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Prophylaxis and Treatment of Food Allergy with Disodium Cromoglycate

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Introduction

A very recent and up-to-date review on this subject has been published [1], but the author is known as a member of the medical team of the firm which produces the drug disodium cromoglycate (DSCG) and he was associated with much of the development of its gastrointestinal use [1]. Therefore an independent assessment of the usefulness of the drug and its role, if any, in gastrointestinal and systemic symptoms of food allergy is needed. We shall review the major studies published in this field since 1973 [2], and we shall discuss the results of our own experiences with this drug, some of which are still unpublished. It is important to state here that all co-authors are members of different medical faculties at Italian Universities, and have no financial involvement with the manufacturer of DSCG. The opinions expressed and the conclusions obtained are solely derived from their experience with the use of the drug, partly previously reported [3–6].

The Rationale for DSCG Use in Food-Allergic Reactions

The drug was developed by Altounyan for the treatment of asthma, but later it was found to be effective also in the treatment of allergic rhinitis and conjunctivitis. Local administration of DSCG at different body sites generated the ques-

tion as whether its action was due to mast cell membrane stabilization. The different types of mast cells present in different tissues and the *in vitro* studies of their sensitivity to DSCG led to the conclusion that the drug would not be useful in treating food-induced symptoms, since skin and intestinal mast cells were not always inhibited *in vitro*. We would have three lines of objection to these conclusions: (1) Some of the studies were performed in elegant animal models whose relationship to human disease is to be demonstrated. (2) Other modes of action of DSCG may be important, and they have not been addressed in the *in vitro* studies. (3) The effectiveness of DSCG is substantiated by the review of the literature and by our experiences.

In the following paragraphs we shall briefly discuss these points. It is important that the reader be aware of the basic fact that we have no satisfactory explanation for the pathogenesis of most symptoms induced by foods, and the present knowledge allows simply to identify the link between a food and the occurrence of a (any) symptom, by validated and time-consuming procedures as DBPCFC, but not the exact mechanism involved. In fact, even if we restrict our discussion to reactions occurring in sensitized patients, i.e. with positive skin reactions to food extracts or specific IgE detectable by *in vitro* methods, the presence of such IgE alone cannot predict the clinical sensitivity of the patient when exposed to the food. Therefore the association of response to DBPCFC and presence of specific IgE may represent a casual event, and it is not a satisfactory way to label the reactions observed as IgE-mediated [7]. Putting the argument in a slightly different light, one should postulate two types of IgE antibodies, only one of them connected with the occurrence of symptoms (as suggested by Lichtenstein [8]). So no firm conclusion about the implication of IgE in the pathogenesis of food-allergic reactions can be drawn until the paradox of people with specific IgE but showing no reaction to the food(s) is resolved. Polla and co-workers [9] have recently argued that the key mechanism in controlling food hypersensitivity is the induction of T-cell tolerance, which can be achieved by oral administration of antigen.

What Is the Mode of Action of DSCG?

No clear conclusive mechanism of DSCG action has been established. The mast cell stabilizing hypothesis does not hold for many mast cell types in different tissues, despite the effectiveness of the drug in systemic mastocytosis [10], particularly on gastrointestinal symptoms. A recent hypothesis suggests that it may work also through inhibition of tachykinins [11]. *In vitro* effects of DSCG have also been described on B lymphocyte switch, inhibiting IgE production at the transcriptional level [12].

Table 1. Review of double-blind studies on DSCG [data from 1]

Author	Year	Cases n	End-point	Outcome
Basomba	1977	20	subjective	positive
Vaz	1978	14	subjective	positive
Harries	1978	10	objective	negative
Kocoshis	1979	14	objective	positive
Ellul-Micallef	1983	20	objective	positive
Papageorgiou	1983	4	objective	positive
Onorato	1986	5	objective	positive
Carini	1987	14	subjective	positive
Wesley	1988	10	subjective	negative
Pelikan	1989	38	objective	positive
Sasai	1992	3	objective	positive

Review of the Literature 1973–1995

Ideally, only studies conducted in a double-blind, placebo-controlled fashion should be evaluated. However, in the field of food allergy other important variables to consider are the diagnostic tests applied to correctly diagnose food allergy, and the objective end-points, i.e. assessed by third-party observation or by measurement of biological relevant parameters. Unfortunately, very few studies have been conducted with all these characteristics. Therefore we shall start by briefly considering the set of studies reviewed by Edwards [1] (table 1).

Of the 11 studies considered, including a total of 152 patients with variously assessed food allergy, 7 (with 94 patients) had objective measurements as end-points, and 6 of them were in favor of a protective effect of DSCG. The remaining 4 studies (58 patients) with subjective or mixed end-points were also in the majority (3 out of 4) showing a significant benefit with the active drug compared with the placebo.

Collins-Williams [13] wrote an extensive review of studies up to 1985, slightly overlapping with those already examined. Businco and Cantani [14] conducted a meta-analysis of 12 clinical trials with DSCG in atopic eczema, including a total of 281 patients. The duration of treatment varied from 1 week to 3 months, the dose was within the usual range (10–50 mg/kg/day), the end-point was clinical in 6 and by means of challenge in the other 6. Eight studies showed beneficial effects of DSCG administration, whereas 4 demonstrated lack of

effect. Limiting the analysis to the 6 double-blind studies, half were in favor and half against the efficacy of DSCG. The largest study on atopic eczema was conducted by Mikawa et al. [15] in Japan. This multicenter study included 169 patients and concluded that beneficial effects on symptoms were observed in 59% of cases receiving DSCG, compared with 36% of those on placebo after 8 weeks ($p < 0.05$). Patients with asthma and eczema showed the greatest benefit. When also a dietary regimen was adopted, the proportion of patients showing improvement rose in both groups, but still with an advantage for the use of DSCG.

The message from this review of the literature can be summarized as follows: (1) Many studies comprise small numbers of poorly diagnosed food allergy, or have not been conducted in double-blind fashion. (2) The dose of DSCG and the duration of administration varied among the studies. (3) The balance seems to tip towards the presence of beneficial effects of the drug. This may also occur because negative results are less often reported.

Personal Experiences with DSCG

DSCG has been shown to inhibit the appearance of symptoms in food provocation tests [3, 4, 16, 17]. This experience has been repeated by different groups, using doses of 1–1.5 g administered shortly before the challenge. In some studies, intestinal absorption of macromolecules has been measured, and constantly found to decrease [3, 4, 16]. Although the precise mechanism of this effect is unclear, it is not unreasonable to link decreased absorption to inhibition of inflammation and lack of symptoms. It may be proposed that DBPCFC be repeated with premedication with DSCG in order to select those patients who will benefit from this drug when needed (see Conclusions).

A separate multicenter study has been conducted in Italy, including a total of 428 patients with diarrheic type of irritable bowel syndrome (DIBS), i.e. the largest series ever published [18]. This study followed the indication that this subgroup of patients might benefit from DSCG, emerging from previous published reports from the leading group, based in Bologna [6, 19]. In the present study, exclusion diet, restricted to very limited types of foods, was compared with a free diet plus 1.5 g/day of DSCG for 4 weeks. Serious side effects were experienced in 6 patients who dropped out of the study, and consisted in fatigue and headache in those on diet, and urticaria, tremor and gastric pain in the 3 on DSCG. Weight reduction and fatigue were the most common complaints in the diet group, whereas nausea and abdominal discomfort in cases on DSCG. Non-adherence to diet caused exclusion of 29 patients, and irregular assumption of the drug excluded 15 patients. The remaining 346 evaluable cases, equally dis-

Table 2. Eosinophilic gastroenteritis due to food allergy

	Diet		Diet + DSCG	
	before	after	before	after
Symptoms	10	1	10	0
Serum ECP	26.3	21	27.8	10.3*

Ten patients were studied in each group of treatment, but only 5 each for measurement of serum eosinophil cationic protein (ECP), determined by the Pharmacia CAP System with mean values expressed as $\mu\text{g/l}$. * $p < 0.01$.

tributed among the two groups, demonstrated that after 4 weeks the effects of diet and DSCG administration without diet were superimposable: 78 and 82% respectively had mild or absent symptoms, compared with 27% having mild symptoms at the beginning of the trial. The percentage of those with severe symptoms also fell dramatically from 13 and 14% (baseline) to 3 and 2% after 4 weeks. These effects were more pronounced in patients with positive tests for IgE antibodies to foods. This study shows the clinical efficacy of DSCG in this syndrome, and its possible application in cases with poor compliance with the diet. Cost should not represent a problem, since patients with irritable bowel syndrome usually abuse many symptomatic drugs (antispasmodics, antidiarrheics, antibiotics and tranquilizers).

Another important study has been conducted in Chieti on 20 patients affected by eosinophilic gastroenteritis and food hypersensitivity. Diagnosis was established by gastroduodenoscopy, biopsy histology, SPT, specific serum IgE, and food challenge (open). In this very selected group, either exclusion diet or diet + 1.5 g/day of DSCG were randomly assigned for 3 months. Foods identified as causing symptoms were cow's milk, cheese, egg white, tomato, apple, peas, cod, chicken and in 1 case gluten (with negative tests for antigliadin antibodies, antiendomysial, negative small bowel biopsy; symptoms consisted in urticaria, without diarrhea). After 3 months a second biopsy was performed and eosinophilic infiltration graded from 1 to 4 using number of eosinophils $\times 100$ magnification field (values below 15, or without glandular infiltration were considered as negative). Symptoms disappeared in all patients except 1 on diet only (table 2) who still complained of diffuse itching. The eosinophil infiltration index decreased significantly only in the group treated with DSCG in addition to diet. Serum eosinophil cationic protein was measured in 10 cases (both diet and

diet + DSCG); mean levels decreased only in the group treated with DSCG. After 12–20 months 7 cases participating in this trial underwent another endoscopic examination with gastric biopsy. In 2/4 patients treated with diet only, the histology was similar to that observed prior to diet. In the other 2 cases a massive eosinophil infiltration was present (40–50 cells p.m.f. at 100 $\times$). The other 3 cases treated with DSCG in addition to diet had continued the diet, with 4 months on and 4 off treatment with the drug. All 3 showed 18–20 eosinophils p.m.f. at 100 $\times$, without glandular infiltration.

This study contributes to another field of food allergy, rarely described as typical due mainly to the invasive methods for diagnosis, and in this disease DSCG seems to be effective in blocking the reactivation of the inflammatory process leading to appearance of symptoms.

Conclusions

We propose that DSCG helps food-allergic patients although this may not be true in the individual case. Its use may be either limited to a single large dose on special occasions (planned breaks in elimination diets for social reasons, work or travel), or continuously given in chronic diseases or presence of multiple food allergies. A short trial with the drug, or its use prior to a challenge, may help to select the patients who will benefit from it.

In eosinophilic gastroenteritis, perhaps also in gastric mucosal damage, associated with sensitivity to foods, and in DIBS, our studies open the possibility that DSCG actively contributes to decrease tissue damage and switch off the disease process.

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