Randomised double-blind trial of bromovinyldeoxyuridine (BVDU) and trifluorothymidine (TFT) in dendritic corneal ulceration

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Abstract

The results of a randomised double-blind clinical trial of 0.1% bromovinyldeoxyuridine (BVDU) and 1% trifluorothymidine (TFT) in 60 patients with corneal dendritic ulceration are presented. There was no significant difference between BVDU and TFT in terms of numbers of ulcers healed ($p=0.61$), mean healing time ($p=0.065$), and cumulative healing rate ($p=0.058$). No serious side effects were observed, though transient stinging was recorded in five patients receiving TFT and in three patients receiving BVDU. One patient in the group treated with TFT developed a punctate epitheliopathy.

Trifluorothymidine (TFT) has been used in the treatment of herpes simplex keratitis since the early 1970s, and its efficacy is well established. Studies have shown that, when TFT eyedrops are used five times daily, up to 97% of dendritic ulcers will be healed within two weeks.¹ It has two modes of action. It directly inhibits the de novo synthesis of thymidine and also acts as a substitute thymidine analogue on DNA polymerase.² Epithelial toxicity has been described in association with TFT use, but is seen infrequently.³

Bromovinyldeoxyuridine (BVDU) is a new, promising antiviral agent. It is a thymidine analogue⁴ with a very high potency and selectivity against herpes simplex virus type I (HSV-1) and varicella zoster virus (VZV). BVDU inhibits the replication of HSV I⁵⁻⁸ and VZV⁹ at concentrations of 0.001–0.01 mg/l, whereas cell toxicity is observed only at drug concentrations of 50–100 mg/l. This highly selective antiherpes activity is due to its phosphorylation by HSV-1 and VZV encoded thymidine kinase.¹⁰ Once converted to the triphosphate form, BVDU inhibits viral DNA polymerase. In this activated triphosphate form it possesses a much greater affinity for viral DNA polymerase¹¹ than for host cellular DNA polymerases. HSV-2 encoded thymidine kinase is less efficient in phosphorylating BVDU, and consequently the drug is less effective against HSV-2.¹⁰ BVDU is also inactive against thymidine kinase deficient (TK-) mutants of HSV.¹⁰

Animal studies have shown topical BVDU to be significantly better than IDU in promoting the healing of epithelial keratitis^{12,13} and superior to TFT in suppressing the development of HSV-1 stromal disease.¹⁴

Short term^{15,16} and long term¹⁷ clinical studies have shown that BVDU is a safe and effective

agent in the treatment of HSV-1 dendritic, geographic, and stromal keratitis. However, so far no randomised clinical trials have been reported comparing it with the currently available antiviral agents.

We report the results of a randomised double-blind comparative study of 0.1% BVDU and 1% TFT eyedrops in patients with corneal dendritic ulceration.

Materials and methods

Patients with a clinical diagnosis of dendritic corneal ulceration were included in the study if they could attend regularly for follow up. Informed consent was obtained from each patient or from the parents in the case of children. Unilateral patients, or those who had received local antiviral treatment or steroids during the preceding two months, were excluded. At all visits a full ocular examination was carried out. Patients were seen as often as clinically necessary but at least twice weekly during treatment.

The trial was conducted in a double-blind randomised fashion. Treatment consisted of either BVDU 0.1% or TFT 1.0% ophthalmic drops, which were packaged in identical bottles and prescribed five times daily. If no improvement occurred after four days, or if the condition deteriorated, the patient was withdrawn from the study and was treated with 3% acyclovir ophthalmic ointment. Healing was deemed to have been achieved when there was no longer any fluorescein uptake. Symptoms of pain, photophobia, lacrimation, and grittiness were scored at each visit on a four point scale (0=absent, 1=mild, 2=moderate, 3=severe). A record was made of any adverse events attributable to the treatment. All patients have subsequently been followed up and any recurrences recorded.

Results

Sixty patients were entered into the study. Thirty received TFT and thirty received BVDU. One patient in the BVDU group was lost to follow-up and was not included in the analysis. There was no significant difference between the two groups with respect to sex and age distribution, duration and severity of symptoms before treatment, and ulcer size (Table 1).

In the TFT group 29 of the 30 ulcers healed while in the BVDU group, 27 of the 29 healed. This difference was not statistically significant ($p=0.61$, Fisher's exact test).

The number of days taken to heal in patients

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Table 1 Comparison of BVDU and TFT treated groups at presentation

	BVDU	TFT
Number of patients treated	30	30
Number (%) female	23 (77%)	20 (67%)
Age range (yr)	15-72	9-66
Average age (yr)	43.3	47.1
Duration of symptoms before treatment		
<1 Week	24	23
1-3 Weeks	6	7
>3 Weeks	0	0
Average severity of symptoms at presentation (range 0-3)		
Pain	1.5	1.6
Photophobia	2.1	2.3
Lacrimation	1.6	1.7
Grittiness	1.2	1.3
Approximate ulcer size at presentation (mm)		
Range	1-8	2-8
Average	4.1	4.1

treated with TFT ranged from 4 to 12 days (average 7.2 days), compared with 4 to 14 days (average 8.5 days) for patients treated with BVDU. This difference between the mean healing time in the two groups was not statistically significant ($p=0.065$, Student's *t* test).

The cumulative rate of healing for both treatment groups is shown in Fig 1. Although patients treated with TFT appeared to heal more quickly, the difference between the two groups was not significant ($p=0.058$, Mantel-Cox test).

Symptoms of pain, photophobia, lacrimation, and grittiness resolved within 10 days in all except two patients, one in each group. The resolution time for each of the symptoms was similar in both groups (Table 2).

Side effects were seen infrequently. Stinging on initial application of the drops was noted by three patients in the BVDU group and in five who were treated with TFT. This settled in all patients within a few days of beginning treatment. One patient in the TFT group developed a punctate epitheliopathy, which resolved within three days after the patient discontinued treatment when the ulcer had healed. There was no evidence of epithelial toxicity in any of the patients treated with BVDU. Summaries of patient data and side effects are given in Tables 3 and 4.

Patients in the study continue to be monitored. The mean duration of follow-up in the TFT group was 7.9 months and in the

Table 3 Patients treated with BVDU (total 30)

Patient's sex and age (yr)	Number of days to healing	Side effects	Follow-up (months)
M 56	13	None	1
M 52	5	None	1
M 50	4	None	1
M 34	8	None	2
M 72	4	None	2
M 30	9	None	3
M 32	12	None	3
M 64	7	None	3
M 30	12	None	4
M 69	7	None	4
M 20	7	None	4
F 47	10	None	5
M 43	8	None	5
M 72	14	None	6
M 37	Lost to follow-up	-	8
M 28	8	None	8
F 33	5	None	9
F 71	7	None	10
F 51	Withdrawn	None	10
M 19	6	None	11
F 49	7	Stinging	11
F 64	7	None	11
M 24	5	None	11
M 29	9	None	11
M 33	13	None	11
F 15	Withdrawn	None	12
M 53	12	None	17
M 30	11	Stinging	18
M 58	14	Stinging	19
M 33	7	None	19

BVDU group 6.8 months. So far there has been one recurrence in each.

Discussion

BVDU is a selective antiviral agent. Like acyclovir it must be phosphorylated by viral thymidine kinase to become active. Acyclovir, probably the most studied of the selective agents, has been shown to be effective in the treatment of HSV epithelial^{18,19} and stromal disease²⁰ with minimal toxicity. However, unlike acyclovir, BVDU has minimal activity against HSV-2. This is important to remember, as HSV-2 infections, though uncommon,²¹ do occur in the cornea and could account for an occasional treatment failure. Cultures may therefore be indicated in selected cases.

Table 4 Patients treated with TFT (total 30)

Patient's sex and age (yr)	Number of days to healing	Side effects	Follow-up (months)
F 60	10	None	1
M 59	12	Stinging	2
M 58	6	None	2
M 57	7	Stinging	2
M 55	9	None	2
M 54	Withdrawn	None	3
M 53	12	None	3
F 48	6	None	3
F 25	8	None	4
M 44	9	None	4
F 66	6	None	4
M 48	6	Punctate epitheliopathy	5
M 55	4	None	5
F 39	7	None	5
F 46	6	None	5
M 33	6	None	5
F 39	12	None	8
M 39	7	None	8
M 42	7	None	8
F 58	5	None	8
F 9	5	None	8
F 66	7	Stinging	8
M 57	9	None	9
M 25	5	None	9
M 55	5	Stinging	10
M 62	8	Stinging	10
M 53	6	None	10
M 56	7	None	17
M 31	4	None	18
M 21	8	None	19

Table 2 Resolution of symptoms in patients receiving BVDU and TFT

Symptom	Number of days to resolve	
	BVDU	TFT
Pain	6.6	6.7
Photophobia	7.4	7.8
Lacrimation	6.8	7.0
Grittiness	6.4	6.4

Figure 1 Cumulative frequency distribution of time to heal dendritic corneal ulcers.

The average healing time of 8.5 days with BVDU in this present study is similar to the healing time (8.6 days) obtained in a large series of patients in a recent open label study.¹⁷ However, in our study BVDU 0.1% was prescribed five times daily, as compared with nine times daily in the open study. Other workers have used BVDU as a 1% ointment and achieved a healing time of 8.5 days.²² Thus it would appear that a concentration of 0.1% BVDU eyedrops, used five times daily, achieves an optimum therapeutic effect and that higher concentrations or more frequent applications are not necessary. Except for mild transient stinging in three patients, no other side effects were noted in the BVDU treatment group.

This study shows BVDU to be a safe and effective agent in the treatment of dendritic corneal ulceration. Further studies are necessary to look at its efficacy in the treatment of stromal HSV infection.

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