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Clinical trial with 2% sodium cromoglycate (Opticrom) in vernal keratoconjunctivitis

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SUMMARY An open assessment study was carried out during the summer of 1972 in which 2% sodium cromoglycate eyedrops were evaluated in the treatment of patients with vernal keratoconjunctivitis. A highly significant number of patients found the eyedrops effective, while a marked improvement was recorded in mild and moderate cases; in severe cases or in acute exacerbations additional steroid therapy was recommended. Sodium cromoglycate eyedrops were found to be as effective as Decadron and superior to Antistin-Privine. Furthermore SCG eyedrops could replace or reduce local steroid therapy in vernal keratoconjunctivitis and so avert the possible rise in ocular tension caused by steroids.

Vernal keratoconjunctivitis (VKC) is a severe perennial form of allergic conjunctivitis involving the cornea and conjunctiva. The condition is found predominantly in children or young adults and commonly in atopic individuals, who may also suffer from eczema, asthma, or hayfever. The disease generally affects the upper tarsal conjunctiva, which shows a papillary hypertrophy which has a 'cobblestone' appearance in severe cases. The main symptoms are severe itching and the production of a tenacious stringy mucous discharge. The limbal conjunctiva may also be affected, either as a localised oedema and hyperaemia or as fleshy isolated vegetations. It is considered to be an atopic disease[1] and has been classified as a type I allergic disease of the outer eye.[2]

Although VKC responds well to the instillation of corticosteroid drops, not all cases achieve complete control, and long-term use of steroids in the eye is known to produce glaucoma.[3] The high incidence rate of the disease in Egypt along with incomplete amelioration with the use of antihistamines, vasoconstrictors, and steroids made the study of other possible therapeutic agents very desirable.

Such an alternative agent was sodium cromoglycate (SCG), which, in addition to its effectiveness in the treatment of asthma,[4,5] rhinitis,[6,7] proctitis,[8] and ulcerative colitis,[9] was reported[10,11] to be effective when applied topically to the conjunctiva in the treatment of VKC. It is thought that SCG acts by inhibiting the release of histamine and other mediators of inflammation which occurs when antigen combines with sensitising antibody on mast cells.[12]

This paper presents the results of an open assessment study carried out at Alexandria University, Egypt, in which 2% SCG eyedrops were evaluated in the treatment of VKC and its effectiveness compared with that of dexamethasone (Decadron) and a solution containing antazoline sulphate 0·5% and naphazoline nitrate 0·025% (Antistin-Privine).

Materials and methods

A total of 89 patients were selected in whom the disease had equal intensity in both eyes and the duration had varied up to 15 years. All these patients were in continual contact with the clinician through the year prior to the study and also during the whole study period. During the 12-month period only 6 patients dropped out of the trial.

The patients were divided into the following treatment groups: group I, 2% SCG eyedrops into both eyes 4 times daily; group II, 2% SCG drops into left eye, Antistin-Privine in right eye, 4 times daily; group III, 2% SCG drops in left eye, Decadron in right eye, 4 times daily.

In patients selected for this study all the other ocular therapy was deliberately discontinued 1 week before the start of the trial in June 1972. After a 1-week baseline period the clinician made subjective and objective measurements in all patients every day for the first 10 days, once a week for 6 weeks,

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and then every month for a total period of 12 months. At each of these examinations the clinician recorded his subjective opinion on the following symptoms, using a 0 to 4 rating (0=no symptoms, 1=minimal, 2=moderate, 3=moderate/severe, 4=severe): itching, grittiness, sticky and watery discharge, blinking, and congestion. A 0 to 3 rating (0=nil, 1=mild (flat topped)=mosaic, 2=moderate (small elevations with definite depressions), 3=severe (giant/or cauliflower)) was used to score the following signs: papillae on upper and lower tarsus and upper and lower fornix, follicles on upper and lower tarsus and upper and lower fornix, chemosis of bulbar conjunctiva, mucous filaments, oedema, nodules, pannus, Trantas spots, punctate epithelial keratitis (PEK), corneal ulceration, and ocular tension.

The formulation of the eyedrops used was an aqueous solution of SCG *BP* 2% w/v with benzalkonium chloride 0·01% w/v and 2-phenylethanol 0·4% w/v. The approach to the statistical analysis was the same for all 3 groups and made use of the paired nature of the data, namely, either before/after treatment or right/left eye. The data from each of the 3 groups were analysed separately.

Results

GROUP I

Fifty-nine patients with acute vernal disease were entered in this group. The incidence of atopy and other allergic conditions was very low (Table 1). The first patient entered in the trial was assessed in a different manner and his results have been excluded from the analysis. The total sample size for this group is therefore 58.

Comparison of the subjective and objective scores recorded before the start of the trial and after subsequent visits showed a statistically significant therapeutic effect with respect to all the variables ($P<0·01$). In addition the ocular tension was found to be significantly reduced after 8 months' treatment (see Table 4 below).

Table 1 *Patient's characteristics*

Characteristics	*Class or measure*	*Group I*	*Group II*	*Group III*
Sex	Male	44	12	11
	Female	14	3	4
Age	Range	4–30	8–20	6–32
	Mean	14·1	12·8	14·8
Duration of condition (years)	Range	1–15	1–10	0–13
	Mean	3·5	5·6	3·9
Atopy	Yes	3	2	0
	No	55	13	15
Other conditions	Asthma	0	2	0
	Eczema	6	2	0
	Hayfever	0	2	0
	Rhinitis	3	2	0

Table 2 *Changes in the symptoms and signs of VKC after treatment with SCG for 1 month and 8 months (group I)*

Variable	*Response*	*After 1 month*		*After 8 months*	
		Right eye	*Left eye*	*Right eye*	*Left eye*
Efficacy	High	32	32	42	42
	Mild/moderate	23	23	13	13
	None	3	3	3	3
Side effects	Yes	4	4	7	7
	No	54	54	51	51
Patient's opinion	Satisfactory	53	54	54	54
	Unsatisfactory	3	4	4	4
Stinging or irritation	Yes	18	19	37	37
	No	40	39	21	21
Did clinical condition improve?	Yes	53		55	
	No	5		3	

Clinical assessments made after 1 and 8 months' treatment of overall efficacy, patient's opinion, clinical response, and side effects showed that a high percentage of patients found the eyedrops satisfactory and effective. In addition the clinical condition had improved in a high percentage of patients (Table 2).

GROUP II

In this group 15 patients always received Antistin-Privine (A-P) eyedrops in the right eye and SCG eyedrops in the left on an open basis. Both treatments were administered 4 times daily. As in the patients in group I the incidence of atopy and other allergic diseases was very low (Table 1).

Comparison of the subjective and objective scores recorded before the start of the trial and after subsequent visits for the right and left eyes respectively showed a statistically significant difference in favour of SCG eyedrops. In the case of the subjective scores after 8 months' treatment a significant difference ($P<0·02$) was seen in 6 out of 7 variables, while in the objective scores all but 2 of the variables showed a significant difference in favour of SCG eyedrops ($P<0·01$).

Clinical assessments made after 1 and 8 months' treatment of overall efficacy, patient's opinion, clinical response, and side effects showed that a high percentage of patients found the SCG eyedrops superior to Antistin-Privine for all the variables (Table 3). Only 1 report of stinging was reported for each treatment after 8 months.

Table 3 *Changes in the symptoms and signs of VKC after treatment with A–P (right eye) and SCG (left eye) after eight months*

Variable	*Response*	*After 8 months*		*Significance*
		Right eye A-P	*Left eye SCG*	
Efficacy	High	0	14	
	Mild/moderate	3	1	P<0·001
	None	12	0	
Patient's opinion	Satisfactory	4	14	P<0·001
	Unsatisfactory	11	1	
Did clinical condition improve?	Yes	4	14	P<0·001
	No	11	1	
Side effects	Yes	0	0	Sample too small (0)
	No	15	15	P=1·0
Stinging or irritation	Yes	2	2	P=1·0
	No	13	13	

GROUP III

In this group 15 patients were given SCG to the left eye and Decadron to the right. The pattern of treatment and method of analysis were similar to that used for group II. All the patients in this group were classified as nonatopic, with no other allergic conditions (Table 1).

The subjective measurements recorded after 10 days and 1 and 8 months did not reveal a significant difference between the 2 treatments for any of the variables except stinging, where SCG eyedrops were found to sting significantly more than Decadron.

Comparison of the objective scores recorded after subsequent visits for the right and left eyes respectively showed that after 8 months' treatment both treatments performed equally for all the variables except 3, the exceptions being pigmentation, corneal vascularisation and ocular tension, which showed significant differences in favour of SCG eyedrops. In the case of ocular tension there was an increase in the eye given Decadron and a decrease in the eye given SCG.

Six right eyes out of 15 receiving Decadron showed an increase of ocular tension, with an average of +0·9 mmHg (Schiøtz) after 1 month's treatment, and SCG-treated eyes showed no difference (Table 4).

Eight Decadron treated eyes showed an increase in ocular tension by an average of +1·2 mmHg after 8 months' treatment, and SCG treated eyes showed a decrease of an average of 0·2 mmHg (Table 4). After 1 year no further change of the tension was recorded.

The clinical assessments made after 1 and 8 months' treatment revealed an equivalent response from both treatments (Table 5).

In all these groups the results after 12 months' treatment were similar to those presented after 8 months.

Discussion

Fifty-eight patients were administered 2% SCG eyedrops as sole therapy, and after 8 months' treatment the efficacy was rated as high in 42 patients, moderate/mild in 13, and nil in 3. Such a response indicates that SCG may block an important element of type I hypersensitivity which is thought to exist in VKC.[10] In some patients additional treatment with topical steroid was found necessary at the start of treatment or during acute exacerbations. Thus, 8 patients out of 88 received steroid therapy for 1 week at the start of the trial in the severe forms of the disease. However, since the overall steroid requirement was removed in many patients and considerably reduced in others, this has helped greatly to remove the unwanted side effects of topical steroid therapy in VKC, such as increased

Table 4 *Differences between changes in ocular tension after 1 and 8 months*

		Mean difference for		*Significance*
		Right eye (Decadron)	*Left eye (SCG)*	
Tension	After 1 month	0·9	0·0	P<0·01
	After 8 months	1·2	−0·2	P<0·01

Table 5 *Changes in the symptoms and signs of VKC after treatment with Decadron (right eye) and SCG (left eye) after 1 and 8 months*

Variable	*Response*	*After 1 month*		*After 8 months*	
		Right eye (Decadron)	*Left eye (SCG)*	*Right eye (Decadron)*	*Left eye (SCG)*
Efficacy	High	12	13	13	15
	Mild/moderate	2	2	1	0
	None	1	0	1	0
Patient's opinion	Satisfactory	14	15	14	15
	Unsatisfactory	1	0	1	0
Did clinical condition improve?	Yes	14	14	15	15
	No	1	1	0	0
Side effects	Yes	0	0	0	0
	No	15	15	15	15
Stinging	Yes	0	0	0	1
	No	15	15	15	14

intraocular pressure. As well as confirming the results of Easty *et al.*[10] and Tabbara and Arafat[11] this study has established that SCG is effective in nonatopic patients with a minimum of other allergic diseases. However, these results are in contrast to that reported by Hyams *et al.*,[13] who failed to show a positive response with SCG in patients without a history of allergy.

When SCG eyedrops were administered to the left eye and Antistin-Privine eyedrops to the right in 15 patients, a significant number of the patients preferred the SCG eyedrops. After 8 months' treatment the clinical condition was found to improve in 14 (93%) on SCG therapy, while only 3 (20%) responded to Antistin-Privine. In spite of the presence of a vasoconstrictor in Antistin-Privine a rebound phenomenon occurred, and reflex vasodilatation was evident after instillation of the drops, which caused discomfort to the patients. Pigmentation was increased after SCG therapy, but no such changes were detected after Antistin-Privine therapy. No change in the ocular tension was observed in either the SCG or Antistin-Privine treated eyes.

When SCG eyedrops were administered to the left eye and Decadron to the right in 15 patients, both treatments were found to give equivalent clinical responses. However, the one important exception was ocular tension, which after 1 month's treatment was found to have increased by 0·9 mmHg in Decadron treated eyes, while SCG treated eyes showed no difference. After 8 months' treatment with SCG a decrease of 0·2 mmHg was recorded, while with Decadron it was increased by 1·2 mmHg. As regards transient stinging, this was a constant feature in the SCG treated eyes but not with Decadron.

In conclusion, this open assessment study has shown that 2% sodium cromoglycate eyedrops are an effective treatment in a high percentage of patients with VKC. Marked improvement was recorded in mild and moderate cases, though in severe cases or in acute exacerbation additional steroid therapy was recommended. Although stinging did occur, the eyedrops were free from important side effects, in particular from the rise in ocular tension found with steroid eyedrops. In steroid-induced glaucoma SCG eyedrops decrease the ocular tension when replacing steroid therapy in VKC. In a within-patient comparison study SCG eyedrops were equal to Decadron and superior to Antistin-Privine with regard to efficacy.

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