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A TRIAL OF DISODIUM CROMOGLYCATe IN PERENNIAL RHINITIS

By

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Disodium cromoglycate (DSCG) (Lomudal, Intal) has been used for several years in the treatment of bronchial asthma. Early work revealed that this drug was capable of inhibiting reactions mediated by reaginic antibodies in several experimental systems (3, 14, 17). DSCG was also shown to be effective in allergen challenge experiments (1, 5, 16, 18), and to a variable extent in the clinical situation (4, 6, 8, 9, 12, 13). The success of this form of medication in bronchial asthma, particularly the allergic type, suggested that it might be effective in allergic diseases of the upper respiratory tract, such as seasonal or perennial rhinitis. Investigations have confirmed the efficacy of this drug in nasal allergen provocation tests (7, 15, 20) in seasonal allergic rhinitis (10, 20) and perennial rhinitis (2, 11, 19, 21). Since disodium cromoglycate is supposed to act via allergic mechanisms, perennial rhinitis presents a severe challenge to the drug, because in most cases allergic components are not demonstrable in this condition. A further possible difficulty is the high incidence of blocking as a predominant symptom in this condition, and the question arose as to whether the drug could reach enough areas of the nasal mucosa when administered by an insufflator.

MATERIALS AND METHODS

The investigation was designed as a double-blind, cross-over study: a capsule containing 10 mg DSCG plus 10 mg lactose was used as the active preparation;

and a capsule containing 20 mg lactose as the placebo. The drug was administered by a special insufflator, and at each dose the contents of one capsule were equally divided between the two nostrils. The drug was given 4 times daily: i.e. on rising, at midday, at around 6 pm and on retiring. The treatment period for each drug was 4 weeks, and neither the patient nor the physician was aware of the nature of the drug being given at any time. The patients chosen were subjects who had had symptoms of perennial rhinitis severe enough to demand treatment of some sort for at least 1 year. Patients with nasal polypi severe enough to cause complete occlusion of either nostril were not included in the trial. An allergological investigation was carried out in all patients. This consisted of clinical history, intracutaneous skin tests to common allergens, and measurement of total IgE in serum with RIST. The patients' sera were also investigated for allergen specific IgE against house dust, mite, animal and pollen allergens with RAST. In some patients, RAST tests against mould allergens were also performed.

As most patients were living in comparatively standard conditions throughout the trial, it was possible to stagger their entry and, therefore, to ease the load of their supervision over an 8-week-period in each case. The first patient entered the trial on 2nd February, 1973 and the last one on 29th April, 1973. Four main symptoms, viz. sneezing, blocking, running and itching, were assessed by the clinician at the start of the trial and at the end of each treatment period. Patients kept diary cards recording these symptoms daily on a scale 0-3 (none, mild, moderate, severe); the use of any other treatment such as antihistamines was also recorded. Side effects noted were reported at the end of each treatment period. At the termination of the trial, the patients were asked to express a preference for one or other treatment.

Patient Characteristics and Initial Symptom Severity

Patient characteristics are summarized in Table 1, and it is clear that the two groups are comparable. Blocking was usually described as the most troublesome symptom, and was most often described as having been marked in severity. All patients were recorded as having had perennial symptoms within the last year. Table 2 gives the distribution of the clinician's initial assessment of symptoms, and again the two order groups were similar. The distribution confirmed that blocking was the worst symptom, followed by running and sneezing. Itching was usually scored as absent.

Four patients had positive skin and RAST tests against house dust and/or mite allergen. They were regarded as having atopic disease. Three of them had a raised IgE level. Four

TABLE 1
Patient Characteristics.

Characteristic		Frequency or Value for:	
		Active-Placebo	Placebo-Active
Sex:	Male	5	7
	Female	7	4
Age:	Mean	27.5	33.7
	Range	17-39	16-54
Duration:	Mean	8.5	8.9
	Range	1-23	1-20
Symptom severity	Mild	1	3
	Moderate	9	3
	Severe	2	5
Most troublesome symptom	Blockage	7	6
	Nasal catarrh	5	3
	Impaired sense of smell	0	1
	Sneezing	0	1
Hyposensitized in last 3 years	Yes	1	1
	No	11	10
Sense of smell	Present	9	9
	Absent	3	2

other patients had normal IgE levels, one or two weakly positive skin tests and a positive RAST test, which could not explain their perennial symptoms. Two of them had a weak positive RAST to birch and timothy pollen, respectively; one had a weak positive reaction to cat, and one a weak reaction to cat and horse allergen. The perennial rhinitis in these cases was regarded as intrinsic in nature, even if it is not impossible that atopic mechanisms may have contributed to the disease symptoms. The other 15 patients had normal IgE levels, a single positive or completely negative skin tests, and negative RAST tests, and were classified as having intrinsic (vasomotor) rhinitis.

TABLE 2
Initial Symptom Severity—Clinician's Assessments.

Symptom	Severity	Frequency by order group:	
		Active-Placebo	Placebo-Active
Sneezing	None	3	0
	Mild	3	6
	Moderate	5	4
	Severe	1	1
Blockage	None	0	0
	Mild	2	2
	Moderate	6	5
	Severe	4	4
Running	None	1	1
	Mild	3	4
	Moderate	4	5
	Severe	4	1
Itching	None	8	6
	Mild	3	3
	Moderate	1	1
	Severe	0	1

RESULTS

A. Clinician's Assessment

For each patient (symptom by symptom), pairs of differences were obtained by subtracting the initial scores from the scores at the end of each treatment period. These were then analysed non-parametrically, to give the results shown in Table 3. Two significant differences in favour of the active drug were found in the data for blockage and running, the two most prominent symptoms.

B. Daily Diary Cards

Each patient's diary card scores were totalled, variable by variable, for each month of treatment, and these paired totals were compared non-parametrically. The results are given in

TABLE 3

Wilcoxon Matched Pairs Signed Ranks Tests of Changes in Clinician's Scores.

Symptom	Group size	Mean difference for :		Wilcoxon T-value*	2-tail significance
		Active	Placebo		
Sneezing	23	-0.7	-0.3	37.5 (16)	$P > .10$
Blockage	23	-0.8	-0.3	12.0 (13)	$.01 < P < .02$
Running	23	-0.8	-0.1	11.0 (14)	$P < .01$
Itching	23	-0.2	0.1	11.5 (9)	$P > .10$

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

TABLE 4

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

Variable	Order group	Group size	Mean totals for :		Wilcoxon T-value*	2-tail significance
			Active	Placebo		
Sneezing	Active-Placebo	12	17.9	24.9	13.0 (10)	$P > .10$
	Placebo-Active	11	21.5	36.0	0.0 (10)	$P < .01$
	All patients	23	19.5	30.2	22.0 (20)	$P < .01$
Blocking	Active-Placebo	12	30.3	30.2	32.0 (11)	$P > .10$
	Placebo-Active	11	28.1	40.6	3.0 (10)	$P < .01$
	All patients	23	29.3	35.2	67.0 (21)	$.05 < P < .10$
Running	Active-Placebo	12	39.5	44.5	28.5 (12)	$P > .10$
	Placebo-Active	11	36.1	50.1	3.0 (10)	$P < .01$
	All patients	23	37.9	47.2	58.5 (22)	$.02 < P < .05$
Itching	Active-Placebo	11	11.4	13.1	7.0 (5)	$P > .10$
	Placebo-Active	10	5.7	18.1	0.0 (6)	$.02 < P < .05$
	All patients	21**	8.7	15.5	13.0 (11)	$.05 < P < .10$

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

** Data incomplete in 2 cases.

Table 4. For the whole group of patients, sneezing and running were significantly less on DSCG compared to placebo. When analysed according to drug order, significant differences were seen for all four symptoms in those subjects who had the drug order, placebo-DSCG; while in those who had

TABLE 5
Patients' Preferences.

Order group	Number of preferences for :			2-tail binomial probability
	Active	Placebo	Neither	
Active-Placebo	6	4	2	$P = 0.754$
Placebo-Active	8	1	2	$P = 0.040$
Total	14	5	4	$P = 0.064$

DSCG first, there was no significant difference of symptoms between the two periods. This suggests there may be a carry-over effect of the active drug.

C. Patient Preferences

These are summarized in Table 5. There were significantly more preferences for DSCG than for placebo in the group that took the latter treatment first; but no statistically significant difference in the group that took DSCG first. Patients expressing no preference were not included in the statistical tests. In the total sample, the difference in favour of DSCG just fails to reach significant at the 5 per cent level.

D. Effect in Atopic and Possibly Atopic Patients

Of the four patients with atopic disease, three had the drug order, active-placebo. According to the patients' diary cards, one was better on DSCG, one was slightly worse, and in two patients the difference was very small. Their preferences were: two for placebo, one for active and one neither. In the other four patients, classified as intrinsic (but in whom weak RAST tests and some positive skin tests were found), two had the drug order, placebo-active, and two the reverse. Judging from the diary cards, two were much better, and two slightly better during DSCG treatment. Their preferences were: three for DSCG, and one for placebo.

TABLE 6
Summary of Side Effects.

Treatment	Frequencies of side effects:				Total
	Itching N. irritation	Sneezing	Headache	Others	
Active	4	0	0	2	6
Placebo	3	3	1	6	13

Other Therapy

The concomittent use of other medication, particularly anti-histamines, was minimal, and was equal during both periods of treatment.

Side Effects

Details of all complaints are summarized by type in Table 6. The chief single complaint was of nasal irritation or of itching, but in general the side effects recorded were comparatively trivial in nature and sometimes doubtfully drug-related.

DISCUSSION

IgE mediated (Type I) allergy could be found in only four patients. The other 19 patients had rhinitis of intrinsic type. Since DSCG is believed to act via allergic mechanisms, it was therefore interesting to find that a number of significant differences were found between the active and placebo drugs in the patients investigated. These differences were not caused by an especially good effect in the atopic patients or in the patients with positive RAST or intracutaneous skin tests. In our patients, the effect of DSCG treatment was not related to the results of the allergological investigation.

There was a greater difference between DSCG and placebo treatment periods (both according to patients' preferences and symptoms) in the group which had the drug order, placebo-DSCG, than in the other group. This could be ex-

plained by a relatively long-lasting carry-over effect of DSCG. This phenomenon has been noted in asthma and rhinitis (21) trials using DSCG, but, to date, has not been fully explained. It is perplexing if one accepts the current opinion of the mode of action of DSCG.

Blockage was the predominant symptom, and this improved on the DSCG according to both the clinician's score and the patients' diary cards. In the latter, the difference just failed to reach the 5 per cent level of significance. One must, therefore, assume that the insufflation of a dry powder resulted in adequate disposal over the mucus membrane of the nose and absorption.

We conclude that DSCG in powder form is an effective drug in the treatment of perennial rhinitis. A therapeutic trial of this drug for 4 weeks is worth considering in patients with symptoms of perennial rhinitis, irrespective of the results of RAST and intracutaneous skin tests.

SUMMARY

In this investigation, a double-blind, cross-over trial of sodium cromoglycate in 23 patients with perennial rhinitis was carried out. An improvement in symptoms was found in actively-treated patients, and a greater preference was expressed for active treatment. There was no relationship between response to sodium cromoglycate and the results of allergological investigation. It is concluded that a therapeutic trial of sodium cromoglycate is worth considering in patients with perennial rhinitis, irrespective of the results of RAST and intracutaneous skin tests.

ACKNOWLEDGEMENTS

We wish to thank Fisons Pharmaceutical Division for financial support and statistical analysis.

We also thank Docent S. G. O. Johansson and Docent Leif Wide for measurement of IgE and allergen specific IgE; and Mrs. Barbro Ekblad for technical assistance.

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