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A comparison of local and systemic acyclovir in the management of herpetic disciform keratitis

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Abstract

Forty-three patients with active herpetic disciform keratitis were entered into an open study to compare the efficacy of oral acyclovir (400 mg) with acyclovir ophthalmic ointment (3%) to inhibit viral replication during treatment with 0·05% prednisolone eye drops. All patients, regardless of the mode of therapy, were treated five times a day until they were healed. The mean time to heal in the oral group was 25·9 days and in the topical group was 25·3 days. Resolution of lacrimation was significantly faster in the oral group (12·1 days versus 27·6 days). The patients on tablets also showed a greater improvement in visual acuity. No statistically significant differences were found between the two groups in the incidence of recurrences over a three-year post-treatment period. It is concluded that oral acyclovir treatment is an effective alternative to ophthalmic ointment in the management of herpetic disciform keratitis.

The pathogenesis of herpetic disciform keratitis is not fully understood, but the disease may be the result of a delayed hypersensitivity reaction to viral replication in the corneal stroma. In moderate and severe disease the use of local steroids with an antiviral therapy is justified.[1] The use of steroids alone can result in a high complication rate of dendritic ulceration,[2] and the use of an antiviral agent alone has been shown to be inadequate.[1]

Acyclovir is a potent and selective inhibitor of herpes simplex virus replication. When administered topically it is well tolerated and effective for the treatment of dendritic keratitis.[3] It has also been used successfully for the treatment of disciform keratitis when combined with betamethasone.[1] Therapeutic concentrations within the eye can be attained by local[4] or systemic administration.[5–7] This study compares local and systemic treatment with acyclovir in a group of patients suffering from active herpetic disciform keratitis to ascertain firstly whether the route of application favourably affects the outcome of active disease, and secondly whether there is any significant difference in subsequent recurrence rates. All patients received local dilute steroids.

Methods and materials

Patients aged 18 years and over with a clinical diagnosis of either primary or recurrent disciform keratitis were entered into this open, randomised comparative study over a period of three years. The diagnosis was based on clinical appearance and history. Patients were excluded if they had been treated with specific antiviral therapy within the previous 14 days or with topical or systemic steroids within the previous 30 days. Patients with active epithelial disease, renal function impairment, or of child bearing potential were also excluded. Informed consent was obtained.

All patients applied prednisolone (0·05%) eye drops[8] five times daily to the affected eye. In addition the patients were randomly allocated to one of two treatment groups. One group received acyclovir ointment (3%) and the other group received acyclovir tablets (400 mg). Both medications were administered at four-hourly intervals, but patients omitted the dose in the middle of the night. They were treated until healing was evident. When the keratitis had resolved, acyclovir treatment was terminated and the steroid dosage was gradually tapered over a one-month period. Mydriatics and glaucoma therapy were given as necessary.

The patients were followed up as often as clinically necessary but at least weekly during treatment and then at 1, 3, 6, and 12 months. Patients were then seen at yearly intervals when possible.

On entry and on subsequent visits the severity of pain, photophobia, lacrimation, and grittiness sensation was assessed on a 0–3 score, where 0= none, 1=mild, 2=moderate, 3=severe. A full ocular examination was also carried out with a slit-lamp biomicroscope. Assessments included the severity of conjunctivitis (redness, scarring, follicles), extent of stromal oedema and infiltration, disturbances in Descemet's membrane, presence and extent of uveitis, and presence of endothelial cells and keratic precipitates. The visual acuity of the affected eye (uncorrected and with pinhole) was assessed by means of the Snellen chart. Intraocular pressure was measured by a tonometer.

Any signs or symptoms potentially attributable to acyclovir administration were recorded.

TABLE I *Patient demography*

	Tablet recipients	*Ointment recipients*
No. of evaluable patients	20	19
No. of females	10	7
No. of males	10	12
Mean age (SD) in years	56·3 (17·86)	49·7 (19·49)
% Patients with previous disciform keratitis	50	63·2
% Patients with previous cutaneous herpes	63·2	47·1
% Patients received previous antiviral therapy	83·3	80·0
% Patients received previous steroid therapy	75·0	71·4
No. of patients using concomitant medication	15	16
No. of patients receiving antiglaucoma therapy	6	4

SD=standard deviation.

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Patients were withdrawn from the trial if there were signs of increased inflammatory activity or if their condition remained static for 14 days.

The main criteria used to assess healing were the absence of stromal oedema, ciliary injection, and keratic precipitates. The times to resolution of individual signs and symptoms and also of healing were analysed by the Mantel-Cox test as applied by the BMDP statistical package. Unaided Snellen visual acuity was used in the analysis except in patients who had been given mydriatics, when a pinhole was used. Visual acuity scores on entry, changes in visual acuity from entry, and changes in intraocular pressure from entry between the two groups were compared by Student's t test. Recurrence rates were analysed by the Pearson χ^2 test. p Values of $\leq 0{\cdot}05$ were considered statistically significant.

Results

PATIENT DEMOGRAPHY

Forty three patients entered the study. Two patients failed retrospectively to meet the entry criteria and two defaulted during the study. The remaining 39 patients were entered. Of these patients 19 received acyclovir ophthalmic ointment and 20 received acyclovir tablets. Table I shows the patient demography for each treatment group.

RESOLUTION OF SYMPTOMS AND SIGNS

The rates of resolution of the clinical symptoms of pain, photophobia, and grittiness were not significantly different between the two treatment groups. However, resolution of lacrimation was significantly faster in the oral group, with a mean of 12·1 days for the tablet recipients and 27·6 days for the ointment recipients (p=0·02).

The mean times to resolution of conjunctivitis (redness, scarring, and follicles), stromal infiltration, stromal oedema, disturbances in Descemet's membrane, and uveitis were not statistically different between tablet recipients and the ointment recipients (p>0·15, Table II).

Complete healing was observed in patients on tablets in a mean time of 25·9 days and in the ointment group in a mean time of 25·3 days. This difference was not statistically significant (p>0·05, Fig 1). An average decrease in intraocular pressure of 4·6 mmHg was noted among patients receiving oral acyclovir, and an average decrease of 4·1 mmHg was noted among patients receiving ophthalmic ointment. This difference was also not statistically significant.

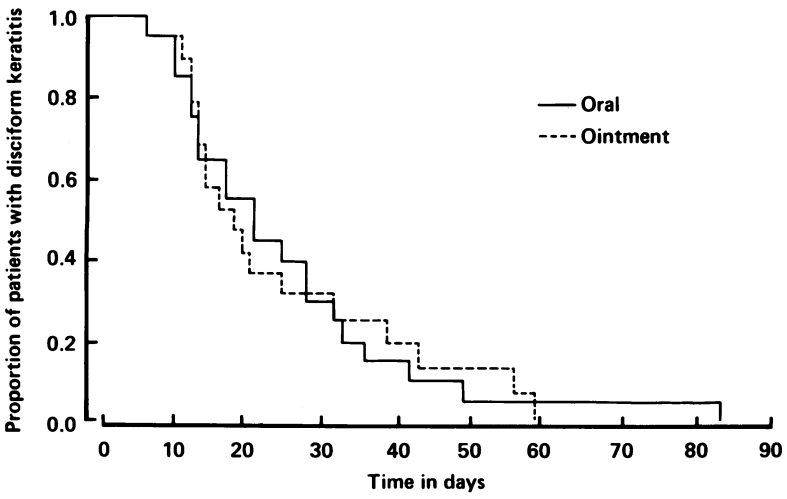

Figure 1: Cumulative frequency distribution of time taken to complete healing.

TABLE II *Resolution times for clinical signs*

	Mean resolution time (days)		
	Ointment	*Tablet*	*p Value*
Conjunctivitis (redness)	14·3	17·2	0·56
Conjunctivitis (scarring)	11·0	4·0	0·16
Conjunctivitis (follicles)	11·0	3·0	0·06
Stromal oedema	26·2	24·3	0·8
Stromal infiltration	92·8	44·8	0·8
Folds in Descemet's membrane	7·4	8·8	0·79
Uveitis (cells)	9·1	8·6	0·94
Uveitis (flare)	6·0	6·5	0·6
Endothelial cells	16·8	12·2	0·29
Endothelial keratic precipitates	73·3	30·4	0·42

The median visual acuity scores on entry for the two treatment groups were comparable (p>0·05), and were 6/24 (0·25) for the tablet recipients and 6/36 (0·17) for the ointment recipients. The mean change in visual acuity from entry was 0·13 in the ointment group, and 0·28 in the tablet group (p=0·02). Thus there was a significantly greater improvement in vision between entry and the end of treatment in the tablet group.

Both acyclovir ointment and tablets were well tolerated. Two patients receiving acyclovir ointment had punctate epithelial keratopathy which persisted throughout the treatment period but cleared immediately on stopping the medication. No adverse reactions were reported by patients receiving acyclovir tablets.

RECURRENCES DURING THE FOLLOW UP

Table III summarises the recurrences of disciform keratitis for each treatment group. Attempts were made to follow up the patients for a maximum of three years. One patient died during the first year of follow-up, one in the second year, and three in the third year. None of these deaths was associated with recurrences or with acyclovir treatment. No significant difference was found between the recurrence rates in the two treatment groups.

Two patients in the ointment group underwent penetrating keratoplasty, one in the first year and one in the second year. Both progressed well and have not suffered any postoperative recurrence.

In the ointment group one patient developed a dendritic ulcer six months after healing. In the oral group three patients each developed one dendritic ulcer at three months, six months, and 12 months. No patient developed a dendritic ulcer during the period of treatment, and in particular none occurred during the month of unprotected reducing-dose steroid therapy. Trophic ulcers occurred in both treatment groups, but there was no difference in frequency between the two groups.

Discussion

No statistically significant differences were

TABLE III *Incidence of recurrent attacks of disciform keratitis in each year of follow-up*

	1st Year *No. of patients*		*2nd Year* *No. of patients*		*3rd Year* *No. of patients*	
No. of recurrences	*Tablet*	*Ointment*	*Tablet*	*Ointment*	*Tablet*	*Ointment*
0	9 (50%)	11 (61·6%)	6 (33·3%)	7 (43·8%)	4 (66·7%)	5 (41·7%)
1	7	6	6	8	1	4
2	2 (50%)	1 (38·4%)	5 (66·7%)	0 (56·2%)	1 (33·3%)	3 (58·3%)
3	0	0	1	1	0	0
Total followed up	18	18	18	16	6	12
	p=0·74		p=0·15		p=0·60	

found between the tablet recipients and ointment recipients in the rates of resolution of pain, grittiness, and photophobia. The duration of lacrimation was significantly longer from patients receiving ointment, which might well be related to the application of a paraffin film to the eye. The mean time to resolution of clinical symptoms in the ointment group ranged from 10 to 28 days. This is longer than previously reported in a study where all patients with deep stromal keratitis treated with acylovir ointment and 2·5% prednisolone showed resolution of symptoms in one week.[9] However, in the latter study patients were entered if they showed signs of stromal infiltration and were excluded if they had oedema of the disciform type. In addition the concentration of prednisolone used was 50 times greater than that used in the present study.

The median visual acuity score on entry was 6/36 in the ointment group and 6/24 in the oral group. Although visual acuity in each group on entry was comparable, tablet recipients showed a significantly greater improvement in visual acuity. The application of a film of paraffin to the eye is likely to have a temporarily detrimental effect on visual acuity; further, in patients whose vision is already impaired because of the disease process, this effect may be more pronounced. In such instances, the oral formulation may be preferred.

The mean time to healing in the present study was 25·3 days for the ointment recipients. This is similar to the results reported by Collum and Grant.[10] They reported that when patients with disciform keratitis were treated with acyclovir ointment and 0·01% betamethasone the mean time to complete healing was 21 days. No significant difference in the mean time to healing was found between oral and topical therapy in the present study.

Topical or systemic acyclovir administration of acyclovir appears to be associated with comparable recurrence rates. This evidence supports the current concept that the antiviral agents available do not eradicate herpes virus, be it latent in the central nervous system or sustained by chronic infection such as dacryoadenitis.[11]

Both acyclovir tablets and acyclovir ointment were well tolerated. Only two patients in the ointment group experienced diffuse superficial punctate keratopathy, while no adverse events were reported by the tablet recipients. No patient developed dendritic ulceration as a complication during treatment. This is consistent with the good safety profile of acyclovir in various formulations established over the past years.

The results of this study have shown that oral acyclovir (400 mg) taken five times a day is as efficacious as acyclovir (3%) ophthalmic ointment administered five times a day in inhibiting viral replication during the treatment of disciform keratitis with prednisolone (0·05%). It is evident that, while local administration of acyclovir is the usual route, systemic acyclovir is an equally effective alternative and may be preferred in certain situations such as the uncooperative child or in an arthritic patient, who may find difficulty in the administration of the ointment. For patients who require topical eye preparations for the treatment of concurrent ocular complications other than herpetic eye diseases the use of oral acyclovir may simplify the treatment regimen, and reduce the potential for local drug or formulation interactions.

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