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Treatment of adenovirus infection of the eye with 5-iodo-2'-deoxyuridine

A double-blind trial

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Epidemic keratoconjunctivitis is usually caused by infection with an adenovirus, generally type 8 (Hanna, Jawetz, Mitsui, Thygeson, Kimura, and Nicholas, 1957). As this is a DNA virus it might be expected to respond to treatment with 5-iodo-2'-deoxyuridine (IDU) which acts by interfering with the normal synthesis of DNA, thus preventing replication of DNA-containing viruses (Herrmann, 1961; Smith, 1963). It has now been shown that IDU is effective in the treatment of acute infections of the eye due to the DNA virus herpes simplex (Kaufman, 1962; Patterson, Fox, Davies, Maguire, Holmes Sellors, Wright, Rice, Cobb, and Jones, 1963). The present study was designed to determine whether IDU applied locally in ointment form to the eyes of out-patients was of value in the treatment of epidemic keratoconjunctivitis associated with adenovirus infection.

Patients and methods

The patients comprised seventy consecutive cases of acute follicular conjunctivitis, with symptoms of less than 4 days' duration, who were referred to the Glasgow Eye Infirmary Out-patient Department during the course of an epidemic affecting the Clydeside area in the winter of 1967–68. At each visit the presence or absence and severity of the following clinical features was noted: foreign-body sensation, tearing, burning sensation, blurring of vision, conjunctival injection, follicles, chemosis, pseudo-membrane, keratitis, corneal opacities, keratic precipitates, lid oedema, and pre-auricular lymphadenopathy. Visual acuity was also recorded. The patients were treated as out-patients either (*a*) with 0·5 per cent. IDU made up in ointment form or (*b*) with the ointment base alone. The treatment was allocated in a random fashion, both patient and doctor being unaware which regime was being used. Treatment was carried out for one week, the ointment being used at 3-hrly intervals during the day and 6-hrly at night. Special emphasis was made to the patients of the need to adhere strictly to the regime of treatment. Progress was assessed at regular weekly intervals until symptoms had completely subsided and there were no signs of active keratoconjunctivitis—usually from 3 to 6 weeks.

For virus isolation, conjunctival scrapings were collected at the initial interview and again one week later and placed in virus transport medium (Grist, Ross, Bell, and Stott, 1966). Paired sera were taken for virus serological tests, the first specimen at the initial visit and the second specimen two weeks later. Virological tests were carried out as described by Bell, Martin, and Ross (1969).

Results

The results of virus isolation from the initial specimens from the seventy patients are shown in Table I (opposite).

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Adenoviruses were isolated from 31 (44 per cent.); sixteen of these were in the IDU group and fifteen were controls. The adenovirus most frequently isolated was type 8—from ten of the treated and seven of the control cases. Serological tests by complement-fixation (CF) technique confirmed adenovirus infection in these patients, all seventeen showing either a fourfold or greater rise in titre or a high titre (1/128 or greater in both sera). Four additional patients (1 treated and 3 controls) were included as adenovirus 8 infections on the strength of positive haemagglutination inhibition (HI) tests for specific type 8 adenovirus antibodies (Bell and others, 1969). Other adenoviruses isolated comprised type 3 (8 cases), type 7 (4 cases), and type 10 (2 cases).

Table I *Virus isolations from conjunctival scrapings in 70 cases*

Group	*Adenovirus type*				*Herpes simplex*	*Virus isolation negative*	*Total cases*
	8	7	3	10			
IDU-treated	10	3	2	1	1	18	35
Control	7	1	6	1	1	19	35

No virus was isolated from any of the second specimens taken at the end of the first week.

CLINICAL PROGRESS

Adenovirus infections

Of the 35 patients with virologically proven adenoviral infection, seventeen were treated with IDU and eighteen were in the control group. The age and sex distribution was approximately similar in both groups (Table II). The two groups were also comparable as regards the initial clinical severity of infection—all cases were unilateral and none of them showed evidence of keratitis at the commencement of treatment. All 35 patients developed keratitis. Moreover there was no significant difference between treated and control groups in respect of greatest severity of keratitis attained or duration of acute keratitis in either (*a*) the total 35 patients with adenovirus infections or (*b*) the 21 patients with type 8 infections (Table III). Of the 35 cases, four developed bilateral involvement.

Table II *Age and sex distribution of 70 cases*

Group	*Age (yrs)*		*Sex*	
	Range	*Mean*	*Male*	*Female*
IDU-treated	19–60	35	12	5
Control	10–64	32	13	5

Table III *Assessment of therapy*

Group	*Total patients with adenovirus infection*	*Severity of keratitis*				*Duration of keratitis (wks)*			
		Punctate Epithelial	*<5 Infiltrates*	*5–15 Infiltrates*	*>15 Infiltrates*	1	2	3	>3
IDU-treated	17 (11)	7 (2)	3 (2)	5 (5)	2 (2)	6 (2)	5 (4)	4 (4)	2 (2)
Control	18 (10)	9 (1)	2 (2)	4 (4)	3 (3)	5 (0)	6 (3)	3 (3)	4 (4)

Adenovirus 8 infections in parenthesis

These were all cases of adenovirus 8 infection, two who had been treated with IDU and two who were in the control group. Conjunctivitis was closely related in severity to the severity of keratitis. No case of pseudo-membrane formation was encountered.

Only three cases sustained a reduction in visual acuity. These were all examples of adenovirus 8 infection (1 treated case and 2 controls) and all three developed numerous deep stromal infiltrates with folds in Descemet's membrane and underlying keratic precipitates.

A follow-up study was carried out 4 months later when eleven treated cases (8 of adenovirus 8 infection) and ten controls (6 of adenovirus 8 infection) attended for review. No patient had sustained any recurrence of symptoms, and there had been no appreciable alteration in the density or number of any sub-epithelial corneal opacities present.

Cases without virological evidence of infection

Of the 33 patients in whom no virological evidence of infection was found, five developed a punctate epithelial keratitis (1 treated and 4 controls). The remaining 28 cases (16 treated and 12 controls) showed no evidence of corneal damage apart from one control patient who developed a corneal abrasion. All 28 made a complete recovery within 2 weeks.

Discussion

Assessment of IDU therapy in epidemic keratoconjunctivitis has mainly been carried out by clinical criteria alone without virological studies (Scullica, 1962; Imre, Korchmáros, Nász, and Kulcsár, 1964; Marré, 1964). Virological investigations were carried out in a study by Hecht, Hanna, Sery, and Jawetz (1965), who found that IDU had no beneficial effect; however, treatment was delayed until the onset of keratitis. Obviously true assessment of IDU in epidemic keratoconjunctivitis can best be made where virological tests have demonstrated infection with a DNA virus such as adenovirus or herpes simplex, and where treatment has been instituted during the phase of active virus proliferation. In the present trial treatment was attempted on an out-patient basis as we were dealing with an epidemic situation where individual hospitalization was not possible. Ointment was used in preference to drops as it was felt that in this way patients were more likely to adhere to the treatment schedule, and thus a more constant local concentration of the drug would be achieved. Treatment was instituted in all cases before the onset of keratitis. With this regime no beneficial effect of IDU was detected in patients with adenovirus infections of the eye. Despite the institution of treatment early in the course of the disease there was no evidence that the drug produced any reduction in the prevalence or severity of the keratitis. The adenovirus infections appeared to run their natural course uninfluenced by the presence of IDU. It is possible that more intensive in-patient treatment might have achieved better results, although this is unlikely in view of the absence of any detectable beneficial response.

Our failure to recover adenovirus from conjunctival scrapings 9 to 11 days after the onset of symptoms in either treated or control groups would suggest that adenovirus is rapidly eliminated after infection. At this time, however, in many patients, there was still active progression of keratitis which might indicate that this manifestation may be wholly or partially due to an antigen-antibody reaction.

Summary

A double-blind trial was carried out on the use of 0·5 per cent. 5-iodo-2′-deoxyuridine, in ointment form, in the treatment of 35 out-patients with virologically proven adenovirus infection of the eye. The adenovirus infections pursued a typical course uninfluenced by treatment with IDU.

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References

BELL, E. J., MARTIN, K. W., and ROSS, C. A. C. (1969) *J. med. Microbiol.* (in press)

GRIST, N. R., ROSS, C. A. C., BELL, E. J., and STOTT, E. J. (1966) "Diagnostic Methods in Clinical Virology". Blackwell, Oxford

HANNA, L., JAWETZ, E., MITSUI, Y., THYGESON, P., KIMURA, S. J., and NICHOLAS, A. (1957) *Amer. J. Ophthal.*, **44**, no. 4, pt 2, p. 66

HECHT, S. D., HANNA, L., SERY, T. W., and JAWETZ, E. (1965) *Arch. Ophthal. (Chicago)*, **73**, 49

HERRMANN, E. C. (1961) *Proc. Soc. exp. Biol. (N.Y.)*, **107**, 142

IMRE, G., KORCHMÁROS, I., NÁSZ, I., and KULCSÁR, G. (1964) *Klin. Mbl. Augenheilk.*, **144**, 81

KAUFMAN, H. E. (1962). *Proc. Soc. exp. Biol. (N.Y.)*, **109**, 251

MARRÉ, M. (1964) *Klin. Mbl. Augenheilk.*, **144**, 728

PATTERSON, A., FOX, A. D., DAVIES, G., MAGUIRE, C., SELLORS, P. J. HOLMES, WRIGHT, P., RICE, N. S. C., COBB, B., and JONES, B. R. (1963) *Trans. ophthal. Soc. U.K.*, **83**, 583

SCULLICA, L. (1962) *Boll. Oculist.*, **41**, 832

SMITH, K. O. (1963) *J. Immunol.*, **91**, 582