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CLINICAL TRIAL OF A TWO PER CENT SOLUTION OF DSCG IN PERENNIAL RHINITIS

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The value of Disodium cromoglycate (DSCG) in the treatment of both seasonal and perennial rhinitis has been studied with a powder formulation applied to the nose by means of a specially designed insufflator (4, 5).

Nasal provocation studies have been carried out using an aqueous solution of DSCG at a concentration of 2 per cent (7, 10). These studies have demonstrated a significant protection of the nasal mucosa against a subsequent challenge with either grass or birch pollen. In one study (10), the investigator assessed the duration of protection by repeated antigen challenges following a single dose of DSCG. The results showed that one dose of DSCG (approximately 1.6 mg) protected the nasal mucosa for at least 4 h. Consequently we decided to investigate the clinical effectiveness of a 2 per cent solution of DSCG administered as a fine spray 6 times daily during the waking hours.

DRUGS AND DOSAGE

DSCG was supplied as a 2 per cent aqueous solution by the manufacturers (Fisons Pharmaceutical Ltd., Loughborough, England), and contained a preservative (Benzalkonium chloride (BKC) 0.01 per cent & EDTA 0.01 per cent). The solution contained a metered dose device which gave a volume of 0.11 ml to

* Fisons Ltd., Pharmaceutical Division, Loughborough, England.

0.15 ml (mean 0.13 ml) per spray. Thus the dose of DSCG applied to each nostril was 2.6 mg. One spray to each nostril 6 times a day gives a mean daily dose of 31.2 mg DSCG, with a possible range between 26.4 and 36.0 mg.

A matching placebo was used, and this consisted of an aqueous solution of BKC and EDTA.

MATERIAL AND METHOD

The trial was designed as a double-blind, crossover study; the DSCG solution and matching placebo were each administered for a period of 4 weeks, the order of treatment being randomised.

Patients were selected on the basis of a history and clinical diagnosis of perennial rhinitis. The disease had to have been present for at least 2 years and had to be of such severity as to have required some form of treatment in the past. The symptoms had to have been present during the whole year, or at least during the winter months. Patients who had in the past been hyposensitised were not excluded, providing they still had symptoms, as it could thus be assumed that this form of therapy had not been successful. Those with nasal polyposis or evidence of nasal infection were excluded.

A total of 49 patients were admitted to the trial. Nine were, however, eliminated from the final analyses: three changed their environment during the trial and could therefore be subjected to a different or even no challenge; two were found to be on other therapy which could influence the disease, e.g. topical steroids and hyposensitive drugs; two did not return following completion of the admission data; and two did not return following the first period of treatment—the latter both received placebo as the first drug.

The characteristics of the 40 patients analysed are given in Table 1. Although the age range of patients is wide, only four were under the age of 16. The duration of the disease was very variable, the mean being 7.7 years. The two most common symptoms were nasal obstruction and rhinorrhea either singly or in combination; both sneezing and itching of the nose were uncommon. Only eight patients had previously been hyposensitised, and all still had symptoms which required treatment.

Patients were divided into two subgroups: 1) *allergic*—based on a sensitivity to common allergens, e.g. house dust, animal dander etc.; and 2) *intrinsic*—based on negative skin tests and also a negative nasal provocation test. The assessment of response was made by both clinician and patient.

The clinician graded the nasal symptoms of blocking, running, sneezing and itching, as well as nasal patency before the trial at the time of crossover, and at the end of the trial. Nasal symptoms were graded on a 0-3 scale as: none, mild, moderate, severe. Nasal patency in each nostril was assessed as open, partially blocked and completely blocked on a 0-2 scale, and thus the examination of the results in both nostrils produced a scale ranging from 0-4.

TABLE 1
Patient Characteristics.

Variable		Value or frequency for:	
		DSCG-Placebo	Placebo-DSCG
Age	Mean	35.1	35.0
	Range	6-69	12-59
Sex	Male	9	6
	Female	10	15
Duration	Mean	7.4	8.0
	Range	3-30	3-25
Seasonality in 1972	All year		
	Jan Feb Mar Apr May	18	20
	Aug Sept Oct Nov Dec	1	0
	Mar Apr May Sept Oct Nov	0	1
Symptom severity	Mild	3	2
	Moderate	9	10
	Severe	7	8
	Moderate/Severe	0	1
Most troublesome symptom	Blocking	8	8
	Running	5	12
	Sneezing	2	0
	Itching	1	0
	Blockage/Running	3	1
Treatment in last 3 months	Antihistamines	17	16
	Nose drops	2	0
	Antibiotics	1	0
	Nitril	0	1
Hyposensitised?	Yes	4	4
	No	15	17
Skin test	House dust	6	5
	Animals	3	2
	Mould/Fungi	2	3
	Aspergillus	1	0
	Flower pollen	1	0
	Tree pollen	0	1
	Negative	11	14

TABLE 1 (cont.)

Variable		Value of frequency for:	
		DSCG-Placebo	Placebo-DSCG
Sense of smell	Present	12	19
	Absent	7	2
Final diagnosis	Intrinsic	13	16
	Allergic	6	5

Patients were provided with diary cards in which they recorded daily their symptoms on a 0-3 scale (none, mild, moderate, and severe) for each symptom.

For the purpose of analysis, the total scores for each month were compared on active and placebo treatment.

Each patient was issued with a supply of one type of antihistamine tablet with instructions to take these only if the coded drug was ineffective. Patients were instructed to record daily the number of antihistamine tablets used, and it was then possible to compare antihistamine consumed on both a DSCG solution and placebo.

A nasal smear was taken from each patient before the trial, at the crossover point and at the end of the trial. The smear was stained according to Holopainen-67 (3), and the degree of eosinophilia was assessed. The number of eosinophils was graded as: - = none or few, + = moderate, ++ = many, and +++ = very many.

At the conclusion of the trial each patient was asked to express a preference for one of the two coded treatments used, or if they were unable to express a preference, this was recorded as a 'no preference'.

RESULTS

The initial symptoms assessed by the clinician are presented in Table 2. The data were not always complete for every parameter, and thus the final sample size analysed was variable. The changes in the clinician's assessment for each of the four symptoms are presented in Table 3. The average score for DSCG was less than that for placebo in all instances, except for sneezing in those patients who received placebo before DSCG. Significant differences were found in all patients for the symptoms of blocking, itching and nasal

TABLE 2
Initial Symptom Severity Assessed by Clinician.

Symptom	Severity	Number of patients for:	
		DSCG-Placebo	Placebo-DSCG
Sneezing	None	7	4
	Mild	5	10
	Moderate	5	6
	Severe	1	1
Blocking	None	1	2
	Mild	2	4
	Moderate	8	9
	Severe	8	6
Running	None	2	0
	Mild	8	3
	Moderate	7	13
	Severe	2	5
Itching	None	10	5
	Mild	3	10
	Moderate	4	6
	Severe	1	0
Nasal smear (eosinophils)	+	7	6
	++	6	12
	+++	4	2
Nasal patency (left nostril)	Open	2	5
	Partially blocked	14	10
	Completely blocked	3	5
Nasal patency (right nostril)	Open	1	3
	Partially blocked	14	13
	Completely blocked	4	4

patency. There were significant differences for the symptoms of sneezing, blocking and rhinorrhea in the group DSCG-placebo.

Analyses of the diary cards are given in Table 4. Significant differences in favour of the active drug were seen for all symptoms, but not for antihistamine usage. The use of anti

TABLE 3
Wilcoxon Matched Pairs Signed Ranks Tests of Clinician's Score.

Variable	Drug order-group	Group size	Mean scores for:		*Wilcoxon T-value	2-tail significance
			DSCG	Placebo		
Sneezing	DSCG-Placebo	18	0.5	1.2	12.0 (13)	$.01 < P < .02$
	Placebo-DSCG	20	0.9	0.8	14.0 (8)	$P > .10$
	All patients	38	0.7	1.0	70.0 (21)	$P > .10$
Blocking	DSCG-Placebo	19	1.2	1.9	19.5 (16)	$.01 < P < .02$
	Placebo-DSCG	21	1.2	1.4	21.5 (11)	$P > .10$
	All patients	40	1.2	1.7	80.0 (27)	$P < .01$
Running	DSCG-Placebo	19	0.9	1.5	12.0 (13)	$.01 < P < .02$
	Placebo-DSCG	21	1.3	1.4	29.5 (11)	$P > .10$
	All patients	40	1.1	1.4	88.0 (24)	$.05 < P < .10$
Itching	DSCG-Placebo	18	0.3	0.8	5.0 (8)	$.05 < P < .10$
	Placebo-DSCG	19	0.6	0.8	15.0 (10)	$P > .10$
	All patients	37	0.4	0.8	35.0 (18)	$.02 < P < .05$
Nasal patency (left nostril & right nostril)	DSCG-Placebo	19	1.0	2.0	7.0 (13)	$P < .01$
	Placebo-DSCG	20	1.0	1.3	35.5 (13)	$P > .10$
	All patients	39	1.0	1.6	78.0 (26)	$.01 < P < .02$
Nasal smear (eosinophils)	DSCG-Placebo	11	1.4	1.9	2.5 (6)	$P > .10$
	Placebo-DSCG	14	1.3	1.5	4.5 (5)	$P > .10$
	All patients	25	1.3	1.7	13.5 (11)	$P > .10$

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

histamine was very variable: many patients recorded a zero score when using both active and placebo solutions, and the average consumption was in fact very low, thus providing little scope for improvement.

There were no significant changes in the degree of eosinophilia of the nasal secretion. However, there was apparently a decrease in the number of eosinophils following treatment with DSCG. The percentage of patients with moderate or severe eosinophilia (++) or (+++) in the active-placebo group fell from 59 per cent to 31 per cent after DSCG, and rose to 53 per cent after placebo. In the placebo-active group,

TABLE 4
Wilcoxon Matched Pairs Signed Ranks Test of Diary Card Monthly Totals.

Variable	Drug order-group	Group size	Mean monthly totals for:		*Wilcoxon T-value	2-tail significance
			DSCG	Placebo		
Blockage	DSCG-Placebo	19	35.4	40.1	40.0 (18)	$.02 < P < .05$
	Placebo-DSCG	21	30.3	38.1	45.0 (20)	$.02 < P < .05$
	All patients	40	32.7	39.1	175.0 (38)	$P < .01$
Running	DSCG-Placebo	19	31.2	38.3	43.5 (19)	$.02 < P < .05$
	Placebo-DSCG	21	30.7	37.3	45.5 (20)	$.02 < P < .05$
	All patients	40	30.9	37.8	169.5 (39)	$P < .01$
Sneezing	DSCG-Placebo	19	16.6	25.7	36.0 (18)	$.02 < P < .05$
	Placebo-DSCG	21	18.2	19.6	99.0 (21)	$P > .10$
	All patients	40	17.4	22.5	248.0 (39)	$.02 < P < .05$
Itching	DSCG-Placebo	19	7.7	14.8	26.0 (16)	$.02 < P < .05$
	Placebo-DSCG	21	16.2	18.0	75.0 (19)	$P > .10$
	All patients	40	12.2	16.5	186.0 (35)	$.02 < P < .05$
Number of antihistamines	DSCG-Placebo	19	6.3	7.9	48.0 (14)	$P > .10$
	Placebo-DSCG	21	17.8	27.0	59.5 (20)	$.05 < P < .10$
	All patients	40	12.3	17.9	199.0 (34)	$.05 < P < .10$

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

there was a fall after placebo from 70 per cent to 53 per cent, and a further fall after DSCG to 27 per cent.

The results of the patients' preferences are given in Table 5. A significant number of preferences in favour of DSCG were expressed in the total sample; there were, in fact, very few "no preferences".

Side Effects

At the end of each period of treatment the investigator recorded any side effects which the patient had noted. These were of a mild nature and generally consisted of nasal irritation, which occurred with equal frequency with both active and placebo solutions (Table 6). No side effect was of sufficient

TABLE 5
Patient Preferences.

Patient group	Number of preferences for:			*2-tail binomial probability
	DSCG	Placebo	Neither	
DSCG-Placebo	13	2	1	0.007
Placebo-DSCG	10	8	1	0.814
All patients	23	10	2	0.035

* Ignoring "no preferences".

TABLE 6
Summary of Side Effects.

Side effect	No. of complaints during treatment:	
	DSCG	Placebo
Nasal irritation	8	9
Headache	1	1
Eczema	0	1
Tiredness	0	1

severity to necessitate cessation of treatment or withdrawal of the patient from the trial.

DISCUSSION

There are many possible etiological factors causing perennial rhinitis. A number of patients will have a proven sensitivity to various allergens. A proportion of patients are classified as intrinsic or vasomotoric. Whether this group do in fact have an allergic element to their disease is not known. In this study, the majority of patients were classified as intrinsic because they had negative skin tests and/or a negative nasal provocation test. Yet all nasal smears examined showed the presence of eosinophils on entry to the trial. The degree of eosinophilia was as follows:

+++	-	6
++	-	18
+	-	13
0	-	0
Not done	-	3
Total	-	40

It has been stated (1) that the presence of eosinophils, goblet cells and mast cells in nasal smears can be taken as evidence of allergic rhinitis. If this is so, then all our patients in this trial could be classified as having allergic rhinitis. The fact that there is an apparent decrease in nasal eosinophilia following the use of DSCG is of interest. The presence of tissue- and secretion eosinophils is thought to be due to the fact that degranulating mast cells release not only histamine but also a specific factor, the Eosinophilic Chemotactic Factor of Anaphylaxis (EFC-A) (8), which attracts eosinophils into the area.

From the experience of a number of investigators assessing the value of DSCG in the treatment of asthma, it would seem that the clinical response is higher in the 'extrinsic' patients than in the 'intrinsic' patients. However, it has been stated that the response to DSCG is good in those patients who have a sputum eosinophilia (6).

The results of this and our previous trial have shown that there is no difference in the degree of the response to DSCG between extrinsic and intrinsic forms of rhinitis. On the basis of this finding and the fact that in both rhinitis forms the number of secretion eosinophils is quite similar, we could assume that the chemical mediators are identical in both forms of rhinitis.

The treatment of perennial rhinitis is, in many cases, unsatisfactory. Antihistamines are often of little value. In our trial, 33 of the patients had previously been treated with them and all had a negative response. Hyposensitisation can only be

employed when a specific allergen has been identified, and even then the results are not always very good.

DSCG in some way protects the mast cells and prevents degranulation, not only when an antigen-antibody reaction is involved, but also when non-immunological factors are important. It has been shown that DSCG will protect mast cells against Compound 48/80, which is a specific degranulator, Phospholipase A and Dextrins (2). In asthma, DSCG has a particular value in preventing exercise-induced asthma in which no specific factors have been isolated as mast cell degranulators (9). Therefore it would appear prudent to conduct a therapeutic trial with DSCG of about 4 weeks' duration in all patients suffering from perennial rhinitis, and then to assess the response. In this study we administered the drug 6 times a day, and we propose to follow patients on an open basis to find out if the frequency of administration can be reduced without loss of control over the symptoms. The incidence of side effects has been minimal and of a very minor nature.

No difference in the occurrence of side effects could be seen when using the drug in powder form or as a solution.

Comparison of the present results with our earlier ones using powder preparation shows that the results are almost the same, even if the dose of DSCG given as solution is only half of that given as powder.

Because of nasal obstruction, it is often difficult to get the powder evenly distributed on the mucosa. This difficulty can be diminished when solution is used, and this and the lower dosage seem to be the most important advantages of the solution.

Special attention is drawn to the fact that no propellant gas is used with this applicator.

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