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DISODIUM CROMOGLYCATÉ NASAL SPRAY IN ADULT PATIENTS WITH PERENNIAL RHINITIS

By

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INTRODUCTION

Since *Altounyan* (1) 1967 found that inhalation of disodium cromoglycate (DSCG) was capable of preventing allergen-provoked attacks in asthmatics, several double-blind trials have demonstrated significant effect of DSCG compared to placebo in the treatment of asthmatic patients (4, 7). It was therefore natural to examine the effect of the substance on similar processes in nasal mucosa. A protective effect of DSCG on allergen provocations of the nasal mucosa was demonstrated by *Engström* (3) and by *Taylor & Shivalkar* (9). In double-blind trials DSCG has been found to have an effect on seasonal rhinitis (5, 9), but not all studies confirm that DSCG is significantly better than placebo (8). Recently DSCG has also been found to have effect on perennial rhinitis (6, 10).

In the above mentioned trials DSCG was used powdered and was applied by means of a special insufflator. The patients received 10 mg DSCG in each nostril 3-4 times daily. Although the frequency of local side-effects at the place of application has been surprisingly low, the powder, which strains the mucociliar apparatus, is no ideal form of administration. It is doubtful, how effectively the drug is distributed over the

entire mucous surface, particularly if the passage of air is reduced on account of abundant secretion and swelling of the nasal mucosa. Patients with perennial rhinitis often have a rather heavy nasal secretion, but the mucosa may intermittently be quite dry, which is also unfavourable in the insufflation of powder.

In an attempt to find a better mode of administration of DSCG to nasal mucosa we have used an aqueous 2 per cent solution of DSCG*, first in an open trial and then in a double-blind cross-over trial in patients with perennial rhinitis.

MATERIALS AND METHOD

The patient material comprises 40 adult patients with perennial rhinitis of at least one years duration. The mean age was 34.7 years and the mean duration of the disease 6.5 years. They all suffered from two or three of the following symptoms: sneezing, watery discharge and nasal blockage on account of a swollen mucosa. A few patients had small nasal polyps, but in none of them this was the dominating symptom. As the patients were admitted from the allergy clinic of Rigshospitalet, to which patients are referred from the whole country, they usually had more vigorous symptoms than an average of patients with perennial rhinitis. None of them were in treatment with corticosteroids, but some used antihistaminics, which had to be maintained during the entire trial. Several patients had previously been in hyposensitization treatment. All patients underwent an otorhinolaryngologic and an allergologic examination including intracutaneous tests. 2-4 blood samples were taken for determination of circulating eosinophilic leucocytes and nasal smears were also examined 2-4 times.

Open Trial

15 patients took part in this trial. For one month they used a 2 % aqueous solution of DSCG in a spray bottle, which delivered 0.5 mg DSCG per squeeze. In diary cards the patients graded sneezing, discharge, and blockage with a scale from 0-3. Before and after treatment nasal smear and nasal biopsy from the inferior turbinate were taken. The biopsy was fixed in formalin, embedded in paraffin, cut into 10 μ m thick sections, and dyed with hematoxylin-eosin. Nasal smears were dyed in 30 + 30 seconds in May-Grünwald's and Giemsa's liquids.

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Double-Blind Cross-Over Trial

27 patients started this trial (regarding their dates, see table I). 2 were left out quickly on account of pregnancy and mental disease. The nasal spray differed from the above mentioned in containing 0.02 % thiomersal as preservative. Apart from this, the manner of administration was as in the open trial. The patients were treated for 4 weeks with DSCG and immediately after for 4 weeks with placebo or conversely. The sequence of the two sets of sprays was

TABLE
Data on Patients in the

Patient Number	Initials	Age and sex	Allergy demonstrated by Patients' history, intracutaneous tests and if necessary, nasal challenge	Blood Eosinophilia ($> 400/\text{mm}^3$)
24	SN	20 F	pos	—
10	KKA	55 M	neg	—
4	AB	35 F	pos	—
25	ABH	28 F	neg	+
16	KWS	54 M	neg	+
3	MB	17 F	pos	—
2	HM	46 M	pos	—
29	MC	14 M	pos	—
15	ES	69 M	neg	+
18	AD	14 F	pos	+
17	PT	33 M	pos	+
12	KMJH	20 F	neg	—
9	SK	63 M	neg	—
8	OM	24 M	neg	+
7	LM	36 F	neg	—
1	NJ	32 F	pos	—
26	JH	24 M	pos	—
21	EE	69 M	neg	—
20	BA	33 F	pos	—
23	RL	31 F	neg	—
14	SRH	22 M	pos	—
11	MT	52 F	neg	—
22	EFA	16 M	neg	—
6	JH	27 F	pos	+
5	BB	34 F	pos	—

made at random. In this way 12 patients received DSCG initially followed by placebo, and 13 patients received placebo initially followed by DSCG. The code was not broken until the end of the trial. After the two periods of 4 weeks the patients were examined and questioned about side effects. At the end of the trial the patients were asked, whether there was any difference with regard to the two sets of spray bottles, and if so which one was the better. Scores from the last three weeks of each period of treatment were registered. To avoid carry-over effect scores from the first week of the periods were not used.

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Double-blind Cross-over Trial

Eosinophilia in Nasal Smear (i. e. when the eosinophils constitute $\geq 10\%$ of total leucocytes diffuse or $\geq 50\%$ focal in the smear)	Duration of Nasal Symptoms in Years	Dominating Symptom	Preference of Nasal Spray
+	1	sneezing	DSCG
+	1	sneezing	DSCG
+	3	blockage	DSCG
+	1	sneezing	DSCG
+	2	blockage	DSCG
+	5	sneezing	DSCG
+	4	sneezing	DSCG
+	2	blockage	DSCG
+	25	blockage	placebo
+	4	blockage	placebo
+	12	blockage	placebo
+	11	sneezing	none
—	10	blockage	none
+	10	blockage	none
+	14	sneezing	none
+	15	sneezing	none
+	3	sneezing	none
+	4	sneezing	none
—	3	sneezing	none
+	2	blockage	none
—	15	sneezing	none
—	3	sneezing	none
—	3	blockage	none
—	5	sneezing	none
—	4	blockage	none

TABLE 2

The effect of Disodium Cromoglycate Nasal Spray on the Subjective Symptoms in Patients with Perennial Rhinitis in the Open Trial

Symptomfree	0 patients
Considerable improvement	4 patients
Moderate improvement	3 patients
Slight improvement	2 patients
No improvement	6 patients

RESULTS

The patients' opinion of the treatment with DSCG nasal spray in the open trial appears from Table 2. There was no observable change in the appearance of the mucosa during the treatment. The blinded examination of nasal smears did not show any reduction of the grade of eosinophilia, and neither did the histopathological examination of the biopsy specimens.

In the double-blind trial the patients stated, whether they preferred the DSCG-period or the placebo-period, or whether there was no difference. The results appear from Table I. Only 21 of the 25 patients had filled in the diary cards so satisfactory that the figures could be used. The results of the diary cards appear from Table 3. No patients became quite free of symptoms during the treatment, but 4 were significantly better in the DSCG-period (patient no. 24, 10, 4 and 25). 4 other patients grew somewhat better in the DSCG-period and 3 grew somewhat better in the placebo-period. As will be seen from Table 3, there is practically no difference between the total scores of the last three weeks of the DSCG- and the placebo-period with regard to blockage. The greatest difference in favour of the DSCG-period is found with regard to sneezing and discharge. The differences are significant for both symptoms ($p < 0.05$)*.

If the material is divided into sub-groups, however, two interesting facts appear. In the first place in case of the 8

* paired t-tests.

TABLE 3

Clinical Data for Each Patient in the Double-blind Cross-over Trial. Sum of Scores for the Last 3 Weeks in Each Period of Treatment

Patient Number	Sneezing		Discharge		Blockage	
	DSCG	Placebo	DSCG	Placebo	Placebo	Placebo
24	3	37	1	18	3	30
10	24	32	25	29	4	7
4	26	63	31	63	45	63
25	8	36	20	43	5	16
16	33	43	54	63	57	63
3	13	14	22	28	23	31
2	2	15	5	16	3	15
29	9	21	29	29	26	35
15	1	9	29	35	18	16
18	13	7	26	15	25	20
17	1	2	38	28	46	35
12	36	29	27	40	9	0
8	5	2	27	26	26	21
7	18	21	26	26	0	0
1	51	52	55	59	0	0
26	23	16	27	20	21	13
21	24	35	16	28	8	20
20	31	22	46	38	4	0
23	28	31	51	52	38	40
14	22	30	28	27	25	19
22	4	0	37	40	35	17

Total Scores

in 21 Patients: 375 517 617 723 421 461

patients who preferred the DSCG-preparation, the average duration of symptoms is only 2.5 years, while it is 8.4 years for the remaining patients. 0/8 of the patients who preferred the DSCG-preparation had had symptoms for more than 5 years, while this was the case in 8/18 of the remaining patients. Secondly 8/8 of the patients, who preferred the DSCG-preparation had eosinophilia in the nasal smear, while this was only the case in 10/17 of the remaining patients.

Four patients complained of a mild nasal irritation immediately after the use of placebo and one after use of the

DSCG-preparation. The inconveniences were mild and the administration was not interrupted. No other side effects were noticed in connection with the spray.

DISCUSSION

Although the mechanism for the effect of DSCG in allergic states has not yet been quite elucidated, there are many indications that the substance inhibits the degranulation of the mast cells and thus counteracts the liberation of histamine in the tissue. It could, therefore, be expected that DSCG would diminish the allergic inflammatory process by reducing dilatation of blood-vessels, mucosal oedema, and eosinophilia. This was not the case in our trial, which may indicate that DSCG did not have the effect on the mast cells which could be expected. This is in agreement with the poor clinical effect, and explains why none of our patients became free of symptoms and why only 8 of 40 patients showed a considerable improvement. If our results are compared with the results of other authors (6, 10) one does not get the impression that the nasal spray as used in our trial represents an improvement compared with the use of DSCG as powder. Our material shows that no effect can be expected on blockage, and that the best effect of DSCG is seen in patients with nasal eosinophilia and symptoms of short duration.

As low-molecular substances in aqueous solutions are absorbed very quickly from the nasal mucosa, a possible explanation of the comparatively poor effect of the spray may be that there is not constantly a concentration of DSCG which is sufficiently high to prevent the mast cells from degranulating. Furthermore it is probable important that DSCG is distributed all over the mucosa of the shock organ, as allergic reactions could otherwise take place in unprotected areas, producing sneezing, discharge, and nasal blockage. In the conjunctiva the liquid can get in contact with the entire surface of mucosa, and a good effect of 1 per cent DSCG eye drops has been demonstrated in vernal keratoconjunctivitis (2).

Five patients complained of a slight nasal irritation in connection with the use of the spray. This is probably due to the preservative thiomersal. There were, however, no indications that this slightly irritating effect drowned a favourable effect of the DSCG.

In conclusion the DSCG spray in this trial had a less favourable effect on a majority of the patients than could be expected. It seems likely that a too low and intermittent concentration of DSCG in the nasal mucosa may be the explanation. On the other hand in provocation trials of patients with seasonal rhinitis several authors have concurrently obtained a good protective effect of both DSCG powder and DSCG in aqueous solution. A probable explanation of this difference may be that the symptoms in the provocation trial are due to a mere type-I allergic reaction, whereas the symptoms in perennial rhinitis may be due to additional non-immunologic mechanisms, e. g. changes in the innervation of the blood-vessels, hyperirritability of the mucosa, "priming of the end-organ", bacterial infection, etc.

In this connection it is of interest to note that in the present study no effect of DSCG nasal spray has been found in patients with symptoms for more than 5 years. This might support the idea that even if a perennial rhinitis has been initially released by type-I allergic reactions, the symptoms are in the course of time produced by non-immunologic mechanisms. The DSCG nasal spray in our trial had only effect on patients with eosinophilia in the nasal smear, which similarly suggests that eosinophilia in the nasal smear shows to what extent type-I allergic reactions take place in the nasal mucosa of patients with perennial rhinitis.

The present results show that the 2 % DSCG nasal spray is insufficient in the clinical treatment of the majority of patients with perennial rhinitis. As there are good experimental reasons for assuming that DSCG has a protective effect on the allergic nasal mucosa, trials with DSCG as nose drops in a higher concentration and in a more viscous liquid will be continued.

SUMMARY

A 2 % aqueous solution of disodium cromoglycate (DSCG) in a nasal spray was tested on adult patients with perennial rhinitis. In an open trial 9 out of 15 patients reported an effect of the medicament. However, after one month's treatment there were no signs of a normalizing of the nasal mucosa, judged by rhinoscopy and by examination of nasal smears for eosinophilia. In a double-blind cross-over trial on 25 patients 8 preferred DSCG, 3 preferred placebo and 14 patients had no subjective effect neither of DSCG nor of placebo. Analysis of diary cards showed that DSCG was significantly better than placebo as regards sneezing and discharge. DSCG had the best effect on patients with eosinophilia in the nasal smear and with short duration of symptoms.

LITERATURE

1. *Althounyan, R. E. C.*: Acta allergol. 22, 487, 1967.
2. *Easty, D. L., Rice, N. S. C. & Jones, B. R.*: Clinical allergy 2, 99, 1972.
3. *Engström, I.*: Acta allergol. 26, 101, 1971.
4. *Georg, J., Hansen, I. & Pedersen-Bjergaard, J.*: Acta Med. Scand. In press.
5. *Holopainen, E., Backmann, A. & Salo, O. P.*: Lancet 1, 55, 1971.
6. *Hopper, I. & Dawson, J. P.*: J. Laryng. Otol. 86, 725, 1972.
7. *Hughes, W. F., Tse, K. S. & Arbesman, C. E.*: J. Allergy 45, 132, 1970.
8. *Smith, J. M.*: Lancet 1, 295, 1971.
9. *Taylor, G. & Shiwalker, P. R.*: Clinical allergy 1, 189, 1971.
10. *Thorne, M. G. & Bradbeer, W. H.*: Acta allergol. 27, ..., 1972.

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