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COMMUNICATIONS

TREATMENT OF HERPES SIMPLEX KERATITIS WITH 5-IODO-2'-DEOXYURIDINE*

BY

M. H. LUNTZ AND F. O. MACCALLUM

Nuffield Laboratory of Ophthalmology, University of Oxford, and Virus Laboratory, United Oxford Hospitals

KAUFMAN, Martola, and Dohlman (1962) and Corrigan, Gilkes, and Roberts (1962) reported that 5-iodo-2'-deoxyuridine (I.D.U.) was uniformly of outstanding value in the treatment of experimental and clinical herpes simplex keratitis, although Davidson (1962) reported a poor response in seven of 22 cases treated with this compound. It is generally agreed that, after treatment with I.D.U., the epithelial ulcer heals rapidly but the stromal lesion is probably not affected. In these reports the diagnosis was made on clinical grounds not confirmed by virus culture; controls were not used. The clinical appearance of keratitis due to herpes simplex virus is characteristic so that confirmation by virus culture was probably considered unnecessary.

The present paper reports the treatment of 22 eyes with herpes simplex keratitis (dendritic ulcer of the cornea) between May and December, 1962, in each of which the diagnosis was confirmed by virus culture. Eleven were treated with I.D.U.†, eleven were used as controls (Tables I and II), and the results were compared. Repeated cultures were done from patients treated with I.D.U. to test its anti-viral activity *in vivo*.

Materials and Methods

The 21 patients (22 eyes) were seen in the Outpatients Department of the Oxford Eye Hospital by one of us (M.H.L.). Alternate patients were put into "treated" (with I.D.U.) and "control" (without I.D.U.) groups.

After the initial examination, each affected eye was photographed and rephotographed at intervals for comparison. A small scraping of corneal epithelium from the ulcerated area was sent to the laboratory for virus culture. A pad and bandage were applied and the patient was admitted to hospital.

Treatment

"Treated" Cases (Table I, overleaf).—Topical instillation of a 0·1 per cent. solution of I.D.U. in saline, one drop every hour, day and night, began immediately the patient was admitted to hospital. The eye was kept bandaged and examined daily by one of us (M.H.L.). Duration of I.D.U. therapy depended on progress and varied from 3 to 21 days (average 8); in most cases repeated courses of I.D.U. were given, each lasting 4 to 5 days. Where I.D.U. was used for longer

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† Cases 1–8 (Tables I and II) were treated with I.D.U. from Calbiochem, California, and Cases 9–11 (Tables I and II) with a sample presented by Smith, Kline, and French. The powder was used as a 0·1 per cent. saturated solution in saline which was freshly prepared for each patient and stored in a refrigerator.

than 5 days it was given only 3-hrly at night, and the number of applications was gradually reduced before it was withdrawn.

"Control" Cases (Table II, overleaf).—All but three of these were admitted to hospital. In nine cases the affected eye was bandaged and Neomycin 1 per cent. ointment twice daily was prescribed. When ciliary injection and pain persisted to the third day, ocul. atropine 1 per cent. was also given daily. The eye was examined each day.

In two cases (Nos 8 and 10) the ulcer was iodized at presentation (application of 70 per cent. iodine in alcohol), and the eye was bandaged; these were seen daily as outpatients. One other case (No. 7) refused admission and was seen daily as an outpatient.

TABLE

TREATED

Case No.	Sex	Age yrs	Duration of Symptoms (days)	Presenting Lesion	Visual Acuity of Affected Eye		Duration (days)			
					Before	After	1	3	5	7
1	F	55	10	Secondary dendritic right Stroma normal	6/9	6/6	S+++		NS ↓	
2	F	66	26	Secondary dendritic Disciform keratitis Iritis Secondary glaucoma	C.F.	C.F.	S+++		S± ↓	S±
3	F	29	10	Secondary dendritic Superficial stromal haziness	6/36	6/12	S+++	S+++	S+	S+ SH ↓
4	M	70	7	Secondary dendritic right Superficial stromal haziness	6/18	6/12	S+++	S+++	S+	
5	M	39	7	Primary dendritic left Diffuse corneal epithelial oedema	C.F.	6/5	S+++	S+		S± CO ↓
6	F	83	4	Primary dendritic left Superficial stromal haziness	6/24	6/18	S+++	S+++	↓	S+++
7	M	60	21	Primary dendritic left on steroid ointment Stromal and endothelial oedema of cornea Iritis Primary simple glaucoma	H.M.	P.L.	S+++	S+ CO SH Iritis		S+ CO SH Iritis
8	M	56	2	Primary dendritic left Stroma clear	6/12	C.F.	S+++	S++	NS CO ↓	
9	F	34	14	Secondary dendritic left Stroma clear	H.M. Amblyopic eye	H.M.	S+++	S± ↓		S±
10	M	35		Primary dendritic left Stroma clear Severe ulcerative colitis	Not recorded		S+++			S+ CO
11	M	27	3	Secondary dendritic right Stroma clear	6/4	6/5	S+++		S+++	S+++

S+++ Typical dendritic corneal staining.
S++ One or more large staining areas on cornea.
S+ Diffuse superficial punctate staining, visible macroscopically.
S± Microscopic punctate staining.
NS No staining. Quiet eye.

Virology

A corneal scraping from the ulcerated area of the affected eye was washed off into 1·0 ml. buffered saline containing 100 μg/ml. streptomycin and sent to the laboratory within an hour.

A sample of this fluid (0·1 ml.) was inoculated into each of two tubes of primary human amnion cell cultures.

Cytopathic effects typical of herpes simplex were seen in 16 hrs to 6 days, and the virus was identified by neutralization tests with herpes simplex hyperimmune rabbit serum.

I

SERIES

and Effect of Therapy

9	11	13	15	17	21	25	30	35	37	40	50	56	110	123
											S ± Disciform keratitis			Tarsorrhaphy
NS ■		Quiet Stroma clear ■					NS							
NS ↓	S ±	NS Stroma clear					NS							
	S ±		NS			NS		NS			NS			
↑	S +	S + ↓	S + iodized	iodized	NS	NS								
	S ± CO Iritis ■		S + + + CO ■		S ± CO ↓	S + CO Iritis	S + Hypopyon Tarsorrhaphy				S +			
S + + CO ↑ ■		S + + CO		S + + CO	S + + CO	NS CO ↓ ■		S + + CO ↑	S + + CO ↓	S + + CO	S + + CO ↑	NS CO ↓		Lamellar keratoplasty
	S + iodized	S +			NS		S ±	S ±	S ±	S ±	S ±	S ±	NS	NS
S + CO ↓	Died													
NS			NS Red + + Carbolized		Healed									

CO Superficial corneal oedema.
SH Stroma hazy.
↑ I.D.U. therapy started.
↓ I.D.U. therapy discontinued.
■—■ Duration of treatment with Predsol drops.

TABLE

CONTROL

Case No.	Sex	Age (yrs)	Duration of Symptoms (days)	Presenting Lesion	Visual Acuity of Affected Eye		Duration (days)			
					Before	After	1	3	5	7
1	M	49	3	Primary dendritic left Stroma clear	6/24	6/6	S+++	NS		
2	M	58	3	Primary dendritic left	6/12 ua	6/12 ua	S+++	NS		
3	M	20	21	Primary dendritic left	6/6	6/6	S+++	NS		Superficial corneal nebula
4	M	39	1	Primary dendritic right Stroma clear	6/4	6/4	S+++		NS	NS
5	F	44	3	Primary dendritic right Superficial stromal haze	6/18	6/6	S+++	S++	S++	S±
6	F	53	10	Secondary dendritic left Old nebula with superficial corneal oedema	6/24	6/6	S+++		S++	
7	M	62	42	Primary dendritic left Stroma clear	6/12	6/12	S+++	S±		S+
8	M	54	3	Secondary dendritic left Superficial stromal haze	6/12	C.F.	S+++ iodized	S++		S+
9	M	81	14	Primary dendritic right Stromal and endothelial oedema of cornea	6/24 ua	6/24 ua	S+++	S+++	S+	
10	M	43	4	Recurrent dendritic left Iodized 1960 Superficial corneal nebulae	6/12 ua	6/9 ua	S+++ iodized	S+		S+
11	M	27	1	Secondary dendritic left Stroma clear	6/4	6/5	S+++	S+	S+	NS Redness++

S+++ Typical dendritic corneal staining.
S++ One or more large staining areas on cornea.
S+ Diffuse superficial punctate staining, visible macroscopically.
S± Microscopic punctate staining.
NS No staining. Quiet eye.
ua unaided

The anti-viral activity of I.D.U. solutions used in treatment was tested twice and confirmed on both occasions by tests with herpes virus infected tissue cultures. One sample was from the bottle of I.D.U. solution used for Patient 6 (Table I), in whom no effect on the corneal virus was apparent *in vivo*.

Results

Table I summarizes the results of treatment with I.D.U. and Table II of the "control" group. The duration of corneal staining in treated cases and control cases is plotted in the Figure. Also indicated in the Figure are the occasions when corneal epithelial culture grew herpes simplex virus after I.D.U. treatment had been started. Comparing the duration of corneal staining in treated and control cases (Figure) does not suggest any significant

II

SERIES

and Effect of Therapy

9	11	13	15	17	21	25	30	40	55	70	110	121	123	130
	NS			NS										
			NS											
NS														
NS (nebula)							NS							
S++	S+			NS				NS						
	-ve			S±						NS				
		S+	S+		S++ Secondary glaucoma	S++ Tarsor-rhaphy								
S++		S++ iodized	S++	S±	NS		S±	S±	NS			NS		
S+		S+ Car-bolized		S+	NS						S+++ Carbolized	S++ iodized	S±	NS
NS			NS Red++ Car-bolized		Healed									

One point requires elaboration. Three "treated" cases were given topical cortisone drops (Predsol 1 per cent.) in addition to I.D.U.; two of these (Nos 7 and 8) had a persistent epithelial oedema of the cornea which appeared after some days on I.D.U. therapy and one (No. 3) had persistent stromal opacification. In Cases 7 and 8, corneal oedema persisted in spite of Predsol, but in Case 3 the stromal opacity resolved. Administration of local cortisone in herpes simplex keratitis is a dangerous procedure; it was thought to be justified in these three cases as they were being treated with I.D.U., which theoretically should act as an "umbrella". But in Case 7 the cornea broke down into a florid dendritic ulcer and Predsol was discontinued. This patient had received topical steroids from his general practitioner before presenting at the Eye Hospital, and did badly in spite of treatment. One individual (No. 11 Tables I and II), had active dendritic ulcers in both eyes; one eye was treated with I.D.U., the other with Neomycin ointment and a bandage. Corneal staining disappeared from both eyes after a week, but they remained red and irritable. Both eyes were carbolized on the 15th day and subsequently healed.

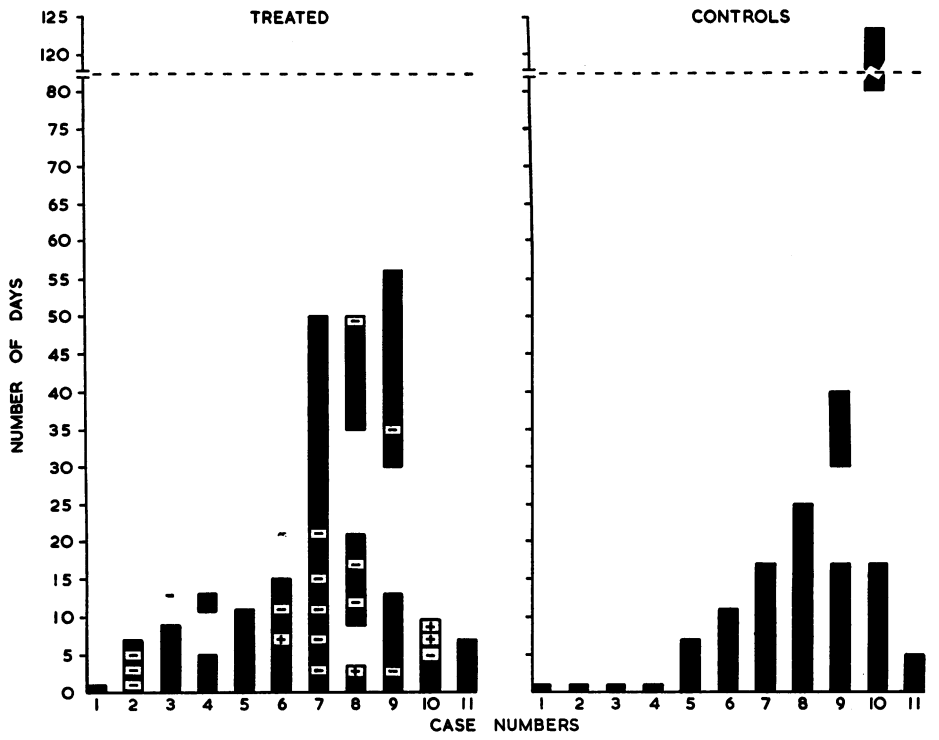

FIGURE.—Duration of corneal staining in treated and control cases, with results of repeated virus cultures in treated cases.

= Duration of corneal staining
\+ = Virus culture positive
\- = Virus culture negative

Case numbers correspond to those in Tables I and II.

Discussion

A series of eleven patients with herpes simplex keratitis treated with I.D.U. is compared with eleven similar patients treated without I.D.U. This is not a "blind" trial. The patients were not matched for age and sex, but these factors did not appear to influence the results of treatment. There was no selection into two groups; the patients being placed alternately as they presented.

The preparation and mode of administration of I.D.U. was that previously described by Kaufman and others (1962). Under these conditions comparison of the results of treatment in the two groups suggests that:

(*i*) In those cases in which resolution of the corneal ulcer occurred rapidly, this occurred equally in both groups and the degree of residual corneal scarring was similar.

(*ii*) Follow-up cultures of the corneal epithelium showed the presence of a virus in three cases on I.D.U. therapy (Nos. 6, 8, and 10, Figure); in one, after 9 days of continuous dosage (No. 10).

(*iii*) A persistent corneal epithelial oedema was observed in four cases (Nos 5, 7, 8, and 10, Table I) after 3 to 5 days of continuous I.D.U. therapy. This was unaffected by the use of Predsol drops; one of these (No. 8) was treated with a lamellar corneal graft, another (No. 7) with a temporary tarsorrhaphy preparatory to a lamellar graft, using I.D.U. to treat recurrences (not shown in Table). In a third patient (No. 5) the keratitis resolved after I.D.U. was withdrawn and in a fourth (No. 10), who had severe ulcerative colitis, it persisted to the 10th day, when he died. The persistent corneal lesion in these cases was apparently due to prolonged I.D.U. administration (possibly from breakdown products of the compound in the corneal epithelium). This observation is contrary to previous reports (Kaufman and others, 1962), in which I.D.U. was used for 10 days without corneal epithelial damage. It is therefore suggested that treatment with I.D.U. be limited to 5 or 6 days in the first instance, and repeated if necessary.

(*iv*) The series is not large enough for conclusions to be drawn on the incidence or severity of recurrences in the two groups, but the clinical impression is that recurrences were controlled more easily, albeit temporarily, with I.D.U. as compared with iodization or carbolization. (Cases 6, 7, and 8 (Table I) were treated with repeated courses of I.D.U., while Cases 9 and 11 (Table I) and 9, 10, and 11 (Table II) were iodized or carbolized.)

Probably I.D.U. is most useful in the treatment of a dendritic ulcer in an "only" eye (the other eye blind or absent) and of recurrent ulcers not responding to traditional treatment, particularly where a tarsorrhaphy has been done or the cornea is being prepared for grafting. Short courses of 4 to 5 days' duration are preferable. The combined use of local cortisone and I.D.U. may be useful but is not without danger.

At present, indiscriminate use of I.D.U. in cases of fresh dendritic ulceration is inadvisable until a larger "blind" clinical trial is done to assess its value. If, as the present series suggests, there is no advantage over traditional methods in these cases, one should also consider that this treatment requires admission of the patient to hospital and hourly administration of the drug throughout the night; it thus is more expensive than traditional methods and less comfortable for the patient.

Summary

The results of treating eleven cases of dendritic corneal ulcer with 5-iodo-2′-deoxyuridine (I.D.U.) are compared with those in eleven controls. In each case virus cultures were positive for herpes simplex; cultures were repeated in individuals being treated with I.D.U. No striking therapeutic advantage was observed in those treated with I.D.U. in comparison to the controls, except perhaps in cases of recurrent ulceration.

We wish to thank the Casualty Officers at the Oxford Eye Hospital who took the specimens for virus culture. We are also indebted to the Consultant Staff of the Oxford Eye Hospital for referring their cases of dendritic keratitis. It is a pleasure to acknowledge the generosity of Smith, Kline, and French, who presented us with a sample of I.D.U. We also wish to acknowledge with thanks the help of Mr. Ivor Chinn, F.I.M.L.T., with the virus cultures.

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