

From the E.N.T. Department and the Department of Pathology, Odense Sygehus, Odense, and the E.N.T. Department, Viborg Sygehus, Viborg, Denmark.

DISODIUM CROMOGLYCAT (LOMUDAL®) IN THE TREATMENT OF HAY FEVER

by

P. ILLUM, U. MEISTRUP-LARSEN, J. MOESNER, K. OLESEN &
S. Z. OLSEN

Previous experimental studies have demonstrated, that Disodium Cromoglycate (DSCG) can protect patients with hay fever from attacks following exposure to the specific allergen.

The mode of action is not fully understood. It is presumed, that DSCG inhibits the degranulating effect of the antigen-antibody reaction on the mast cells and in this manner prevents the liberation of histamine and other compounds, which are of importance in triggering the allergic reaction. Electron microscopic studies have shown, that mast cells, pretreated with DSCG, remain intact following antigen-antibody challenge, inasmuch as the granula of the cells becomes surrounded by a thick homogenous zone, which apparently prevents the content of the granula from being released (9). This mode of action of the drug differs from that of other known therapeutic compounds for the treatment of allergic diseases. It is thus a prophylactic compound and has no effect on an allergic attack already in progress. It is rapidly destroyed within the organism and must therefore, in order to be effective, be administered topically to the mucous membranes that it is to protect.

Altounyan (1) showed in 1967 that DSCG could protect patients against attacks of asthma. Thereafter reports appeared on trials of treating the closely related disease hay fever

with the compound. These investigations were partly carried out in the laboratory and partly as clinical studies.

Engström (4) showed that after prophylactic intranasal administration of DSCG to children with birch pollen allergy considerably higher concentrations of pollen were required to trigger a hay fever attack. *Taylor & Shivalkar* (10) demonstrated, using rhinomanometry, that DSCG inhibits the usual nasal stenosis brought about by the antigen-antibody reaction. The clinical trials have given diverging results. A very convincing effect was demonstrated in Finland by *Holopainen et al.* (7) and by *Engström et al.* (5) in Sweden, whereas the trials in England (2, 3, 10) have given less definite results. *Taylor & Shivalkar* (10) explain this as a result of geographic and climatic variation in the exposure to antigen challenge. The higher stable air concentration of birch pollen in Scandinavia must give more ideal trial conditions than the more fluctuating grass pollen concentration in England.

The previous clinical trials have been carried out by the insufflation of DSCG in powder form into the nose. A few local side-effects in the form of itching and a feeling of dryness in the mucosa of nose and throat have been observed. Systemic toxic side-effects have not been seen neither during prolonged treatment of patients with asthma nor during trials on hay fever patients.

DSCG is now available as a 2 per cent aqueous solution for administration by a special spray bottle. We have employed this form of administration in a double-blind study using DSCG/placebo in the treatment of grass pollen hay fever in Denmark in the period 1st to 21st of June 1972.

MATERIAL AND METHODS

The material consists of 38 patients who all fulfilled the following criteria: Symptoms of hay fever requiring treatment in the grass pollen season for at least 2 years and a typical positive intracutaneous and nasal provocation test for grass pollen. However, 1) patients with total nasal obstruction, or simultaneous pollen asthma requiring treatment, 2) children under the age of 15 years and 3) pregnant women were excluded.

The trial period commenced on the 1st of June and continued for the following 3 weeks. The patients were examined before start of the trial, after 1 week, and at the conclusion. Intracutaneous tests using three common grasses (*Avena elatior*, *Dactylis glomerata*, and *Phleum*) were carried out at the first examination. The grass giving the strongest reaction was employed for the nasal provocation test. The following laboratory studies were performed: Erythrocyte sedimentation rate, leucocyte and differential count, eosinophile cell count and determination of serum IgE.

A special ear-nose and throat examination was carried out, special regard being taken to the occurrence of a reduced air passage owing to nasal polyps, hypertrophy of the concha, septum deviation and adenoids. The possible allergic appearance of the mucosa and the amount and type of nasal secretion was noticed at all three examinations. In addition a sample of nasal secretion was taken for counting of eosinophilic cells according to the method of Hansel (6) in which the results are given using a semiquantitative scale from 0 to ++++. Further a biopsy of the concha was taken for histological examination at the last physical examination. The biopsies were fixed in cetyl pyridinium chloride in order to facilitate the evaluation of the mast cells.

Code marked spray bottles containing DSCG in 2 per cent solution or placebo, sufficient for the whole trial period, were given to the patients at the first examination, using double-blind technique. The patients were instructed to squeeze the bottle twice into each nostril. They were also instructed to blow the nose first and to take the first dose immediately after awakening in the morning, and subsequently every third hour of the waking day. A supplement of antihistamine tablets (Tavegil® of 1 mg) was given to each patient at the same time. It was emphasized that the tablets should be used only if the symptoms, despite spray treatment, became so severe that they were considered absolutely necessary. All other treatment was avoided as far as possible during the period of study.

Each patient recorded on a dairy card the type of symptoms, their severity, possible consumption of antihistamine tablets and information as to their general condition. The individual symptoms, nasal obstruction, nasal secretion, sneezing and nasal itching were graduated according to a points system, using a semi-quantitative scale (0 = no symptoms, 1 = a single attack or slight symptoms, 2 = frequent attacks or moderate symptoms, 3 = constant attacks or severe symptoms). Symptoms from the eyes were merely registered as yes or no.

The patients were questioned at the last control examination regarding their subjective evaluation of the treatment and possible side-effects.

RESULTS

One of the 38 patients failed to come to the control examination. On opening the code it was found that there were 19 patients in the DSCG group and 18 in the placebo group. On

TABLE 1.
The Patients Evaluation of the Treatment.

	DSCG	Placebo
Success	14	7
Failure	2	6
Indifferent	3	5
Total	19	18

statistical analysis it was seen that the two groups were fully comparable with regard to age, sex, family disposition, duration of symptoms and severity of these, including previous asthma requiring treatment.

There was no significant difference between the two groups as regards physical appearance of the nasal mucosa, amount of secretion, or its appearance.

A large number of parameters were evaluated blindly and semiquantitatively during the histological examination of the biopsy taken from the concha. No significant difference was found between the DSCG and placebo groups, especially regarding the occurrence of eosinophilic cells and the relation between the mast cells containing granula and those degranulated. The biopsies have, however, not been subjected to electron microscopy.

TABLE 2.

	DSCG (19 patients)			Placebo (18 patients)		
	Before	Week 1	Week 3	Before	Week 1	Week 3
0	14	12	12	10	8	7
+	4	4	4	5	3	1
++	0	2	2	0	2	2
+++	1	1	1	3	5	8

Table 2: Eosinophile cells in the nasal smear before, after 1 week and after 3 weeks of treatment with DSCG/placebo.

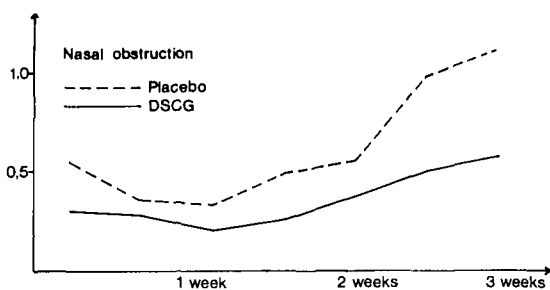


Fig. 1.

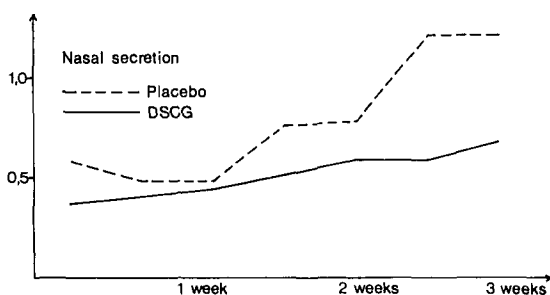


Fig. 2.

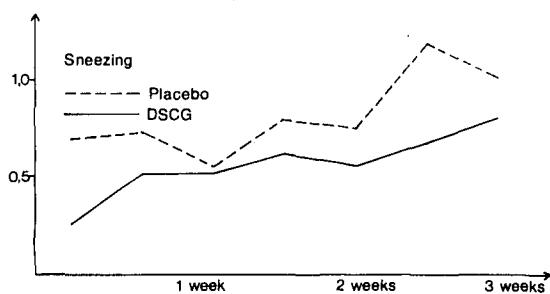


Fig. 3.

Fig. 1-3.

Nasal secretion, nasal obstruction and sneezing, given as the daily score per patient for the DSCG and placebo groups respectively.

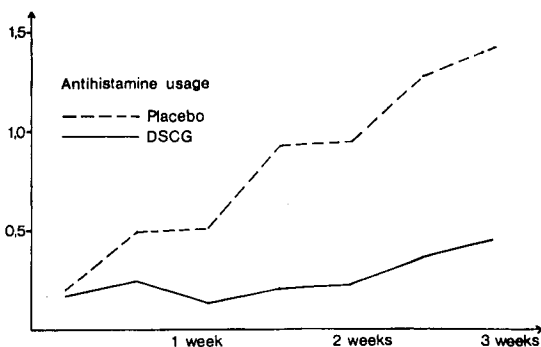


Fig. 4.

Daily consumption of antihistamine tablets per patient.

Patients in both groups of the study evaluated the treatment, on the whole, as a success; however, it was possible to demonstrate a more favourable evaluation by the DSCG group ($p < 0.1$). (Table 1).

The number of eosinophilic cells in the smear of nasal secretion taken before, after one week and three weeks of treatment is shown in Table 2. At the end of the trial significantly more eosinophile cells were found in the placebo group ($p < 0.05$, using Spearmans rhotest). The diary cards were completed by 35 patients, since one patient from each group (both with severe symptoms) had either forgotten to fill in the card or done so incorrectly. The statistical evaluation of the results showed, as could be expected, no effect on the eye symptoms; this agrees with the presumption that DSCG has to be applied topically. (Dropping DSCG into the conjunctival sac has not been attempted in this study, but can be carried out without risk according to other investigators). Evaluation of the general condition of the patient did not reveal any difference between the two groups (Mann-Whitney test).

Evaluation of the three symptoms: Nasal obstruction, nasal secretion and sneezing (Figures 1, 2, 3) demonstrated, when the study is considered as a whole, that these symptoms were significantly less pronounced in the DSCG group than in the

placebo group ($p < 0.1$). In the third week of study, when the weather was at its best, a significantly higher value was found for the symptom: nasal secretion ($p < 0.05$). A significantly higher consumption of antihistamine tablets (Figure 4) in the placebo group than in the DSCG group ($p < 0.05$) was found (in the third week only: $p < 0.01$). It should be mentioned that within the period of study four patients in the placebo group supplemented or replaced the antihistamine tablets given them with other drugs belonging to the same group, and that one patient also in the placebo group received an injection of a depot steroid. None of the patients in the DSCG group considered it necessary to make recourse to other drugs.

It was not possible to demonstrate any significant difference between the two groups with regard to the symptom: nasal itching, this agrees with the experience of other investigators, that nasal itching is the most unspecific of the symptoms in the complex, and that it occurs particularly in the initial phase of the disease.

Four patients in the DSCG group and two in the placebo group complained of slight irritation in the throat during the study. No systemic side-effects could be demonstrated during the treatment.

DISCUSSION AND CONCLUSION

It is remarkable that the difference in the results in the DSCG group and the placebo group manifest themselves most clearly in the third week of the study (Table 2, Figure 1-4). This must be related to the weather, which in the two previous weeks had been rainy, and in the last week more dry and with more sunshine. It is well-known that the symptoms of hay fever are more pronounced in periods with stable, dry weather, which presumeably bring about a higher concentration of pollen in the air. Daily counts of the pollen concentration during the period under study failed unfortunately owing to a defect in the apparatus.

A number of drugs are already available for the treatment of hay fever, the most effective of which is probably depot steroid. A far more difficult problem is the treatment of non-seasonal allergic rhinitis owing to the side-effects of prolonged use of depot steroids. Hopefully the favourable results obtained by us in the present study can be transferred to the treatment of non-seasonal allergic rhinitis, as these diseases have undoubtedly a closely related trigger mechanism. This presumption is strengthened by the good results obtained by *Holopainen et al.* (8) in the treatment of patients with allergic rhinitis of non-seasonal character, using DSCG intranasally in a cross-over study.

Treatment of non-seasonal rhinitis with sympathomimetic drugs in the form of nasal drops or spray is not advisable since these when used for longer periods induce a secondary hypertrophic rhinitis, which leads to increased use of the drug, in other words a regular misuse. At the present stage of our knowledge of DSCG nasal spray this is very unlikely to occur.

The spray employed in the present study has been found effective in the treatment of hay fever. Although it is unlikely to replace the previous forms of therapy we consider it an important and harmless alternative. In slight cases the spray can be used as the only treatment, in severe cases it can be employed as a valuable supplement.

SUMMARY

A double-blind clinical study of Disodium Cromoglycate (DSCG) in the treatment of hay fever was carried out using 37 patients in the period 1st to 21st of June 1972. A significantly lower number of eosinophilic cells were demonstrated in the nasal smears in the DSCG group and the consumption of antihistamine tablets was significantly lower in this group also. The symptoms: nasal obstruction, nasal secretion and sneezing were significantly more pronounced in the placebo group, particularly in the last week of the study, where the weather

was considerably more dry and sunny than in the previous two weeks of the study.

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