new lesions, the time to first crusting of lesions, the time to healing of original external genital lesions and all lesions at all sites, the duration of pain and the duration of all symptoms combined in all patients compared with the controls (Table II and Figure 1). When only those patients from whom positive cultures were obtained were analysed the results were almost identical (Table II). The only treatment/centre interaction was for new lesion formation, the major centre demonstrating an effect whilst the others did not.

Separate analyses were also performed for male and female patients alone (Table III). For females the results were very similar to those reported above. In addition the duration of dysuria was significantly reduced in women receiving acyclovir compared with those given placebo and the duration of discharge was also shortened, with the difference approaching significance ($P = 0{\cdot}08$). The results from male patients appear less impressive, but the numbers are small and the infections were generally less severe (comparing placebo groups). The duration of the lesions in males was significantly reduced by acyclovir therapy but symptom duration was not affected. Although the duration of viral shedding was not significantly curtailed the trends favoured acyclovir.

Recurrent genital herpes

One hundred and thirty-seven patients were enrolled in this study at four centres but only 85 (62%) returned during the trial period with a treated recurrence. The remaining

Table V. Results for all patients and centre one patients with recurrent genital herpes

	All patients			Centre 1 patients		
	Placebo $n = 41$	ACV $n = 44$	1-tailed P-value	Placebo $n = 21$	ACV $n = 20$	1-tailed P-value
			Median duration (days)			
Crusting time	4	4	> 0·1	4	3	> 0·1
Healing time						
Original external lesions	4·5	4	> 0·1	6	4	< 0·1
All sites	6	5	< 0·01	6	4	< 0·01
Pain	4·5	3	< 0·01	5	2	0·05
Itching	5	3	< 0·001	8	5	0·001
Combined symptoms	5	3	< 0·001	6	3	< 0·001
			% after day 0			
Positive culture	63	27	< 0·01	70	29	< 0·05
New lesion formation	22	5	0·001	29	5	< 0·01

Table VI. Results for male and female patients with recurrent genital herpes

	Males			Females		
	Placebo $n = 22$	ACV $n = 30$	1-tailed P-values	Placebo $n = 19$	ACV $n = 14$	1-tailed P-value
			Median duration (days)			
Crusting time	4	4	> 0·1	3	3	> 0·1
Healing time						
Original external lesions	6	6	> 0·1	3	3·5	> 0·1
All sites	6	6	0·05	5	3·5	< 0·05
Pain	5	3	< 0·1	4	2	< 0·05
Itching	8	3	< 0·01	3	3	> 0·1
Combined symptoms	6	3	< 0·01	5	3	< 0·05
			% after day 0			
Positive culture	71	30	< 0·05	56	17	> 0·1
New lesion formation	18	7	< 0·05	26	0	< 0·05

patients either had no recurrences, did not use the medication or failed to return for assessment. Of the patients who returned 41 (48%) were recruited from a single centre. The acyclovir and placebo groups were similar, except that 14 (32%) of patients treated with acyclovir were female, compared with 19 (46%) of patients treated with placebo (Table IV).

Viral shedding, new lesion formation, time to complete healing of all lesions, duration of pain, duration of itching and duration of all symptoms combined were significantly reduced in all patients receiving acyclovir compared with those treated with placebo (Table V and Figure 2). The results from the major contributing centre alone were comparable (Table V). The only treatment/centre interaction for the whole study was for crusting time, one centre demonstrating a significant effect whilst the others did not. The numbers of patients were too small for statistically valid comparison of males and females separately (Table VI). Nevertheless the results for each group were similar to the overall analysis although it was noticeable that pain remained a predominant symptom in females while itching was the major complaint in males.

Adverse events

The incidence of local adverse reactions to acyclovir cream in initial genital herpes patients and those with recurrent infections, and the duration of treatment in the two groups are similar (Table VII). In fact the major complaint of burning on application was probably due to physical trauma of raw surfaces which is a common problem of topical therapy. More patients in the placebo group of initial disease sufferers also experienced disease or other drug related adverse events. It is interesting to note that therapy was continued longer in this group than in the acyclovir group and the median duration of treatment appeared to follow closely the healing of external genital lesions. Rather fewer adverse events were reported in placebo-treated patients with recurrent genital herpes which probably reflects the reduced severity of the disease compared with initial episodes rather than the shorter period of treatment.

Discussion

The results show that acyclovir cream is effective in the treatment of both initial and recurrent episodes of genital herpes. Although cross-trial comparisons are not entirely satisfactory, it is possible because similar protocols and methods of analysis have been used to consider these results in comparison with some obtained using systemic acyclovir. For initial genital herpes a summary of the median durations of various key parameters for patients in the different studies has been compiled (Table VIII). Unfortunately reference to median values may hide certain facts but space does not permit reproduction of all the curves for each study. The statistical analyses apply to the curves in fact, although for convenience median values are used when presenting data. Intravenous and oral acyclovir appear able to reduce the duration of viral shedding very dramatically, the median durations being only one or two days. More importantly all the patients were culture negative by the end of five days treatment with systemic acyclovir. With topical therapy the median duration was only three days but some patients continued to shed virus for up to 10 to 12 days. New lesion formation was also curtailed very rapidly or prevented altogether by systemic therapy whereas a few patients receiving topical acyclovir developed new lesions for up to a week after starting treatment. The duration of lesions and symptoms were similar for patients with initial disease treated with either

Table VII. Adverse events in patients with initial and recurrent genital herpes treated with acyclovir or placebo

	Initial disease		Recurrent disease	
	Placebo $n = 47$	Acyclovir $n = 54$	Placebo $n = 41$	Acyclovir $n = 44$
Median days of treatment	10	7	5	5
Adverse events due to therapy:				
Burning/stinging on application	7	3	0	1
Flaking of skin	0	0	1	2
Itching	0	1	0	0
Total no. (%) of patients	7 (15%)	4 (7%)	1 (2%)	3 (7%)
Adverse events due to disease				
Retention of urine	2	2	0	0
Meningism	2	0	0	0
Paronychia	1	0	0	0
Adverse events due to other drugs:				
Rash (co-trimoxazole)	3	0	0	0
Total no. (%) of patients	8 (17%)	2 (4%)	0	0

Table VIII Comparison of results with different formulations of acyclovir in the treatment of initial genital herpes; differences are significant except where noted (n.s.)

	Median days duration in patients receiving:			
	Intravenous	Oral	Ointment	Cream
	Mindel *et al.* (1982) (15/15)	Nilsen *et al.* (1982) (16/11)	Data on file-W.R.L. (34/36)	Table II (54/47)
Viral shedding				
ACV	2	1	3	3
Placebo	8·5	13	8	9
Crusting time				
ACV	3	4	6	4
Placebo	5	6	7	7
Healing time				
ACV	7	7·5	9	8
Placebo	14	14	13	13
Pain				
ACV	4 } n.s.	3	5	3
Placebo	4 }	7	9	5
All symptoms				
ACV	6·5	4 } n.s.	6 } n.s.	5
Placebo	8·5	9 }	8 }	8
	New lesions (%) in patients receiving:			
ACV	33	0	12	35
Placebo	73	55	36	55

Table IX. Comparison of results with different formulations of acyclovir in the treatment of recurrent genital herpes; differences are significant except where noted (n.s.)

	Median days duration in patients receiving:		
	Oral	Oral	Cream
	Nilsen *et al.* (1982) (41/42)	Salo *et al.* (1983) (30/30)	Table V (41/44)
Viral shedding			
ACV	1	1	(27%)*
Placebo	2	4	(63%)
Crusting time			
ACV	4 } n.s.	3 } n.s.	4 } n.s.
Placebo	4 }	3·5 }	4 }
Healing time			
ACV	5	5	5
Placebo	6	6	6
Pain			
ACV	3 } n.s.	2 } n.s.	3
Placebo	2·5 }	3 }	4·5
All symptoms			
ACV	1 } n.s.	2	3
Placebo	2 }	4	5
	New lesions (%) in patients receiving		
ACV	2	3	5
Placebo	19	23	22

* Percentage patients with positive cultures after day 0.

systemic or local acyclovir. It is also interesting to note that there was little difference between 5% acyclovir cream and ointment in the treatment of initial disease.

Similar comparisons can be made for results of studies in patients with recurrent genital herpes (Table IX). Here it should be noted that there were differences in the entry criteria for the various trials. Nilsen *et al.* (1982) allowed inclusion of patients in whom lesions had been present for up to 48 h, although on completion the mean duration was found to be only 24 h. Salo *et al.* (1983) restricted entry to up to 24 h after onset of lesions but the mean duration was still 21·6 h. Patients initiated treatment themselves in the trial of acyclovir cream as soon as possible after the onset. The mean delay before treatment was started was 9·6 h in those for whom data were available. In addition because drug was applied before viral swabs were obtained the duration of viral shedding was not calculated for this latter study. Nevertheless from the available data there would seem to be little difference between acyclovir cream and oral acyclovir in the treatment of recurrent episodes. The slight increase in the trend in favour of acyclovir from left to right across Table IX, predominantly in the relief of symptoms, may be the result of earlier onset of therapy, although it is possible that topical treatment may offer some advantage for symptom relief.

In conclusion acyclovir cream offers a well-tolerated and effective alternative for out-patient management of genital herpes. For severe initial episodes in hospitalized patients intravenous acyclovir may be preferred, otherwise oral therapy will probably be chosen for most initial infections. Whether topical treatment as an adjunct would offer

any advantages remains to be determined. It seems likely though that acyclovir cream will be used mostly for intermittent treatment of recurrent episodes. Here there may be advantages from topical therapy alone and certainly the formulation seems suitable for patient-initiated treatment. Fiddian *et al.* (1983) have also reported efficacy in recurrent herpes labialis using this form of therapy. Early onset of applications is clearly important and there is evidence that patients require some training before maximal benefit is achieved (Fiddian & Ivanyi, 1983). Where continuous suppression of recurrences is required in patients with very frequent or chronic infections, oral acyclovir may be the treatment of choice (Halsos & Gabrielsen, personal communication). Nevertheless, topical acyclovir will probably have an important role in the future management of less severe cutaneous herpes simplex infections, particularly recurrences of genital (and labial) herpes.

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