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Randomised double-blind trial of acyclovir and idoxuridine in dendritic corneal ulceration

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SUMMARY The results of a randomised double-blind clinical trial of 3% acyclovir and 0·5% idoxuridine (IDU) ophthalmic ointments in 60 patients with corneal dendritic ulceration are presented. Ulcers in all 30 patients treated with acyclovir healed compared with 22 (76%) of 29 patients treated with IDU ($P < 0.01$). Patients treated with acyclovir healed more rapidly (average 4·4 days) than those who received IDU (average 9·2 days) ($P < 0.01$). No serious side effects were observed, though transient stinging was recorded in 8 patients receiving acyclovir and in 2 patients receiving IDU. Other side effects in the IDU treated group were watering in 2 patients and superficial punctate erosions in 6 patients.

Idoxuridine (IDU) has been used for the treatment of herpes simplex keratitis since 1962,[1] and its efficacy in treating this infection has been established. Results from controlled trials indicate an average cure rate of 76%.[2–10] However, the drug is known to produce toxic effects, including follicular conjunctivitis, contact dermatitis, epithelial keratitis, and occlusion of the punctum.[11] More effective and less toxic alternatives have been sought. Adenine arabinoside (ara-A) has a similar level of efficacy to IDU,[6] while trifluorothymidine (F3TDR) is somewhat more effective.[12]

Acyclovir (Zovirax, 9-(2-hydroxyethoxymethyl)-guanine) was developed by Elion, Schaeffer, and Bauer.[13 14] In vitro acyclovir is over 10 times more active against herpes simplex virus (HSV) type I than either IDU or F3TDR. The first step in the phosphorylation of acyclovir to the active triphosphate is carried out by viral specified thymidine kinase. Acyclovir triphosphate inhibits HSV DNA polymerase 10–30 times more effectively than cellular DNA polymerase, resulting in preferential inhibition of viral DNA synthesis.

Acyclovir has been shown to be superior to IDU in the treatment of experimental corneal infections with HSV in the rabbit[15] and has also shown promise in treating dendritic ulceration in man. In patients treated with minimal wipe debridement Jones *et al.*[16] showed that topical treatment with acyclovir prevented early recurrences in comparison with placebo.

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Recently acyclovir was shown to be effective without debridement in treating a series of patients with dendritic ulceration, a proportion of whom had failed to respond to other antiviral agents.[17] This report describes the results of a randomised double-blind controlled trial of acyclovir and IDU ophthalmic ointments in patients with superficial corneal ulceration.

Materials and methods

Sixty patients were included in the study. Informed consent to participation in the investigation was obtained from patients or parents as appropriate. Uniocular patients and those who had received local antiviral treatment or steroids during the preceding 2 months were excluded. Diagnosis was based on clinical criteria; full ocular examinations were carried out initially and during the follow-up assessments. Patients were examined as often as clinically necessary, but all were seen at least twice weekly. Conjunctival swabs were taken for virus culture, and sera were collected for titration of complement fixing (CF) antibodies to herpes simplex virus (HSV). Treatment 5 times daily with either 3% acyclovir or 0·5% IDU ophthalmic ointments was randomly allocated. The ointments were of similar appearance and packed in identical tubes. In addition all patients received 1% homatropine eye drops twice daily and the infected eyes were padded. If no improvement had occurred after 4 days' treatment, the patient was withdrawn from the study and treated with 3% ara-A ophthalmic oint-

ment. Ulcers were considered to have healed when there was no fluorescein uptake, and the day of healing was noted. Symptoms of pain, photophobia, lachrymation, and grittiness were scored at each visit on a four point scale (0—absent, 1—mild, 2—moderate, 3—severe).

VIROLOGY

Conjunctival swabs were placed in virus transport medium immediately after collection. As soon as possible thereafter 0·2 ml of the transport medium was inoculated into available cell cultures. The cultures in routine use were Vero, HeLa, primary African green monkey kidney, and human embryo lung (HEL) fibroblasts. Specimens were considered positive if they produced cytopathic effects (CPE) in HEL fibroblasts and one or more of the other cell cultures, and negative if they failed to produce CPE in HEL fibroblasts and at least 2 other cell types. Virus isolates were identified by neutralisation with antisera supplied by the standards laboratory for Serological Reagents, Public Health Laboratory Service, Colindale. Sera were titrated for CF antibody to HSV type I by standard methods.

Results

Thirty patients were entered into each group; 1 patient in the IDU treated group failed to attend for follow-up. The 2 groups of patients were similar with regard to sex and age distributions, duration and severity of symptoms before treatment, occurrence of uveitis, and size of corneal ulcers (Table 1). Herpes simplex virus type I was recovered from 19 (33%) of 54 conjunctival swabs. CF antibody to HSV type I was present in 48 (96%) of sera. There were no differences in the rate of recovery of HSV or in the percentage of patients with CF antibody between the 2 groups.

All ulcers treated with acyclovir healed, while ulcers in 7 (24·1%) of 29 patients were not improved or had become worse after 4 days' treatment with IDU ($P<0·01$, Cox's logit procedure). These patients were withdrawn from the study. The number of days taken to heal in patients treated with acyclovir ranged from 2 to 9 days (average 4·4 days), compared with 3 to 17 days (average 9·2 days) for patients treated with IDU (Tables 2 and 3).

Table 1 *Comparison of acyclovir and IDU treated groups at presentation*

	Acyclovir	*IDU*
Number of patients treated	30	30*
Number (%) female	11 (36·7%)	5 (16·7%)
Age range (yr)	4–79	18–62
Average age (yr)	39	43
Duration of symptoms before treatment		
<2 weeks	22 patients	24 patients
2–4 weeks	8 patients	3 patients
>4 weeks	0 patients	3 patients
Average severity of symptoms at presentation (range 0–3)		
Pain	1·6	1·5
Photophobia	1·3	1·7
Lachrymation	1·5	1·9
Grittiness	1·4	1·4
Approximate ulcer size at presentation		
Range	1–36 mm²	1–49 mm²
Average	8·3 mm²	8·3 mm²
Number of patients with uveitis	5	3†

*One patient failed to attend for follow-up. †Two additional patients developed uveitis during treatment.

Table 2 *Thirty patients treated with acyclovir*

Patient sex, age (yr)	*Number of days to healing*	*Side effects*	*Recovery of HSV from conjunctival swabs*	*Titre of complement fixing antibody to HSV*	*Follow-up period (months)*
M48	4	Nil	—	1/16	13
M58	4	Nil	—	1/64	13
M12	4	Nil	+	1/256	13
M53	4	Nil	—	1/32	13
F54	3	Stinging	—	1/32	12
M70	4	Sore tongue	—	1/32	12
M40	3	Nil	—	1/32	12
F58	5	Nil	+	1/16	11
M55	6	Nil	—	1/16	11
F4	9	Stinging	+	ND	10
M37	4	Nil	+	1/16	10
M62	3	Stinging	—	1/8	10
M35	4	Nil	+	1/32	10
F22	4	Nil	+	1/16	10
F22	4	Stinging	+	1/16	9
M79	5	Nil	+	1/32	9
F11	7	Nil	ND	ND	8
M23	6	Nil	+	ND	8
F12	4	Stinging	—	1/64	8
F73	5	Stinging	—	1/32	8
M41	5	Nil	—	1/32	7
F12	2	Nil	—	1/32	7
M57	3	Stinging	—	1/32	6
M25	4	Nil	—	1/32	6
F26	5	Nil	ND	ND	5
M42	4	Nil	—	1/32	4
M8	4	Nil	—	ND	4
M52	3*	Nil	—	1/32	4
M49	3	Nil	—	1/32	4
F26	6	Stinging	—	1/32	2½

ND = Not done. *Recurred after 3 weeks.

Table 3 *Thirty patients treated with IDU*

Patient sex, age (yr)	*Number of days to healing*	*Side effects*	*Recovery of HSV from conjunctival swabs*	*Titre of complement fixing antibody to HSV*	*Follow-up period (months)*
M51	7	Nil	—	1/32	13
M55	8	SPE	—	1/32	13
M52	10	Nil	—	1/32	13
M50	9	SPE	ND	ND	12
M34	Withdrawn	—	+	1/64	—
M61	8	Nil	+	1/32	11
F47	Withdrawn	—	ND	ND	—
F41	10*	Irritation	—	1/64	11
M60	Defaulted	—	—	1/32	—
M40	11	Nil	+	1/32	11
M34	7	Nil	—	1/16	10
M25	10	SPE	—	1/64	10
M40	7	SPE	+	1/32	10
M35	8†	Stinging	—	1/8	10
M60	8	Nil	—	1/16	10
M40	8	Nil	—	1/16	10
M18	8	Nil	—	1/16	9
F49	8	Nil	+	1/32	9
M49	Withdrawn	—	ND	ND	—
M24	Withdrawn	—	—	1/8	—
F50	10	Nil	+	1/32	7
F62	Withdrawn	—	ND	ND	—
M40	11	Nil	—	1/32	6
M40	Withdrawn	—	+	1/32	—
M48	17	SPE	+	1/32	6
M23	3	SPE	—	1/32	4
M27	7	Watering	—	1/32	4
M56	Withdrawn	—	+	1/8	—
M22	10	Watering	+	1/64	3
M58	6	Nil	—	1/64	3

ND = Not done. SPE = Superficial punctate erosion. *Recurred after 8 weeks. †Recurred after 4 months.

The cumulative rate of healing for both treatments is given in Fig. 1. The difference between the 2 groups in terms of healing rate was significant ($P<0.01$, log rank analysis). Two of 30 patients treated with acyclovir and 20 of 29 patients treated with IDU took more than 6 days to heal.

Five patients presented with uveitis in the group treated with acyclovir, which resolved in 3–11 days (average 7 days). Uveitis was present in 3 patients treated with IDU and developed during treatment in a further 2. Two patients were withdrawn from the study, while the other 3 resolved, respectively in 2, 7, and 23 days.

Symptoms of pain, photophobia, lachrymation, and grittiness resolved within 11 days in all except 4 patients—all of whom were treated with IDU.

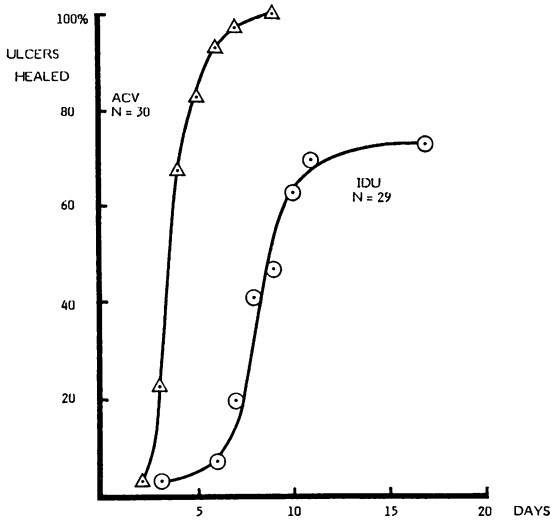

Fig. 1 *Cumulative frequency distribution of time to heal dendritic corneal ulcers. ACV = acyclovir. IDU = idoxuridine.*

For each symptom, resolution was more rapid after treatment with acyclovir (Table 4).

Stinging on initial application of the ointment was noted by 8 patients treated with acyclovir and by 2 patients treated with IDU. One patient treated with acyclovir complained of a sore tongue. Watering of the eye was experienced by a further 2 patients treated with IDU. This necessitated dilatation of the puncta and syringing of the duct in 1 patient. Superficial punctate epitheliopathy was noted in 6 other patients treated with IDU. Summaries of side effects for both treatment groups are given in Tables 2 and 3.

Patients in both groups have been followed up for 2·5–13 months (average 8·7 months acyclovir, 8·9 months IDU). One recurrence occurred 3 weeks after treatment with acyclovir, and 2 patients had recurrences after treatment with IDU, at 8 weeks and 4 months respectively.

Table 4 *Resolution of symptoms in patients receiving acyclovir and IDU*

Symptom	*Number of days to resolve*	
	Acyclovir	*IDU*
Pain	7·0	8·0
Photophobia	8·4	11·2*
Lachrymation	8·8	11·0†
Grittiness	7·6	9·0*

*One patient failed to resolve during treatment. †Three patients failed to resolve during treatment.

Discussion

Acyclovir was found to be superior to IDU in the treatment of superficial dendritic ulceration of the cornea, healing a larger proportion of ulcers at a more rapid rate. The proportion of IDU treated ulcers which failed to respond to treatment is similar to the average reported in previous trials. Significant side effects were not observed with acyclovir, but some patients complained of transient stinging on instillation of the ointment. No epitheliopathy was observed even in 3 patients in whom treatment was given for 20 days. Residual corneal scarring seemed to be less in the patients treated with acyclovir. This may be related to the shorter healing time in comparison with those treated with IDU.

Further studies of acyclovir are needed in patients with deeper HSV infections of the eye. Clearly the effects of topically administered acyclovir should be evaluated first. However, the drug has been administered intravenously in immunosuppressed patients with severe local and disseminated HSV infections with apparent benefit and without significant side effects,[18 19] and combined topical and systemic administration may be an approach for the future.

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