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Perennial Rhinitis - its causation and treatment, a trial of a new formulation of sodium cromoglycate

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SUMMARY

A double blind cross over study on the effect of 2% aqueous solution of sodium cromoglycate in perennial rhinitis has been performed in 37 patients. It is concluded that SCG solution is a useful and effective therapy irrespective of whether the disease is due to exogen allergy or vasomotoric (intrinsic) type.

INTRODUCTION

Perennial rhinitis may be defined as a chronic condition of the nasal mucous membrane resulting in nasal obstruction, sneezing attacks and watery nasal discharge.

There are two major aetiological groups – allergic and non-allergic, the latter also called intrinsic or vasomotor rhinitis.

The two major groups of allergic and non-allergic or vasomotor rhinitis are differentiated by means of history and investigation. In the allergic group there is an association between symptoms and specific allergens such as house dust, animals, occupational dusts and perhaps ingested agents together with positive skin tests and positive nasal provocation tests. In the vasomotor group the symptoms are mainly associated with unspecific environmental changes such as temperature, humidity and chemical irritants and all allergic investigations are negative.

Sodium cromoglycate is a drug that when applied to mucous membranes prevents the release of chemical mediators from the sensitised mast cells which is caused by an allergic reaction as reported by Cox (1971).

There have been indications from trials of this drug (Salo et al., 1973; Fagerberg and Zetterström, 1975) that it may be of value in treating patients with vasomotor rhinitis. The objective of this present study was to investigate this further and to conduct a trial on a new formulation of the drug delivered by a metered dose nasal spray, containing a 2% aqueous solution of sodium cromoglycate with 0.02% Benzalkonium chloride as a preservative.

METHOD

Patients with perennial rhinitis were entered into the study regardless of the causation of the disease. Thus patients with both allergic rhinitis and vasomotor rhinitis were included. They were selected on the basis of: a) constant symptoms present for at least one year, b) symptoms of such severity as to require treatment. Patients were excluded if they had any evidence of an infective rhinitis or a medically induced rhinitis or if they had nasal polyps of sufficient size as to cause obstruction. Those who had received steroid treatment in the last three months were also excluded.

At the beginning of the investigation a full history was taken with respect to duration of disease, age of onset, family history of atopy, previous hyposensitisation and severity of present symptoms of rhinitis.

All patients were intracutaneously tested against common allergens and nasal provocation tests were carried out where indicated. Nasal smears were taken and examined for eosinophils and bacterial growth. A full naso-pharyngeal examination was carried out and assessment made of the degree of patency of each nasal passage and the severity of the three symptoms of sneezing, blocking and running on a 4 point scale. Eosinophils in the nasal smears were estimated on the following scale:

less than 10% eosinophils	=	negative	= ÷
10% eosinophils	=	positive	= ++
50% eosinophils	=	positive	= +++
More than 50% eosinophils	=	positive	= ++++

Serum IgE levels were measured in some patients on entry to the trial. Patients were then treated for four weeks with either a solution of sodium cromoglycate or placebo solution given on a double blind, randomised basis. At the end of this time they were re-examined, and assessment made of severity of nasal symptoms and degree of nasal patency. A further nasal smear was taken. The patients were then treated for a further four weeks with the alternate preparation and the examinations and investigations repeated at the end of that time.

At the end of the investigation patients were asked which of the two treatments they preferred. The occurrence of any side effects was recorded. Throughout the eight week period of the investigation all patients kept a daily record card on which they recorded the severity of their nasal symptoms of blocking, sneezing and rhinorrhoea on a 4 point scale. Patients were permitted to take anti-histamine tablets if symptoms were not controlled by the nasal spray they were using. They recorded each day the number of anti-histamine tablets they used.

The active treatment used was a 2% sterile aqueous solution of sodium

cromoglycate containing benzalkonium chloride as a preservative and sodium edetate as a chelating agent. The placebo solution was a sterile aqueous solution containing the same concentrations of benzalkonium chloride and sodium edetate. Both solutions were delivered to the nasal mucosa using a metered dose spray in which each activation of the spray delivers 0.13 ml (±15%) of solution. The solution is contained in a non-pressurised plastic container.

RESULTS

The investigation took place between December 1974 and May 1975. Thirty-nine patients were entered into the investigation but two were excluded from the analysis of the results. One was withdrawn because of an operation unconnected with the trial and the second did not use the placebo treatment regularly as it caused nasal irritation. For the purpose of analysis patients were divided into two groups according to whether they received sodium cromoglycate or placebo as their first treatment.

Table 1 shows the characteristics of the patients included. The mean age was 34.2 years (range 11-54) with 11 males and 26 females. The mean duration of their illness was 9.65 years (range 1-40). On entry into the investigation 11 patients were classified by the clinician as having mild symptoms, 18 with moderately severe symptoms and 8 with severe symptoms. The most troublesome single symptom was nasal blockage re-

Table 1.

Variable		Value of Frequency
Age	Mean	34.2
Sex	Range	11-54
Duration of Disease	(year)	9.65
	Range	1-40
Symptom Severity	Mild	11
	Moderate	18
	Severe	8
Hyposensitised	Yes	9
	No	28
Skin Test*	Positive	12
	Negative	15
Nasal Provocation*	Positive	9
	Negative	14
Final Diagnosis	Allergic	9
	Intrinsic	21
	Allergic and Intrinsic	5
	Not stated	2

* Not all patients tested.

ported by 21 patients and a further 8 giving blocking and running together as the most severe symptom. Twenty-five patients had received no treatment in the last three months and seven had been treated with antihistamines.

Nineteen patients had total IgE levels measured during the trial. The mean value was 255 ug/100 ml with a range of 30 to 1575. Of the 19 patients, 2 had a diagnosis of allergic rhinitis (IgE levels 30 and 97), 12 had a diagnosis of vasomotor rhinitis (mean total IgE 81 range 30-210) and 5 were diagnosed as having a mixture of allergic and vasomotor rhinitis (mean total IgE 751 range 30-1575).

Twenty-seven patients were skin tested against common allergens and 23 had nasal provocation tests. Of those skin tested 15 had negative tests, seven positive tests to perennial antigens and five positive tests to seasonal antigens. Fourteen patients had negative nasal provocation tests, nine positive nasal provocation tests.

Table 2. Initial Symptom Severity as Assessed by the Clinician.

		Frequency for:	
Variable	Severity	SCG - Placebo Group	Placebo - SCG Group
Sneezing	None	2	5
	Mild	13	5
	Moderate	3	5
	Severe	1	3
Blocking	None	0	0
	Mild	5	6
	Moderate	10	5
	Severe	4	6
	Mild/Moderate	0	1
Running	None	2	4
	Mild	7	6
	Moderate	8	5
	Severe	2	3
Nasal-Patency-Left Nostril	Open	2	2
	Partially blocked	15	11
	Completely blocked	2	5
Nasal Patency-Right Nostril	Open	4	3
	Partially blocked	12	12
	Completely blocked	3	3
Nasal Smear*-Eosinophils	—	3	0
	++	3	3
	+++	1	4
	++++	2	3

* Sufficient data for patient numbers 1-20 only.

The final diagnosis on entry into the investigation was that nine patients had allergic rhinitis, 21 patients had intrinsic or vasomotor rhinitis and five patients had a mixed illness, that is perennial disease but positive skin tests against seasonal allergens.

Table 2 shows the initial symptom severity as assessed by the clinician. Nasal blockage is the most predominant symptom with 26 patients having moderate or severe blocking. Thirty-one patients had one or both nostrils partially or completely blocked on examination.

Table 3 shows the effects of treatment on the clinician's evaluation of the disease. Figure 1 presents the same data in graphical form. During the first four weeks of treatment all patients improved. During the second four weeks of treatment those changing from placebo to active treatment continued to improve whereas those changing from active to placebo treatment either became worse or remained at the same level of symptomatology. Overall the trend was in favour of the active drug and this reached statistically significant

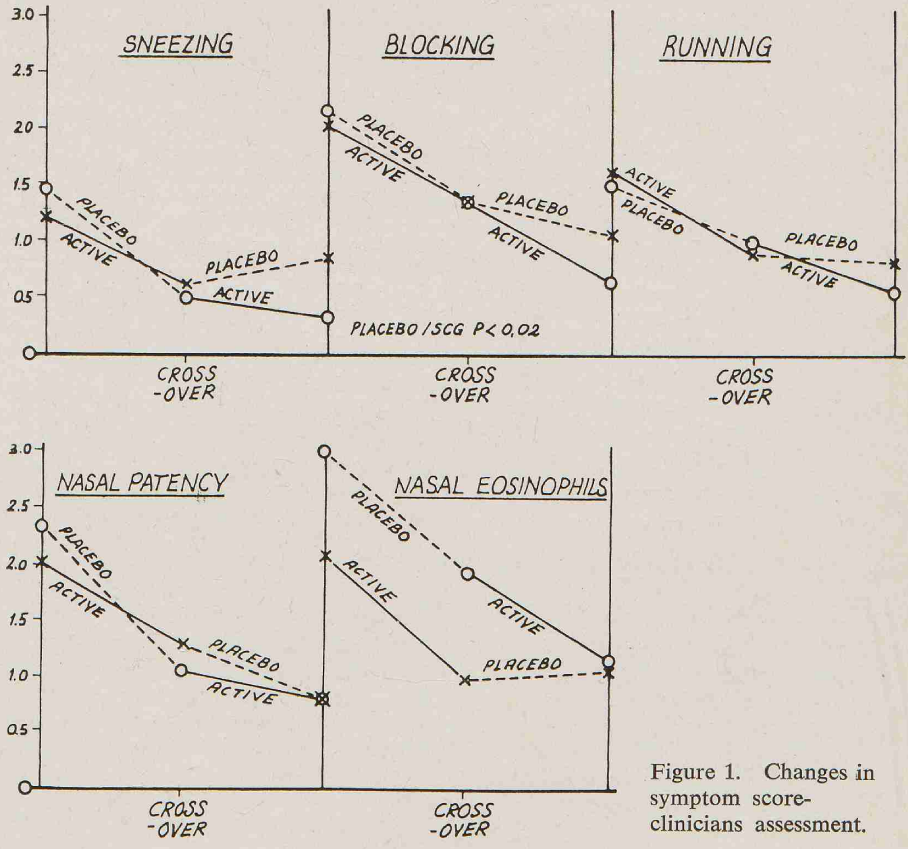

Figure 1. Changes in symptom score-clinicians assessment.

proportions in the group who were treated placebo-active sodium cromoglycate.

In Table 4 the analysis of the three symptoms of blockage, running and sneezing, taken from the patients daily diary card is shown. A comparison is made between the mean monthly totals for each symptom (maximum possible score 284) in the SCG and placebo periods. In all cases the symptom scores are less during the SCG period than during the placebo and, in many cases, the difference is statistically significant.

At the end of the eight week study patients were asked which of the two treatments they preferred. The results are shown in Table 6.

Table 5 summarises the side effects reported.

DISCUSSION

The significant differences shown between active sodium cromoglycate and placebo in this investigation show that sodium cromoglycate solution is effective in the treatment of perennial rhinitis. Patients with both allergic rhinitis and vasomotor rhinitis were included in the trial and there is evidence of efficacy irrespective of diagnosis. This suggests that some patients with a diagnosis of vasomotor rhinitis have in fact an allergic disease in which it

Table 3. Wilcoxon Matched Pairs Signed Ranks Test of Clinican's Scores.

Symptom	Treatment Order Group	Group Size	Mean Scores for: SCG	Placebo	*Wilcoxon T-value	2-tail Significance
Sneezing	SCG - Placebo	18	0.6	0.8	19.0 (10)	$p > .10$
	Placebo - SCG	17	0.3	0.5	Number too small (4)	
	All Patients	35	0.5	0.7	32.0 (14)	$p > .10$
Blocking	SCG - Placebo	18	1.3	1.1	7.0 (6)	$p > .10$
	Placebo - SCG	17	0.7	1.3	0.0 (7)	$.01 < p < .02$
	All Patients	35	1.0	1.2	28.5 (13)	$p > .10$
Running	SCG - Placebo	18	0.9	0.8	17.5 (9)	$p > .10$
	Placebo - SCG	17	0.6	1.0	9.0 (9)	$p > .10$
	All Patients	35	0.8	0.9	72.0 (18)	$p > .10$
Nasal Patency	SCG - Placebo	18	1.3	0.8	12.0 (9)	$p > .10$
	Placebo - SCG	17	0.8	1.1	10.5 (8)	$p > .10$
	All Patients	35	1.1	0.9	69.0 (17)	$p > .10$
**Nasal Eosinophils	SCG - Placebo	8	1.0	1.1	6.0 (5)	$p > .10$
	Placebo - SCG	10	1.2	1.9	8.5 (8)	$p > .10$
	All Patients	18	1.1	1.6	27.5 (13)	$p > .10$

* Figures in brackets are the numbers of non-tied pairs included in the test; tied pairs are excluded.

** Data from patients 1-20 only used.
2 patients were not included as the data for second period was incomplete.

Table 4. Wilcoxon Matched Pairs Signed Ranks Test of Diary Card 28 Day Totals.

Symptom	Treatment Order Group	Group Size	Mean Monthly Totals for: SCG	Placebo	Wilcoxon * T-value	2-tail Significance
Blockage	SCG - Placebo	16	36.1	39.9	32.5 (13)	$p > .10$
	Placebo-SCG	18	29.5	41.9	18.0 (16)	$p < .01$
	All Patients	34	32.6	41.0	87.5 (29)	$p < .01$
Running	SCG - Placebo	16	24.5	26.8	39.0 (14)	$p > .10$
	Placebo-SCG	18	18.9	24.9	29.0 (16)	$.02 < p < .05$
	All Patients	34	21.5	25.8	139.5 (30)	$.05 < p < .10$
Sneezing	SCG - Placebo	15	15.2	24.6	14.0 (14)	$.01 < p < .02$
	Placebo-SCG	18	12.1	19.9	14.5 (15)	$p < .01$
	All Patients	33	13.5	22.0	61.0 (29)	$p < .01$

* Figures in brackets are the numbers of non-tied pairs included in the test; tied pairs are excluded.
Not all patients included as diary card data was incomplete.

Table 5. Side Effects.

Side Effect	Frequency For SCG	Placebo
Nasal irritation	3	5
Nausea	0	1
Headache	1	2
Cough	1	0
Sneezing	0	2

Table 6. Treatment Preferences.

	Number of Prefereences For SCG	Placebo	Neither	
SCG - Placebo	6	4	8	$p > .05$
Placebo - SCG	12	1	4	$p < .01$
All patients	18	5	12	$p < .05$

Table 7. Mann-Whitney U-Tests Comparing Allergic Patients and Intrinsic Patients for Diary Card Totals.

Variable	Mean Total Differences for: Intrinsic	Allergic	Mann-Whitney U-Statistic	* 2-tail Significance
Blockage	-11.0 (20)	- 6.9 (7)	54.5	$P > .05$
Running	- 6.3 (20)	- 0.1 (7)	58.0	$P > .05$
Sneezing	- 8.5 (20)	-11.8 (6)	49.5	$P > .05$

* Figures in brackets are the numbers of patients.

has not been possible to identify the allergen involved.

In the original diagnosis on entry, nine patients were classified as having allergic rhinitis, 21 patients with vasomotor rhinitis and five with a mixed aetiology. Table 7 shows the difference in scores between active and placebo treatments in allergic and intrinsic patients. No significant differences were shown indicating that both groups responded to treatment equally well. It must be pointed out, however, that the sample sizes are small.

As the investigation demonstrates overall that the active treatment is successful in this group of patients then the conclusion may be drawn that the present definition of vasomotor rhinitis is wrong and that many of these patients have an allergic disease which is not detectable by present methods of diagnosis. However, in vasomotor rhinitis there are so many unknown aetiological factors that a satisfactory objective evaluation of the treatment is hard to give. It seems that clinical studies which do not incorporate a double blind, cross over technique should be viewed with some scepticism.

In evaluating the results, it will be noted that there are more significant differences between SCG and placebo treatments when placebo was given as the first treatment. This suggests that SCG treatment has a "carry-over" effect and that symptoms do not fully return until some time after the treatment has been stopped.

Skin tests and nasal provocation tests appear to be unhelpful. The presence of eosinophils in the nasal smear may be of more use: of the 30 patients in the two main groups (21 vasomotor, 9 allergic) 27 had eosinophils in the nasal smear (18 vasomotor, 9 allergic); of these 11 had an eosinophil score of three or more (8 vasomotor, 3 allergic). A further point to be made is that 21 of these 30 patients gave a history of allergic disease in their family.

It would seem reasonable to conclude that sodium cromoglycate solution is a useful and effective therapy in the treatment of perennial rhinitis irrespective of whether this is due to allergic disease or is vasomotor in type. Conventional methods of diagnosing allergic rhinitis are unhelpful but if a patient had eosinophils present in a nasal smear and has a positive family history of allergic desease then they are likely to respond to treatment with this drug.

ZUSAMMENFASSUNG

In einem Doppeltblind-Crossover-Studium wurde der Effekt von einer 2%-igen Lösung von Natrium Cromoglicicum in Spray-Form an 37 Patienten mit perenniale Rhinitis untersucht.

Zusammenfassend kann gesagt werden, dass die 2%-ige Lösung von Natrium Cromoglicicum eine gute und effektive Therapie ist, unabhängig davon, ob die Ätiologie von einem exogeen-allergischen oder einem vasomotorischen Charakter ist.

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