

DISODIUM CHROMOGLYCATATE IN THE TREATMENT OF PERENNIAL ALLERGIC RHINITIS

By

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It is established that the compound Disodium Chromoglycate (D.S.C.G.) is an effective prophylactic therapy in patients with allergic asthma (*Howell, J. B. L. & Altounyan, R. E. C., Morrison Smith, J. & Davey, G. F.*) and that its efficacy depends on its local action on the bronchial mucosa. It is also recognised that this compound is effective in the treatment of certain subjects with seasonal allergic rhinitis. (*Capel, L. H. & McKelvic, P., Holopainen, E., Backman, A. & Salo, O. P.*). It was decided therefore to evaluate D.S.C.G. in patients with perennial allergic rhinitis. The aim of the trial was to compare by means of a double blind crossover design the relative effectiveness of D.S.C.G. and placebo when administered as a powder to the nasal mucosa.

METHOD

The trial was of 8 weeks' duration. Patients received either active or placebo compounds according to random numbers at the beginning of the trial; and after 4 weeks crossed over to the alternative treatment. Assessment was both subjective and objective. Subjectively the patients were assessed on the following:

- 1) Patient preference: the patients being asked at the end of the trial whether either of the two coded compounds had helped them and if so, which and to what degree.
- 2) Daily symptom scores. These were calculated from Diary cards on which the patient recorded daily and separately the degree of nasal obstruction, of discharge and of sneezing. The score 0 represented no symptoms, one—oc-

casional symptoms, two—intermittent symptoms, and three—constant symptoms. A high total score therefore indicated severe symptoms and a low total score relatively minor symptoms.

3) Clinical assessment by both of us before entry to the trial, at the time of the Crossover and at the end of the trial. As part of this assessment the nasal mucosa was examined and the patients were specifically asked about their sense of smell.

Objectively the patients were assessed by ventilation tests performed through the nose. These tests comprised:

1) Assessment of FEV^1 and FVC and FEV^1/FVC ratios using a Vitalograph machine.

2) Peak flow measurements using a Wright's Peak Flow meter. Three readings were taken during each test, the highest being recorded.

For both these tests a child's (size) anaesthetic mask, applied to the nose, was substituted for the usual mouthpiece.

Nasal Peak Flow (PFN) and Nasal Ventilation readings (FEV^1N , $FVCN$) were taken at the beginning of the trial, at the time of the Crossover and at the end of the trial. Conventional oral FEV^1 , FVC and FEV^1/FVC ratios were assessed at the same times.

Patient Selection

- 1) All patients had had symptoms of perennial rhinitis for at least two years.
- 2) The symptoms were severe in that they did not respond to antihistamines; and were constant and perennial. Patients with seasonal symptoms were excluded.
- 3) The age range was from 10 years upwards.

TABLE 1
Analysis of Patient Preference Data.

Degree of preference	No. of patients who preferred	
	D.S.C.G.	Placebo
Great	7	2
Moderate	8	2
Slight	6	4
Total no. of preferences*	21	8

$$\text{Chi}^2 = 4.966 \quad 0.025 > P > 0.0125^{**}$$

* A further 6 patients were unable to state a preference.

** One tailed probability.

TABLE 2

Patient Preferences^o According to Predominant Symptom on Admission.

Predominant symptom	No. of patients who preferred**		Chi ² *	p §
	D.S.C.G.	Placebo		
Blockage**	9	6		0.304
Discharge	12	3		.018
Sneeze	1	0		
Total	22	9	4.645	0.025 > P > 0.0125

* With Yate's correction.

** One further patient in this group was unable to state a preference.

^o Based on total daily symptom scores.§ One tailed either by binomial or (Chi)² test.

The following patients were excluded; those who had received oral or systemic steroids within the previous three months, those with large polyps occluding the nasal airway, those with infective rhinitis as shown by purulent nasal discharge, and pregnant women. On these terms 40 patients were admitted to the trial.

Drugs

Active consisted of 10 mg D.S.C.G. with 10 mg Lactose supplied in capsules.

Placebo consisted of 20 mg Lactose in similar capsules. The powders were applied by means of special insufflators. The patient was told to blow his nose immediately before insufflation and to try to refrain from blowing it for as long as possible after insufflation. One capsule was insufflated into each nostril four times a day—on rising, at midday, at 5 pm and on retiring to bed.

RESULTS

Of the 40 patients admitted to the trial four did not complete it, one because of pregnancy and three because of lack of interest. One other was subsequently excluded because he was found to have been taking oral steroids throughout. This left 35 patients.

Patient Preference — Of the 35 remaining patients 21 preferred D.S.C.G. and thought it benefitted them; 8 patients

TABLE 3
Analysis of Diary Card Data for All Patients.

Symptom	No. of patients	Scores*		t	p**
		Placebo	Intal		
Blockage	32	38.5 ± 21.7	35.7 ± 24.6	-1.349	N.S.
Discharge	32	32.3 ± 18.7	26.7 ± 15.9	-2.857	0.005 > P > 0.002
Sneezing	32	24.5 ± 14.1	18.5 ± 13.7	-3.458	0.0025 > P > 0.0005

* Mean ± S.D.

** One tailed probability.

N.S. Not significant.

preferred Placebo; 6 patients had no preference and did not think that either compound benefitted them. This information together with the patients' estimate of degree of benefit afforded by each compound is shown in Table 1.

Daily Symptom Scores — Diaries were kept adequately by 32 patients. Judging from these, the most troublesome symptoms while on Placebo were "Blockage" and "Discharge". Total symptom scores were lower in 22 patients while on

TABLE 4
Effect of Treatment on Individual Symptoms.
(32 subjects)

	Blockage	Discharge	Sneeze	"Effective therapy"
	16	20	25	D.S.C.G.
	11	8	6	Placebo
	5	4	1	Neither
Chi ²	0.593	4.32	10.45	
Probability	N.S.	0.025 > P > 0.01	0.002 > P > 0.0005	

Chi² was calculated, using Yates correction, all probabilities are one tailed.
 N.S. Not significant P 0.05.

TABLE 5

Optimum benefit assessed by symptom cards over serial fortnights for both DSCG and Placebo (32 patients)

Weeks	DSCG		Placebo	
	1 & 2	3 & 4	1 & 2	3 & 4
Patients	8	22	13	16
	2 equal		3 equal	

D.S.C.G. and in 9 patients while on Placebo. They were equal in one patient. Of the mainly Blockage patients 9 had lower total scores with D.S.C.G. and 6 with Placebo, one being equal. Of the mainly Discharge patients 12 had lower total scores with D.S.C.G. and 3 with Placebo. The Sneezing patient had lower scores with D.S.C.G. (Table 2). An analysis of mean diary scores is shown in Table 3. This shows significant benefit from the use of D.S.C.G. for discharge and sneezing.

A comparison between the effects of D.S.C.G. and Placebo, symptom by symptom, reveals that *Blockage* was less with D.S.C.G. in 16 patients and with Placebo in 11 patients—remaining unchanged in 5 patients. *Discharge* was less with D.S.C.G. in 20 patients and with Placebo in 8 patients—remaining unchanged in 4 patients. *Sneezing* was less with D.S.C.G. in 25 patients and with Placebo in 6 patients being equal in one patient (Table 4). Here again the figures for

TABLE 6

	Placebo		D.S.C.G.	
	Weeks 1 & 2	Weeks 3 & 4	1 & 2	3 & 4
Blockage	643	594	598	542
Discharge	532	502	443	422
Sneeze	401	401	300	303
	1576	1477	1341	1267
	3053		2608	

TABLE 7

Analysis of Diary Card Data for Patients who Received Placebo First.

Symptom	No. of patients	Scores*		t	p**
		Placebo	Intal		
Blockage	14	40.5 $\pm$ 16.0	32.0 $\pm$ 18.9	-1.912	0.05 > P > 0.02
Discharge	14	38.1 $\pm$ 13.9	29.9 $\pm$ 12.7	-2.518	0.0125 > P > 0.01
Sneezing	14	26.3 $\pm$ 11.1	19.3 $\pm$ 13.8	-2.068	0.05 > P > 0.025

* Mean $\pm$ S.D.

** One tailed probability.

N.S. Not significant.

discharge and sneezing show a significant improvement with D.S.C.G.

When each monthly period was assessed as two separate fortnights and these two fortnights were compared serially, it was seen that the D.S.C.G. cards showed better performances during the second fortnight in 22 patients and in the first fortnight in 8 patients. In two cases the fortnightly scores were equal. The Placebo cards show better performances in the second fortnight in 16 and in the first fortnight in 13, 3 being equal (Table 5).

A comparison of total symptom scores of all the patients through sequential fortnights of the trial showed lower scores for all symptoms and for all periods in the trial, when the patients were on D.S.C.G.; except that the total scores for Blockage for the last Placebo fortnight was less than that of the first fortnight on D.S.C.G. (Table 6). Table 6 also shows serial improvement in scores for all symptoms during the second fortnights of both D.S.C.G. and Placebo treatment except for Sneeze on D.S.C.G.

On analysing mean Placebo diary scores, a comparison between those patients receiving Placebo first and those receiving Placebo after D.S.C.G. showed lower scores for

TABLE 8

Analysis of Diary Card Data for Patients who Received DSCG First.

Symptom	No. of patients	Scores*		t	p**
		Placebo	Intal		
Blockage	18	37.0 $\pm$ 25.7	37.6 $\pm$ 28.6	0.211	N.S.
Discharge	18	27.8 $\pm$ 21.0	24.3 $\pm$ 18.0	-1.511	N.S.
Sneezing	18	23.2 $\pm$ 16.2	17.9 $\pm$ 13.9	-3.065	0.005 > P > 0.0025

* Mean $\pm$ S.D.

** One tailed probability.

N.S. Not significant.

those patients who had received D.S.C.G. before Placebo, but a greater difference between the Placebo and D.S.C.G. scores, when Placebo was given first. (Tables 7 and 8).

Clinical Assessment and Sense of Smell

As a method of assessing the relative efficacy of the two compounds, inspection of the nasal mucosa was not found to be helpful. On the whole the appearance of the mucosa accorded with the patients' opinions of their symptoms, but no proper objective assessments could be made.

At the beginning of the trial 16 of the 35 patients stated that their sense of smell was impaired. Of these 7 noted an improvement with treatment, 6 while on D.S.C.G. and one while on Placebo.

Ventilation Tests

Ventilation tests were performed in 35 patients. In 32 of these complete recordings were obtained for both Conventional and Nasal FEV₁, FVC, FEV₁/FVC ratios and for nasal Peak Flows, at the start of the trial (Control), at the time of Crossover and at the end of the trial.

In one patient Control readings for all nasal tests were unsatisfactory as was the Nasal Peak Flow estimation after D.S.C.G. In one patient Control and Placebo Nasal Peak

TABLE 9
Results of Nasal Ventilation Tests.

Test	Preferred drug		No preferences	Chi ² *	P**
	D.S.C.G.	Placebo			
FEV ¹ (N)	21	12	2	1.939	N.S.
FVC (N)	18	13	4	.516	N.S.
FEV ¹ /FVC (N)	19	14	2	.485	N.S.

* With Yate's correction.

** One tailed.

N.S. Not significant.

TABLE 10
Results of Oral Ventilation Tests.

Test	Preferred drug		No preferences	Chi ² *	P
	D.S.C.G.	Placebo			
FEV ¹	13	18	4	.516	N.S.
FVC	12	19	4	1.161	N.S.
FEV ¹ /FVC	14	14	7	0	N.S.

* With Yate's correction.

N.S. Not significant.

Flow measurements were unsatisfactory. In one patient Placebo and D.S.C.G. Nasal Peak Flow measurements were unsatisfactory. A comparison between D.S.C.G. and Placebo ventilation tests using the nasal vitalograph was thus obtained in 35 patients, while a comparison of Nasal Peak Flows in D.S.C.G. and Placebo treated patients was possible in only 32 patients. In the ventilation tests more patients showed higher performance figures when on D.S.C.G. than when on Placebo—a trend demonstrated for FEV¹, FVC and FEV¹/FVC ratios, but not reaching statistically significant proportions. (Table 9).

The possibility that the nasal ventilation readings were affected by changes in bronchial rather than nasal airway resistance was checked by estimating simultaneously the

TABLE 11

Results of Nasal Ventilation Figures Expressed as Ratio of Oral Ventilation Figures Taken at Same Time.

Ratio	Preferred drug		No preferences	Chi ² *	P**
	D.S.C.G.	Placebo			
FEV ¹ (N)/FEV ¹	22	13	1		.500
FVC(N)/FVC	22	11	2	3.03	0.05 > P > 0.025
(FEV ¹ /FVC(N))/ (FEV ¹ /FVC)	21	14	0	1.029	N.S.

* With Yate's correction.

** One tailed.

N.S. Not significant.

ventilatory capacities by conventional oral rather than nasal means. These results are shown in Table 10 which demonstrates that nasal insufflation of D.S.C.G. or Placebo did not affect bronchial air flow. An additional cross check was afforded by dividing the patients' nasal ventilation figures by their conventional oral ventilation figures taken on the same days. (Table 11). The results so obtained did not differ materially from the results obtained by estimating the nasal figures alone. (Table 9).

TABLE 12

Comparison of Nasal PF in D.S.C.G. and Placebo Groups.

Compound giving optimum performance	No of patients
D.S.C.G.	19
Placebo	11
None	2
Chi ² *	1.633
P	N.S.

* With Yate's correction.

N.S. Not significant.

TABLE 13

Comparison of Patients Optimum Performances by Nasal Ventilation and Peak Flow Results—Pretreatment (Control), on Placebo and on D.S.C.G.

Variable	No. of patients whose best performance is on:			Chi ² *	P
	Control	Placebo	D.S.C.G.		
Highest FEV ¹ (N)	2	12	20	17.776	<0.01
Highest FVC (N)	5	13	15	4.068	N.S.
Highest FEV ¹ / FVC (N)	4	13	17	6.597	<0.05
Highest Peak Flow (N)	8	8	15	2.332	N.S.

* With Yate's correction.

N.S. Not significant.

A comparison of Nasal Peak Flows showed that a majority of patients had higher flows after D.S.C.G. than after Placebo (Table 12). Here again the differences are not statistically significant.

These results, all of which imply that D.S.C.G. benefits the clinical features of Perennial Rhinitis depend for validity on an assurance that the insufflation of Lactose (Placebo) does not itself aggravate those symptoms. A comparison of pretreatment—Control—Ventilation and Peak Flow results with those obtained after Placebo and D.S.C.G. afforded an opportunity to examine this possibility. Table 13 shows that, except with Nasal Peak Flow tests, more patients registered their optimum performances while on placebo than they did at the time of the control tests.

A breakdown of the 31 patients in whom Nasal Ventilation tests were performed, and who also kept diaries, into groups according to whether they were primarily affected by obstruction or by discharge demonstrated that those patients whose main symptom was discharge rather than blockage had higher results and generally responded better to D.S.C.G. (Table 14).

TABLE 14

Summary of Analysis of Various Tests in 15 Patients with Discharge,

Variable	Control	Placebo	D.S.C.G.	S.E. †	F §
Mean Nasal FEV ¹ in ml	1353.3	1553.3	1721.7	105.9	3.028
Mean Nasal FVC in ml	3150.0	3188.3	3500.0	93.5	4.214*
Mean Nasal FEV ¹ in ml	42.8	48.3	50.4	4.1	0.918
Mean Peak Flow in ml	181.7	181.3	205.3	11.9	1.345

Summary of Analysis of Variance Test in 16 Patients with Blockage.

Variable	Control	Placebo	D.S.C.G.	S.E. †	F §
Mean Nasal FEV ¹ /FVC%	1145.3	1456.3	1504.7	86.	5.142*
Mean Nasal FVC in ml	2800.0	3251.6	3289.1	145.5	3.498*
Mean Nasal FEV ¹ /FVC%	44.2	47.1	48.0	2.6	0.576
Mean Peak Flow in ml	165.6	170.9	175.6	8.5	0.344

Values in body of table are means for control (C), Placebo (P) and D.S.C.G.

(1) periods.

† Standard error calculated during analysis of variance.

§ Variance ratio.

* $P < 0.05$.

DISCUSSION

These results suggest that D.S.C.G. plus Lactose nasal insufflations are more effective than plain Lactose insufflations, when assessed by every method used in this Trial, the comparative figures reaching a degree of statistical significance in the cases of Patient Preference, Diary Counts, Improvement of Sense of Smell and FVC(N)/FVC. The results also show that over a period of one month D.S.C.G. insufflations retain their effectiveness and that after stopping them, there is no rebound exacerbation of symptoms. There may even have been some increase in the effectiveness of the compound as shown by assessment over sequential fortnights of treatment; (Tables 5 and 6) and some carry-over of effect after cessation of treatment (Tables 7 and 8). D.S.C.G. was more effective in patients whose main symptoms were discharge or

sneezing (Tables 2 and 3) and more effective in abating those symptoms (Tables 3 and 4). It was less helpful in the treatment of Blockage. This difference may be due to the fact that the powder does not reach such a wide area of the mucosa in patients with nasal obstruction. Thus patients treated by local insufflations of this sort should have as clear an airway as possible, obstructions such as polyps being removed first. Sometimes too a particular obstructive difficulty might be overcome by giving a short course of oral steroids before starting insufflations.

The measurement of nasal airflow presents difficulties and it is not suggested that the use of a Vitalograph and of a Wright's Peak Flow Meter, as described, is necessarily the best or most accurate means available; the methods are relatively simple however and the results obtained in this trial are consistent with those obtained by the subjective parameters. We believe that they provide a valid assessment of nasal airflows in the same patient under varying conditions. It has been seen that the nasal insufflation of D.S.C.G. had no effect on the ventilation tests as measured conventionally by mouth (Table 10) and that the pattern of D.S.C.G. to Placebo effectiveness was unchanged when the nasal results were weighted by the integration with them of the conventional Ventilation figures (Table 11). Analysis of Ventilation and Peak Flow results according to whether the patients complained mainly of Blockage or mainly of Discharge confirm the higher figures in the Discharge group. This at once vindicates the accuracy of the patients' assessment of their own predicament and the validity of the tests. The superior effectiveness of D.S.C.G. in Discharge patients demonstrated by the Diary Scores is confirmed by Ventilation Tests (Table 14).

The Ventilation Tests and the Peak Flow readings imply that some patients obtained benefit from continued use of Lactose (Placebo) (Table 13). The benefit was not so great as that conferred by D.S.C.G. + Lactose; but one may deduce either that the regular insufflation of intranasal

Lactose by itself was beneficial in some of these patients, or that their awareness that they were taking part in a trial which was designed ultimately to benefit them led to improved results after the start of the trial. At the same time this improvement in Ventilation Test results when Placebo is compared with Control excludes the possibility, which would vitiate the apparent superiority of D.S.C.G., that the Placebo aggravated the nasal symptoms.

While taking the case histories of these patients the importance of an intact of smell sense especially to women two of whom had previously set fire to their kitchens, became evident. Improvement in the sense of smell was noted in 7 out of 16 affected patients, 6 while on D.S.C.G. and 1 while on Placebo.

No serious side effect from the use either of D.S.C.G. or Placebo were reported by any of the patients; but in one, the insufflation of D.S.C.G. was immediately followed on occasion by a sneeze. This also occurred with two patients on Placebo, and in one other it occurred with both D.S.C.G. and Placebo. One patient complained of slight soreness of the nose with D.S.C.G., and one other with Placebo.

SUMMARY

In a double blind crossover trial of two months duration nasal insufflations of Disodium Chromoglycate and Lactose were found to be superior to insufflations of pure lactose in the treatment of patients with perennial allergic rhinitis. Results were assayed subjectively by Patient Preference, Daily Symptom Scores and Assessment of nasal airflow using a Vitalograph machine and a Wright's Peak Flow Meter.

ACKNOWLEDGEMENTS

We are indebted to Dr. G. W. Scott, Guy's Hospital, for his suggestions on nasal airway assessment and to our colleagues Dr. R. S. Crow and Mr. J. W. T. Dixon, and the late Dr. G. D. Middleton for their help in referring patients to

us; to Mr. P. Mills, Head of Data Processing, Medical Group, Fisons Limited, and to Miss Cheryl Shum for her technical assistance with the Ventilation tests.

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