Treatment of perennial rhinitis with 2% solution of sodium cromoglycate

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SUMMARY

This trial has demonstrated that S.C.G. is significantly better than placebo and therefore that a 2% solution of S.C.G. is effective in the treatment of perennial rhinitis. It would appear that better results can be obtained in patients who have a demonstrable allergic aetiology with a nasal eosinophilia.

INTRODUCTION

Perennial rhinitis is a disease which at present constitutes a problem for both the otorhinolaryngologist and the allergologist.

There are, as with bronchial asthma, two well defined forms; the extrinsic which has an allergic aetiology and the intrinsic in which it is not possible to find a specific allergen; the latter is clinically very similar to the extrinsic.

Sodium Cromoglycate (S.C.G.) applied locally effectively blocks a response to antigen challenge in both the lungs (Pepys et al., 1968) and the nose (Engstrom, 1971; Taylor and Shivalkar, 1971). Although the exact mechanisms of action of S.C.G. is not known, clinical benefits in the treatment of bronchial asthma are definite. (Altounyan and Howell, 1969; Lobation and Macias, 1972).

The object of this study was to assess the therapeutic effect of S.C.G. in the treatment of perennial rhinitis.

METHOD AND MATERIALS

The study was carried out using a double blind crossover technique, each patient receiving both active and placebo each for a four week period; the drug order was randomised.

The active was a 2% solution of S.C.G. with 0.01% benzalkonium chloride as a preservative and 0.01 EDTA as a chelating agent; the placebo consisted of BKC and EDTA.

The solutions were contained in identical glass bottles which were placed inside a small spray pack about the size of a cigarette lighter; when activated a fine spray was delivered to the nose. The volume of solution per spray was 0.13 ml with a variation of 0.02 ml.

A total of 24 patients completed the study; 11 received drug order active-placebo and 13 placebo-active.

All patients had clinical evidence of perennial rhinitis and the symptoms were of such a degree as to require treatment. The symptoms were constant and had been present for at least one year. Both allergic and intrinsic patients were admitted to the study, the former were classified on the basis of a positive skin test and nasal provocation. All patients remained in their normal environment throughout the period of the study. Only one other therapy was permitted, this was an antihistamine (Chlorphenaramine 2mg); tablets were to be taken only if and when the patient considered necessary, the number used per day was recorded.

The following categories of patients were specifically excluded; those with mild symptoms who responded to antihistamines or decongestants; those who had received corticosteroid therapy within the preceding three months, patients with large nasal polyps, those with evidence of infective rhinitis or asthma and finally, pregnancy.

The dose administered was one squeeze to each nostril six times a day, thus the total daily dose of S.C.G. to each nostril was approximately 15.6 mgs.

In order to assess the relative efficacy of each treatment, the following parameters were recorded:

a) The symptoms running, blocking, sneezing and itching were assessed by the clinician at the beginning and end of each treatment period on a four point scale.
   0 = none, 1 = mild, 2 = moderate, 3 = severe.
b) Nasal patency was assessed at the beginning and end of each period as:
   Open = 0, partially blocked = 1, completely blocked = 2.
c) Nasal smears were examined for eosinophils at the beginning and end of each period and classified as follows:
   — = no eosinophils, + = isolated, ++ = abundant plus other cells seen, +++ = very abundant.
d) Each patient kept a daily diary card to assess symptoms of blocking, running, sneezing and itching on a 0—3 scale; they also recorded the daily consumption of antihistamines.
e) At the end of the trial, the patient expressed a preference for one of the treatments; if this was not possible a no preference was recorded.
f) Side effects were noted at the end of each treatment period.
   In all statistical tests a two-tailed probalility of 5% has been used to indicate significance.

RESULTS

1) *Patients Characteristics*

There was no significant differences (Student t-test) between the groups with respect to mean age and duration of disease. The distribution of sex, symptom severity, whether hyposensitized or not, positive or negative skin tests, sense of small and final diagnosis were tested for differences between the drug order groups using the Fisher Exact Test; no significant differences were found. The pre-trial assessment of symptoms showed that 75% of al patients were rated as moderate or severe. (Table 1).

Table 1. Some patient characteristics

Variable		Value or Frequency for SCG-PLACEBO	PLACEBO-SCG
Age	Mean	37.1	30.5
	Range	16 - 58	10 - 56
Sex	Male	7	7
	Female	4	6
Duration of Disease	Mean	5.8	4.6
	Range	2 - 18	3 - 10
Symptoms	Mild	1	4
	Moderate	8	7
	Severe	1	2
Hyposensitized	Yes	2	6
	No	9	7
Sense of smell	Present	10	12
	Absent	1	1
Skin Test results	Housedust mite +	5	9
	Moulds +	0	2
	Animals +	1	6
	Negative	6	4
Final diagnosis	Allergic	5	9
	Intrinsic	6	4

2) *Clinical Assessment*

The four symptoms, nasal patency and eosinophilia were analysed for each patient, tied pairs were excluded. The results are given in Table 2. In all parameters the mean for S.C.G. was always less than for placebo. Three of the six variables yielded statistically significant differences; blocking, itching and nasal eosinophilia.

Table 2. Wilcoxon Matched Pairs Signed Ranks Tests of Clinician's Scores

Variable	Means for: SCG	PLACEBO	Wilcoxon T - value	Significance
Sneezing	1.1	1.3	8.0	P>.10
Blocking	0.9	1.6	7.0	P<.01
Running	0.9	1.3	8.5	P>.05
Itching	1.0	1.6	0.0	P<.01
Nasal eosinophilia	0.9	1.5	0.0	P<.01
Nasal patency	0.4	0.8	6.0	P>.05

3) *Diary Card Scores*

Patient diary cards were analysed using the Wilcoxon test (Table 3). There was a highly significant difference (P 0.01) for all symptoms and also for the concom-

mitent use of antihistamines; the latter were reduced on average by approximately half whilet S.C.G. was used.

Table 3. Wilcoxon Matched Pairs Signed Ranks Tests of Diary Card Monthly Totals

Variable	Mean Monthly Totals for 24 patients		Wilcoxon T - value	Significance
	SCG	PLACEBO		
Blocking	27.7	53.3	8.5	P<.01
Sneezing	27.9	51.9	6.5	P<.01
Running	32.5	56.2	12.0	P<.01
Itching	29.9	55.7	6.5	P<.01
No. of antihistamines	31.1	66.3	6.0	P<.01

4) *Patient Preferences*

The results are given in Table 4. In those patients who received drug order S.C.G.-placebo, there was no significant difference due to a high number of no preference, this is probably due to a carryover effect of the active drug. However, in the group placebo-S.C.G. and in all patients, the difference is significant.

TABLE 4. Patients Preferences

Patient Group	Number of Preferences for:			Probability
	SCG	PLACEBO	NO REFERENCE	
SCG - Placebo	3	2	6	P = 1.000
Placebo - SCG	9	0	4	P = 0.004
All patients	12	2	10	P = 0.012

Side Effects

The common side noted was slight nasal irritation during, and for a short time after, the administration of the solution; it was noted in then patients whilst using S.C.G. and in six when using placebo. Also noted were headache, sore throat and itching to a minor degree. None of the patients stopped treatment because of side effects and all were therefore considered to be trivial. A summary is shown in Table 5.

Table 5. Side Effects

Side Effects	Number of complaints for:	
	SCG	Placebo
Nasal irritation	10	6
Headache	4	6
Throat complaints	3	0
Itching	0	1

DISCUSSION

Taylor and Shivalkar (1970) used a 1%, 2% and 4% solution of S.C.G. and found that a 2% was more effective in blocking a nasal reaction than either the 1% or 4% solutions. In this study we used a 2% solution of S.C.G. which appears to be effective in the clinical situation.

The device used is small (100 x 35 x 23 mm), easy to use, light and therefore very acceptable to the patient. The volume of solution delivered is consistent so that the daily dose of S.C.G. per nostril varies between 13.2 mgs and 18.0 mgs.

It is of interest to note the number and changes in eosinophils in the two types of patients, allergic and intrinsic, and the changes which occur during treatment with S.C.G. and placebo.

On analysing statistically the relationship between the diagnosis of patients as allergic or intrinsic and the degree of eosinophilia on entry into the trial, we noted that the differences were highly significant, the allergic patients usually had abundant eosinophils whereas the intrinsic group usually had only isolated eosinophils (Table 6).

Table 6. Diagnosis and Eosinophilia on Entry

		Initial Nasal Smear Results - Eosinophilia			
		Isolated	Abundant	Very Abundant	TOTAL
Diagnosis	Allergic	1	7	6	14
	Intrinsic	8	1	1	10
	TOTAL	9	8	7	24

Fischer Exact Probability = 0.001

An analysis of changes in eosinophils following treatment with S.C.G. or placebo showed that after S.C.G. significantly more allergic than intrinsic patients showed a reduction. After placebo treatment there was no difference in the two types of patient although more than half the allergic group showed some reduction (Table 7).

Table 7. Diagnosis and Change in Nasal Eosinophilia Following Treatment

AFTER SCG TREATMENT

		Change in Eosinophilia		TOTAL
		None	Decreased	
Diagnosis	Allergic	1	13	14
	Intrinsic	7	3	10
	TOTAL	8	16	24

Fisher Exact Probalility = 0.002

AFTER PLACEBO TREATMENT

		Change in Eosinophilia None	Decreased	TOTAL
Diagnosis	Allergic	6	7	13
	Intrinsic	7	3	10
	TOTAL	13	10	23

Fisher Exact Probability = 0.402

This pattern is, to some extent, similar to that seen in asthma when examining the sputum, thus we conclude that when S.C.G. is administered nasally the decrease in eosinophils is due to the activity of the drug on the mast cells with consequent diminution of the Eosinophilia Chemotactic Factor of Anaphylaxis (ECF-A).

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RÉSUMÉ

Cet essai a démontré que le S.C.G. est significativement meilleur que le placebo et, par conséquent, qu'une solution au 2% de S.C.G. est efficace pour le traitement de la rhinite perenne. Il semblerait que les meilleurs résultats puissent être obtenus chez les malades ayant une étiologie allergique démontrable avec une éosinophilie nasale.

ZUSAMMENFASSUNG

Dieser Test hat bewiesen, dass S.C.G. signifikant besser als Placebo ist und dass eine 2%ige S.C.G.-Lösung für die chronische Rhinitis therapeutisch wirksam ist. Bessere Erfolge können erzielt werden in Patienten mit beweisbarer allergischer Aetiologie und nasaler Eosinophilie.

REFERENCES

1. Altounyan R. E. C. and Howell J. B., 1969: Treatment of asthma with Disodium Cromoglycate. Respiration 26, 131.
2. Engstrom I., 1971: The effect of disodium cromoglycate on nasal provocation tests in children with seasonal allergic rhinitis. Acta allergol. 26, 101.
3. Lobaton P. and Macias A., 1972: Disodium Cromoglycate; a new drug for the prevention of bronchial asthma. Rev. Clin. Esp. 124, 6, 595.
4. Pepys J., Hargreave F. E., Chen M. and McCarthy D. S., 1968: Inhibiting effects of disodium cromoglycate on allergen inhalation tests. Lancet ii, 134.
5. Taylor G. and Shivalkar P. R., 1971: Disodium cromoglycate; laboratory studies and clinical trial in allergic rhinitis. Clinical Allergy 1, 189.
6. Taylor, G. and Shivalkar P. R., 1970: The effect of disodium cromoglycate on Nasal Airways Resistance following antigen challenge in sensitive subjects. 7th Int. Congr. of Allergology, Special Sectional Meeting. Florence. October 17th, 1970. C.E.P.I. Rome.

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