Pharmacology and activity of disodium cromoglycate in the nose

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SUMMARY

Disodium Cromoglycate will inhibit the allergic response when given before but not after an antigen challenge. The drug appears to stabalize the cell membrane and to prevent the release of the chemical mediators of anaphylaxis. D.S.C.G. has proved to be of value in the treatment of perennial rhinitis. Not all patients are helped, and those in whom sneezing and watery discharge are the dominant symptoms, respond best. It is probable that the immunological reaction in these patients is mediated by Ig E. There is a second group of patients whose main problem is nasal obstruction and this symptom is much less frequently relieved by D.S.C.G. Ig G. is probably the most important immunglobulin in this group.

INTRODUCTION

DISODIUM Cromoglycate is the only fundamentally new drug which has been introduced for the treatment of allergic diseases during the past decade, although of course during this time there have been some developments in Steroid and immunotherapy. It now seems to be an opportune moment to review the numerous basic scientific and clinical investigations which have been made on this drug, with particular reference to its role in the treatment of nasal disease.

Chemically DSCG is the disodium salt of 1,3-bis (carboxychrom-5-yloxy)-2-hy-

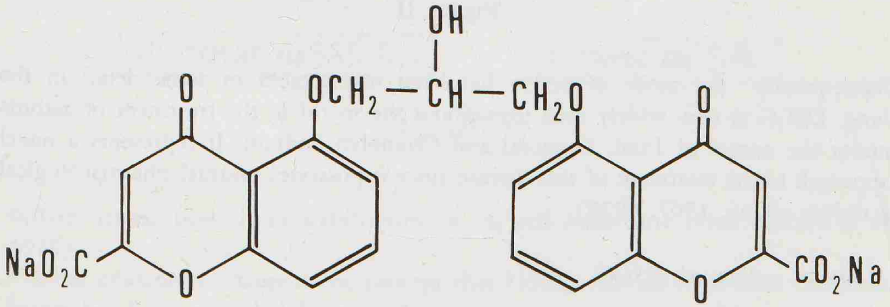

Figure I

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droxy propane. It is a white crystalline material readily solube in water and is odourless although it has a slightly bitter taste.

The initial investigation showed that DSCG inhibited the allergic response in the lung when inhaled before an antigen challenge but that it had little or no protective effect if inhaled after a challenge (Altounyan, 1967).

Protective effect of disodium cromoglycate against antigen aerosol challenge

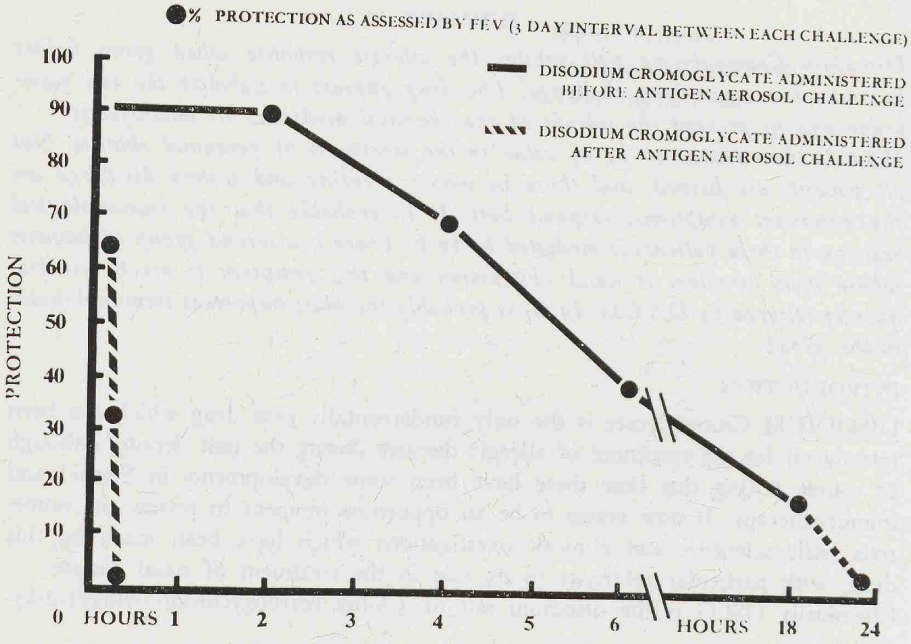

Figure II

Subsequently the mode of action has been investigated in some detail in the lung. DSCG is now widely used throughout the world in the treatment of asthma under the names of Intal, Lomudal and Cromolyn Sodium. It represents a novel approach to the treatment of this disease since it possesses unusual pharmacological activities. (Cox, 1967, 1970).

Mode of action of DSCG

Studies in the anamal model have shown that DSCG prevents the release of pharmacological mediators of anaphylaxis. It does not prevent the fixation of reaginic antibody on to the surface of the mast cell nor does it prevent the interaction between antigen and fixed antibody. The action is probably one of hyposensitization of

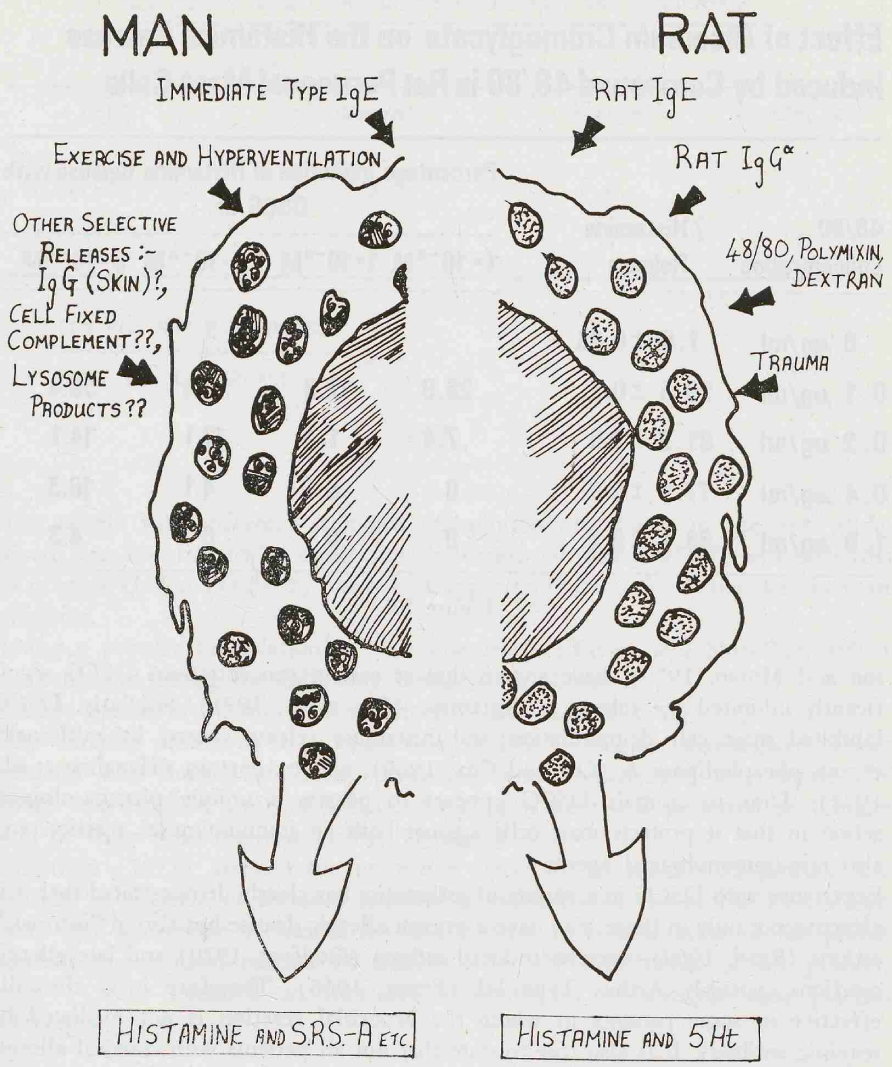

Figure III

certain tissues, possible by stabilization of the cell membrane (Orr, Pollard et al., 1970).

Further evidence to support the concept that DSCG stabilizes the mast cell membrane has been provided by animal experiments where it has been found that DSCG will maintain the integrity of the mast cell when specific non-immunological degranulating compounds are used. Experiments with Compound 48/80, which is described as a selective release of histamine from rat mast cells (John-

Effect of Disodium Cromoglycate on the Histamine Release Induced by Compound 48/80 in Rat Peritoneal Mast Cells

48/80 Concentration	% Histamine Release	Percentage Inhibition of Histamine Release with DSCG at:			
		1×10^{-5}M	1×10^{-4}M	2.5×10^{-4}M	5×10^{-4}M
0 µg/ml	1.60 ± 0.03				
0.1 µg/ml	29.5 ± 0.7	26.9	12.9	59.4	59.4
0.2 µg/ml	61.2 ± 1.5	7.4	1.5	12.1	14.1
0.4 µg/ml	77.1 ± 0.8	0	6.6	4.1	16.3
1.0 µg/ml	85.1 ± 0.5	0	0	0	4.3

Figure IV

son and Moran, 1970), have shown that at certain concentrations DSCG significantly inhibited the release of histamine (Orr et al., 1971). Similarly, DSCG inhibited mast cell degranulation and histamine release caused by rattlesnake venom phospholipase A (Orr and Cox, 1969), and by dextran (Hanahoe et al., 1972). Thus in animals DSCG appears to possess a unique pharmacological action in that it protects mast cells against both an immunological reaction and also non-immunological agents.

Experience with DSCG in a variety of asthmatics has clearly demonstrated that it is effective not only in those who have a proven allergic disease but also in "intrinsic" asthma (Read, 1969), exercise induced asthma (Godfrey, 1970) and late allergic reactions, possibly Arthus Type III (Pepys, 1968). Therefore it is clinically effective in some patients in whom the bronchial reaction is not mediated by reaginic antibody. It is also true to state that not all patients with classical allergic airways disease respond (Altounyan and Howell, 1969).

Clinical experimental studies in the nose

Nasal challenge studies have been performed using both DSCG powder and also an aqueous solution.

Taylor and Shivalkar (1971) studied a group of subjects sensitive to grass pollen by intracutaneous tests. The nasal sensitivity of each subject was assessed and defined as that concentration of pollen which doubled the baseline Nasal Airway Resistance (NAR). DSCG was then administered either as a solution or powder 15 minutes before the antigen challenge and the protective effect measured by changes in the NAR.

EFFECT OF SOLUTIONS OF DSCG INDUCED NAR INCREASES

DSCG	10mg/ml	20mg/ml	40mg/ml
NO EFFECT	8	4	9
EFFECT (*)	13	17	12

* $\frac{\text{CONTROL NAR \% INCREASE}}{\text{DSCG NAR \% INCREASE}} > 2$

Figure V

The results with different strengths of solution are shown in the next slide. There was no statistically significant difference between the different strengths (Cochrane Q Test PO.2-0.1) however it appeared that a 2% solution was the most effective.

Using a powder formulation at two dose levels (Taylor and Shivalkar, 1971) of 1 mg and 10 mg the following results were obtained.

Clearly a dose of 10 mg is more effective than that of 1 mg.

The duration of activity of a single dose of DSCG was also investigated. Those subjects who showed an initial protection were rechallenged at 4 hours. Of those who received 1 mg of DSCG, 5 out of 8 were still protected at 4 hours and of those who received 10 mg, 12 out of 15.

Engstrøm (1971) assessed the protective effect of 10 mg DSCG powder and placebo in a group of children sensitive to birch pollen. 10 of the 13 children were able to tolerate at least a ten-fold increase in concentration of the pollen applied to the nasal mucosa 10 minutes after the insufflation of the powder, only 1 child tolerated an increased concentration of antigen with placebo (P0.006).

D.S.C.G. powder in allergic rhinitis

Taylor and Shivalkar

	1 mgm	10 mgm
No effect	10 (53%)	9 (29%)
Effect	9 (47%)	22 (71%)
Total	19	31

$0.2 > P > 0.1$

Figure VI

Positive response to challenge (Taylor)

	Immediate (type I)	Late (type III)
Nasal challenge	54 (100)	20 (37)
Skin test	54 (100)	16 (30)

Figure VII

Further challenge studies have been performed by Taylor (1973) and Jenssen (1973) who used a 2% aqueous solution of DSCG and also by Pelikan et al. (1970) who used a 1% solution.

Only Pelikan et al. (1970) have carried out challenge experiments on patients sensitive to house dust, they found that the application of a 1% solution of DSCG gave significant protection.

In all the challenge studies a proportion of subjects were not apparently protected by DSCG. The reason for this remains obscure; it does not appear to be related to either local or systemic sensitivity or to any other obvious parameter.

Taylor (1971) suggests that fundamentally different mechanisms operate in the two groups; this idea is supported by recent work by Bryant et al. (1973) who suggests that in asthma the majority of patients have a immediate reaction mediated by IgE but a minority have an IgG mediated reaction. The authors suggest that DSCG responders belong to the IgE group and non-responders to the IgG group. A similar situation may exist in rhinitis.

Clinical use of DSCG in rhinitis

This subject can be conveniently discussed under two broad headings, a short term disease, seasonal rhinitis (hay fever) and a more chronic long term diseases, perennial rhinitis. For the purposes of this article we will discuss only the latter. The diagnosis and treatment of this disease has for many years presented problems to the clinician. One main problem is that of terminology. Should the disease be classified as allergic based only on positive skin test or should one consider other investigations such as nasal challenge, IgE estimations, examination of nasal secretions or nasal biopsy? A positive skin test is probably obtained in only 60-65% of patients. However, those with a negative response can still be classified as allergic on the basis of nasal examination and, therefore, the diagnosis of vasomotor rhinitis of unknown aetiology should be limited to very few patients. The use of wiped nasal smears has been advocated (Bryan and Bryan, 1959); who noted that a marked increase of goblet cells was a reliable feature in smears obtained from allergic patients and they therefore regard the presence of goblet cells as a fairly definite sign of allergy. Murray and Anderson (1969) found no association between goblet cells and clinical evidence of nasal allergy; this study was undertaken in children and it is possible that in the young, goblet cells do not easily foliate in that there is difficulty in obtaining a wiped smear.

Trials carried out with DSCG have included patients with proven allergic

perennial rhinitis and also those in which an allergic diathesis has not been shown. It would appear from the analysis of results that the question of allergy is of little importance with regard to the clinical response. Analysis of the individual symptoms of perennial rhinitis have shown that in some trials sneezing, rhinorrhoea and nasal obstruction have improved significantly when compared with placebo (Holopainen et al., 1973; Sunderman and Crawford, 1973), however, other investigators have only been able to show that sneezing and rhinorrhoea are improved (Thorne and Bradbeer, 1972; Mygind et al., 1972). From observations of a large number of studies it is evident that those patients who have a thin watery secretion and sneezing respond to DSCG whereas those who complain of nasal obstruction show a minimal response, this was noted in both "allergic" and "intrinsic" groups. A large unpublished trial clearly demonstrates this point (McAllen and Littlejohn).

	Analysis	
	Preference	Diary cards
Allergic runners	P = 0.01	2 Parameters significant
Allergic Blockers	P = NS	0 Parameters significant
Intrinsic runners	P = 0.01	3 Parameters significant
Intrinsic blockers	P = NS	0 Parameters significant

Figure VIII

These facts suggest that perennial rhinitics fall into two main categories which differ clinically, immunologically, histologically and in their response to DSCG. Although no accurate survey has been conducted on the symptomatology of perennial rhinitis there is an impression that the majority of patients complain predominently of sneezing and rhinorrhoea and that such patients can often be classified as allergic. It seems possible that in such patients the immediate type reaction is mediated by IgE and therefore a good response to DSCG would be anticipated. The minority of patients complain of nasal obstruction and it seems likely that these have a different immunological reaction which may be biphasic or mediated by IgG. It appears that in this group the histological changes in the mucosa are those of chronic inflammation.

It has been demonstrated (Booij-Noord et al., 1972) that some asthmatics on challenge show a dual response with an immediate and late reaction. Likewise, in a group of hay fever subjects (Taylor and Shivalkar, 1971) have shown that all have an immediate skin an nasal reaction to challenge, a proportion have a late skin reaction (30%) and also a late nasal reaction (37%).

It was noted that the immediate reaction was accompanied by nasal discharge and sneezing but in the late reaction patients complained of nasal obstruction. The late skin reaction resembled an Arthus Type III reactivity and biopsies showed inflammatory cell infiltration which was perivacular in distribution, unfortunately no biopsies were taken of the late nasal reaction.

A recent study (Brain et al.) in which a 2% solution of DSCG was used, biopsies

Engstrøm

Nasal provocation - Birch pollen concentration

Patient No.	Control	D.S.C.G.	Placebo
1	-4	-4	-4
2	-2	-1	-2
3	-3	-1	-3
4	-5	-2	-5
5	-5	-4	-4
6	-2	Undiluted	-2
7	-4	-3	-4
8	-7	-4	-5
9	-4	-1	-3
10	-5	-5	-4
11	-6	-5	-6
12	-4	-1	-4
13	-4	-3	-4

Figure IX

of the nasal mucosa were taken from a few patients both before and after therapy. It was noted that a minority of patients had a histological picture of chronic inflammatory cellular infiltration of the submucosa similar to that seen in the skin by Taylor; these patients did not respond to DSCG.

It is possible therefore that perennial rhinitis presents in two different forms. The common type is the patient who complains of sneezing and rhinorrhoea, the reaction being mediated by local IgE with degranulation of mast cells release of histamine resulting in vasodilation, tissue oedema and a watery secretion; these patients respond to DSCG. The second group complain of nasal obstruction presumably because they have both an immediate and late reaction and the latter predominates, this in turn results in chronic inflammatory changes in the submucosa which is thickened; such patients are unlikely to respond to DSCG which has no anti-inflammatory action.

The use of DSCG in the treatment of nasal polyps has been investigated by Donovan and Kapadia (1972). Patients were divided into sub groups labelled reaginic, doubtfully reaginic and non reaginic. All subjects selected were awaiting polypectomy and therefore one assumes that they had moderate to severe symptoms. The results showed that there was a significantly greater reduction of sneezing in the reaginic compared to the non reaginic but no significant reduction in rhinorrhoea except in those patients who had fewer sneezing attacks. The authors conclude that DSCG has a limited role to play in the management of nasal polyps; they also raise the question as to whether patients can be placed into one of two groups; the first are reaginic and such patients complain of sneezing and rhinorrhoea, the other are non reaginic in which other immunological mechanisms are responsible for their symptoms. It would appear that there is some similarity between perennial rhinitis and nasal polyps and one questions the relative roles of IgE in the disease.

Side effects

Only very rarely does one find a drug which is effective and also extremely safe. In the many hunderds of patients who have been treated with DSCG for rhinitis, the number of side effects reported has been very few. It is common for patients to complain of nasal irritation but it is very difficult to know whether this is a symptom of the disease or whether it is due to a direct effect of a dry powder or a solution on a sensitive mucosa. A survey of clinical trials using Rynacrom powder has shown a total incidence of side effects reported to be 5% and of these the majority are nasal irritation, some patients have stated that the powder produces sinus pains or headaches but these have not been troublesome as the patient has continued in the trial.

CONCLUSIONS

There is no doubt that DSCG either applied as a powder or solution is efficacious in the treatment of rhinitis, nevertheless there is a minority of patients who do not respond and the reason for this is not yet clear. It is suggested that the tissue reaction and therefore the clinical symptoms, depend on the immunological reaction and that this may be mediated by IgE or possibly IgG. There appears to be a correlation between symptomatology, histological changes, immunological reactions and response to DSCG but this has not yet been established. If this is proven then not only will there have been a major advance in the understanding of rhinitis but also an advance in the treatment of this disease.

RÉSUMÉ

D.C. inhibe la reponse allergique, s'il est administré avant et non pas après une provocation antigène. Ce produit semble stabiliser la membrane cellulaire et empêcher la décharge des médiateurs chimiques d'anaphylaxie.
D.S.C.Q. a prouvé sa valeur dans le traitement de la Rhinite pérennielle. Tous les malades ne sont pas sonlagés et ceux chez qui l'éternuement et l'écoulement aquiuse sont les symptomes prédominants ont les meilleurs résultats. Il est probable que la réaction immunologique, chez les malades est par l'intermédiaire de Ig E. Il y a un deuxième groupe de malades dont le principal symptome est l'obstruction nasale et ce symptome est bien moins souvent sonlagé par D.S.C.Q. Ig C est probablement le (? la) plus important(e) immunglobulie dans ce groupe.

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