

Sodium cromoglycate in childhood atopic dermatitis treatment

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Atopic dermatitis is a common disease of childhood that is often related to food hypersensitivity (1). In the treatment of allergic disease, especially of airways, sodium cromoglycate (SCG) has been successfully used in addition to symptomatic drugs (2, 3). More recently SCG has been evaluated for the treatment of food allergy. SCG, synthesized in 1965, is the salt of a bis-chromone carboxylic acid (4). The chromone, called Khellin, is derived from the seed of *Ammi visnaga*. It is not lipid-soluble and thus is poorly absorbed (0.8%) through the intestinal mucosa, is not metabolized, and is excreted via urine and bile (5). SCG, therefore is believed to act in the gastrointestinal tract before absorption. Although its exact mechanism of action is not understood completely it is thought to inhibit mediator release from mast cells (MC) (6).

In man, two populations of MC are found. The first, similar to rodent mucosa MC, is found in lung and gastrointestinal mucosa, and contains only tryptase (T mast cell); the second, similar to rodent peritoneal MC, is found in skin and gastrointestinal submucosa, and contains tryptase and chitinase (Tc mast cell).

SCG is reported to inhibit histamine release only in rat peritoneal MC, and so also may have a variable effect in human MC (7). However, human lung and gastrointestinal MC do not respond differently to functional and pharmacological stimuli. It is possible that effectiveness of drugs varies in the same cluster of MC because of differing responses to changes in stages of activation or maturity (8).

More recently, clinical studies have shown that SCG inhibits membrane receptor expression, and the cytotoxic capacity of leucocytes

and *in vitro* activation of human neutrophils, eosinophils and monocytes (9, 10). Given orally, SCG is reported to reduce absorption of ovalbumin (11) and α -lactalbumin (12), circulating immunocomplexes after food ingestion (13) and intestinal permeability to sugars (14).

In food allergy the effectiveness of SCG may be mediated by an anti-inflammatory action or other unidentified mechanisms (15) that probably reduce the intestinal uptake of macromolecules. SCG appears to be a safe drug and there are few reports of side effects.

Adverse reactions associated with oral administration are: lethargy, gastroenteritis, dermatitis, myositis, pulmonary infiltration and eosinophilia.

SCG is currently available in Italy for oral use as capsule (100 mg) or powder (250 mg). In the past, the capsule was made of a lactose carrier that could worsen lactase deficiency or could be contaminated with cow's milk proteins: but now capsules are lactose-free.

CLINICAL STUDIES

a) Personal studies

In a first study (16) we selected 13 children presenting atopic dermatitis with allergy to cow's milk and/or egg and/or fish, who improved after elimination diet.

SCG was administered at a dose of 200-400 mg four times a day 15 min before ingestion of the offending foods. SCG was effective in 8 patients at a dose of 800 mg/24 h, and in 2 children at a dose of 1600 mg/24 h without significant differences between the two groups.

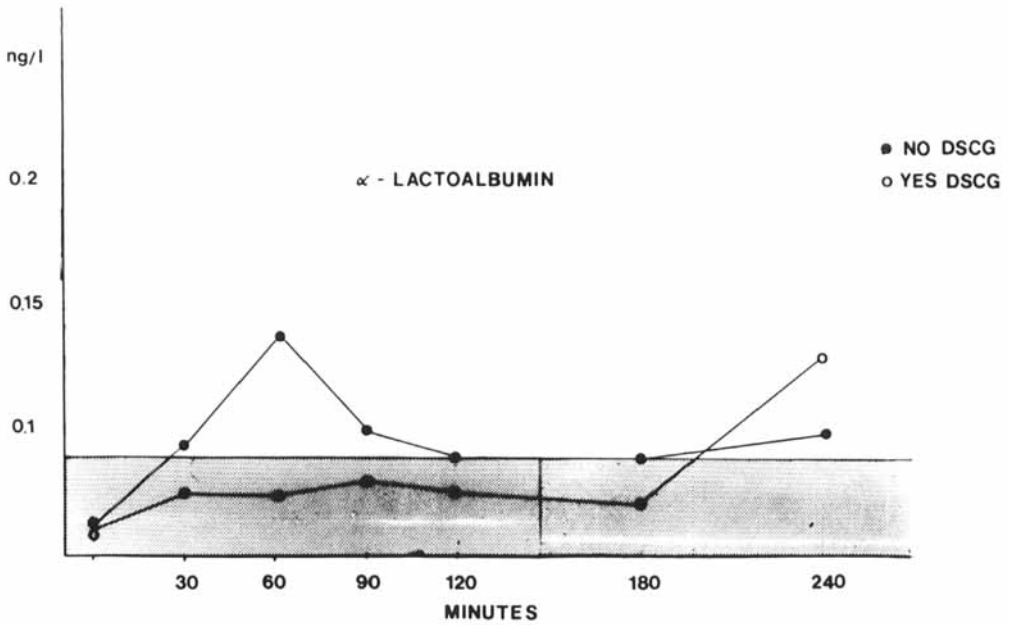


Fig. 1. Serum α -lactalbumin levels after challenge with or without sodium cromoglycate (DSCG) administration.

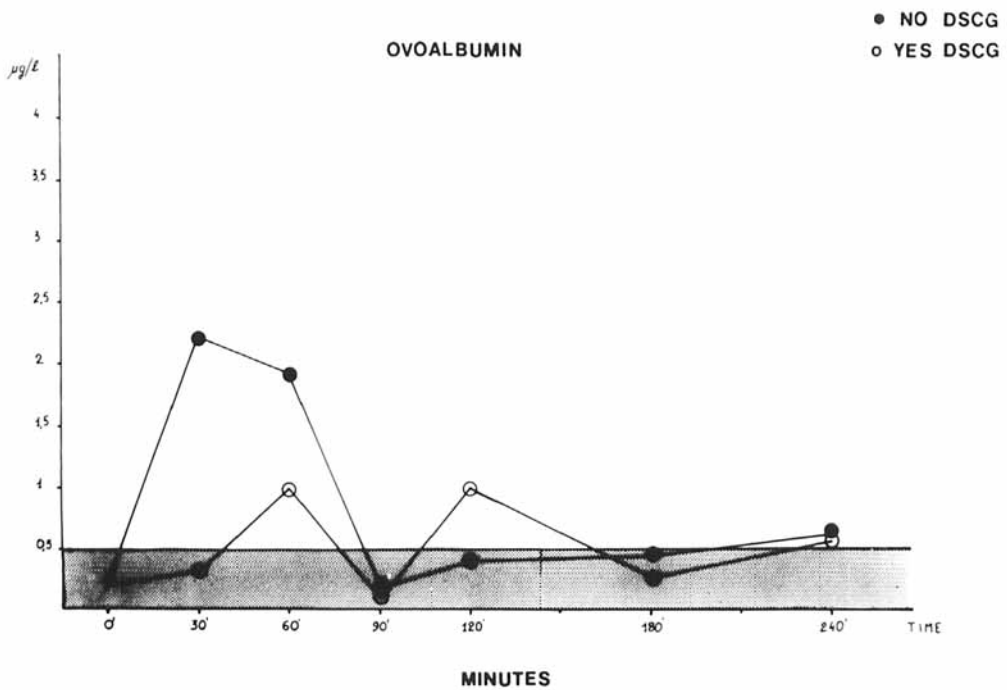


Fig. 2. Serum ovalbumin levels after challenge with or without sodium cromoglycate administration.

When SCG was interrupted, the ingestion of the offending foods caused the onset of symptoms in all cases but one. Encouraged by these positive results we selected 17 children with atopic dermatitis with positive specific IgE and skin prick tests to cow's milk and egg and who did not improve after the elimination diet. We administered 200–400 mg of SCG four times a day 15 min before meals. Only 3 out of 17 improved after 3 weeks of therapy (17).

To further investigate clinical findings we studied the effect of SCG on intestinal absorption of food antigens (12). Ten children were selected with *in vivo* and *in vitro* hypersensitivity to ovalbumin (6) and α -lactalbumin (4). After avoiding the offending food for one month, patients were challenged with egg (1.5 ml/Kg) or milk (10 ml/Kg). After 2 weeks, patients were given 40 mg/Kg SCG after 15 min. re-challenged. In both tests, blood samples were collected via an indwelling cannula before allergen ingestion every 30 min for 4 h. After the first challenge all patients showed both immediate and delayed skin and/or gastrointestinal symptoms.

Pretreatment with SCG prevented the occurrence of symptoms in all patients. The detection

of serum food antigens performed by solid phase radioimmunoassay (18) showed that SCG was able to reduce and delay the absorption of α -lactoalbumin (Fig. 1) and ovalbumin (Fig. 2).

This study suggests that SCG can protect from the offending food and that the effectiveness may be related to a reduction of macromolecular intestinal uptake.

Other clinical studies

Our studies show that SCG could be effective in the management of infantile atopic eczema. A review of the literature (Table 1) indicates conflicting results in open studies; positive (19–21) and doubtful results (22) have been reported in children with atopic dermatitis. Positive (23, 24) and negative (25, 26) results have been reported in double-blind studies as well. In all surveys some patients did not improve with drug.

Businco et al. (23) found that SCG significantly improved eczema more than placebo when it was administered during a 4-week elimination diet. SCG also was significantly better than placebo in preventing symptom exacerbation.

Table 1

Reported studies on the use of sodium cromoglycate in childhood atopic dermatitis. O: open; DB: double blind; NR: not registered; ND: not determined.

Author	Year	Pat.	Age (years)	Study	Dosage mg mg/Kg/day	Dose mg/Kg/day	Duration	Food allergy	Efficacy
Molkou et al. (20)	79	39	0.5–12	O	100–600		1 mo	+	+
Cavagni (17)	81	13	1–9	O	800		1–3 mo	+	+
Atherton et al. (25)	82	30	2–10	DB	400		1–3 mo	N.D.	–
Harris et al. (22)	83	29	7	O	100–200		1–3 mo	+	?
Graham et al. (24)	84	29	3–12	DB	N.R.		3–6 mo	+	+
Boner et al. (21)	85	28	0.5–9	O	200–1600		1–3 mo	N.D.	+
Businco et al. (23)	86	31	0.5–10	DB	400–1600	40	1–3 mo	+	+
Burks et al. (26)	88	10	3–15	DB		30–40	7 days	+	–

tion after food challenge. Conflicting clinical results may depend on the variable differences between investigations such as severity of symptoms of the selected children, dose of SCG (100–1600 mg/day), administered, and duration of treatment (1 week - 6 months). Furthermore, evaluation of challenge test was performed in only four studies.

Couturier et al. (27) state that SCG should be administered for a minimum of two months at a dose of 45–90 mg/Kg/24 h to obtain positive results. Burks et al. (26) probably failed to confirm SCG efficacy because the treatment lasted only 7 days.

The different amount of food antigens ingested during the trial can also influence results too.

We think that Atherton et al. (25) failed to gain benefit because SCG was administered on a free diet containing offending foods. Our data suggest it is necessary to block the allergic inflammatory reaction before checking SCG efficacy. Moreover investigators often ignore the compliance. When capsules are given, the patient must correctly dissolve the powder in a little hot water, and dilute it to 1/2 cupful with cold liquid and then stir the drug before ingestion. Immunological studies performed in some surveys (12, 16, 17, 20, 22, 23, 24, 26) were inconsistent, so that the underlying immunological mechanisms remain unclear. The literature offers no solid grounds for predicting which patients might be protected by SCG.

CONCLUSIONS

In accordance with findings of other authors (19–24) our studies (12, 16, 17) on pharmacological mechanisms and clinical effectiveness of SCG have shown that the drug can be of benefit in atopic dermatitis related to food intolerance.

Because adverse reactions are minimal and clinical response unpredictable, we suggest that SCG should always be tested at an adequate dose (not lower than 60–80 mg/Kg/24 h) and administered 15 min prior to meals for at least 2 months (27).

The avoidance of the offending food is the treatment of choice of atopic dermatitis.

Before starting therapy with SCG, offending foods should be adequately documented and eliminated, and immediate and delayed allergic inflammatory reactions should be treated. We think that the administration of SCG can be useful when given prophylactically:

- 1) To protect children from offending foods when avoidance is difficult (party, birthday etc.).
 - 2) When the offending food is largely present in the diet or is contained in many foods so that it cannot be avoided.
 - 3) When there is hypersensitivity to many foods that cannot be completely excluded from diet.
 - 4) To increase efficacy of elimination diet (26).
- We think that administering SCG for a long period (months or years) is not warranted if atopic dermatitis does not improve and there is no direct evidence of effectiveness of the drug.

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