Oral acyclovir in the management of dendritic herpetic corneal ulceration

S. O. HUNG,¹ A. PATTERSON,¹ D. I. CLARK,¹ AND P. J. REES²

From ¹St Paul's Eye Hospital, Liverpool and the ²Wellcome Research Laboratories, Beckenham, Kent

SUMMARY A controlled trial of oral acyclovir in herpetic dendritic corneal ulcers was carried out on 31 patients. All patients received minimal wiping debridement of the ulcer, following which they were randomly allocated to receive either oral acyclovir or placebo for 7 days. At the end of treatment 67% of dendritic ulcers in patients receiving acyclovir had healed compared with 43% in placebo recipients. The proportion of ulcers healed in the 2 groups at 7 days showed no significant difference ($p=0.18$), but the rate of healing was significantly faster in the acyclovir group ($p=0.03$).

Acyclovir is a potent antiviral agent with selective activity against virus infected cells. Many studies have shown that topical acyclovir is effective in the management of superficial dendritic ulceration of the cornea.¹⁻⁹ Satisfactory plasma and aqueous levels can be achieved following oral administration of acyclovir without toxic systemic effects.¹⁰⁻¹³ There is evidence that systemic therapy with intravenous acyclovir is effective in the treatment of severe herpetic keratitis.¹⁴ This preliminary study is designed to determine whether oral acyclovir has any therapeutic activity in herpes simplex dendritic corneal ulceration in a randomised placebo-controlled trial in which either oral acyclovir or placebo was given after a minimal wiping debridement of the ulcer, which can cure about 50% of dendritic ulcers.¹⁵

Materials and methods

Patients who presented in the casualty department of St Paul's Eye Hospital, Liverpool, with a superficial dendritic herpetic ulcer and had given their informed consent were included. Patients excluded were those who had deep stromal disease, were unable to attend regularly for assessment, had received steroid therapy within the last 2 months, had received antiviral therapy within the last month, were women of child bearing potential, or had poor visual acuity in the other eye. Patients were examined by slit lamp after staining the cornea with rose Bengal. All patients received minimal wipe debridement with cotton tipped swab at the slit lamp.¹⁶ They were then

randomly assigned to oral acyclovir 400 mg or placebo 5 times daily for 7 days. The patients were seen on alternate days and examined by slit lamp microscopy and the ulcer stained with rose Bengal to assess healing or recrudescence. Patients were immediately withdrawn from the trial if there was evidence of recrudescence or recurrence and given topical antiviral therapy. Patients were reviewed 3 months after the end of the trial. All patients included were assessed as healed or failed on day 7.

Results

Thirtyone patients were included in this study. Two patients were excluded from the analysis because no clinical assessment was made on day 6, 7, or 8. Fourteen patients received placebo and 15 patients received acyclovir tablets. The groups were compared for age, ulcer size, duration and severity of symptoms, and severity of stromal disease and uveitis (Table 1)

Table 1 Patients' characteristics at presentation

		Placebo	Acyclovir
Sex	Male	10	13
	Female	4	2
Age (years)	Median	61	51
	Range	7-76	6-76
Ulcer type	Large	7	6
	Small	5	5
	Multiple	2	4
Ulcer size (mm)	Median	2.5	2.7
	Range	1-10	1-10
Duration of symptoms (days)	Median	6	5
	Range	1-14	1-14
Severity of symptoms (score)	Mean	1.5	1.4
	Range	0-3	0-3
Stromal disease (score)	Mean	0.9	0.5
	Range	0-3	0-3
Uveitis (score)	Mean	0.5	0.5
	Range	0-3	0-3

Correspondence to: Mr S. O. Hung, St Paul's Eye Hospital, Old Hall Street, Liverpool L3 9PF.

Table 2 Clinical response

	Placebo	Acyclovir
Percentage healed	43%	67%
Days to healing (median)	>8	7

by Mann-Whitney U tests. Proportions of each sex and ulcer type were compared by χ^2 tests. No differences were found between the groups at the 5% level of significance. 67% of dendritic ulcers healed within 7 days following oral acyclovir, and 43% of dendritic ulcers healed in those treated with placebo (Table 2). The proportion of dendritic ulcers healed in the 2 groups were compared by Fisher's exact test. No significant difference was found (1-tailed $p=0.18$). However, the acyclovir group healed significantly faster (log rank analysis, 1-tailed $p=0.03$, Fig. 1).

All ulcers that failed to heal were treated with topical idoxuridine. No adverse reaction was found in the acyclovir treated group.

Discussion

Most recurrences of dendritic ulcers occur within 7 days after minimal wiping debridement.¹⁵ Therefore, dendritic ulcers that failed to heal in 7 days should be regarded as recrudescence. 43% of ulcers in patients treated with minimal wipe debridement and placebo healed. This result is similar to those of other studies,¹⁵⁻¹⁷ and it shows no significant difference from the healing rate of 67% in the acyclovir treated group. If oral acyclovir has a therapeutic effect on dendritic ulceration, one would expect a higher healing rate in the acyclovir group.

There can be 2 possible reasons for the healing rate of only 67% in the acyclovir treated group. The first is

that the minimal wiping debridement was improperly carried out. Consequently the debridement was insufficient to remove all infected epithelium. This reason is unlikely, as the result of 43% healing rate in the placebo treated group is comparable with that in other studies. The second reason is that there may be an inadequate level of acyclovir in the tears, which may be important in the treatment of superficial corneal ulceration. Studies have been carried out to determine the plasma and aqueous levels of acyclovir following oral administration. Levels well in excess of the *in vitro* ED₅₀s for herpes simplex virus type 1 and type 2 were found,¹⁰⁻¹³ and indeed acyclovir has been used systemically in advanced herpetic corneal disease with good response,¹⁴ but no data are yet available on the levels of acyclovir achieved in tear fluid.

Oral administration will inevitably lead to some delay in achieving therapeutic levels of acyclovir in ocular tissues. This delay may have allowed virus replication to continue for some time following minimal wiping debridement and may explain the healing rate of only 67% at 7 days. A longer course of oral therapy may be required.

Topical acyclovir provides immediate therapeutic levels in the area of infection and has been shown to offer complete protection against recrudescences following minimal wiping debridement.¹⁷ While the efficacy of oral acyclovir in the management of superficial herpetic keratitis must remain in question, further studies with a longer duration of therapy may be justified, since oral therapy may be more acceptable to those patients who are unwilling or unable to comply with frequent applications of ophthalmic ointment.

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Fig. 1 Healing time of dendritic ulcers.

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