

Disodium Cromoglycate and Food Allergy

The Effect of Oral and Inhaled Disodium Cromoglycate in a Food Allergic Patient

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In a food allergic patient challenge evoked a dual asthmatic response. These reactions could be partly or completely blocked by pretreatment with disodium cromoglycate (Intal®, Lomudal®) orally, depending on the doses given. Pretreatment with inhalations of disodium cromoglycate gave no protection.

Key words: asthma; disodium cromoglycate; eosinophil cationic protein; eosinophil leucocyte; food allergy.

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Inhaled disodium cromoglycate (Intal®, Lomudal®), (DCG) has been shown to block the asthmatic reaction induced by inhaled and ingested allergen (2, 7). Orally administered DCG has been shown to block both the gastrointestinal and skin reactions to ingested allergens (6, 8). Therefore the effect of oral and inhaled DCG has been studied in a patient who exhibits an asthmatic reaction to an ingested allergen.

MATERIAL AND METHOD

The patient is a male of 57 years with perennial asthma since early childhood and seasonal exacerbations during the summer months. He sometimes showed deterioration after eating meat balls, and therefore became a vegetarian; but not for long. His diet during this period regularly included pea-soup, lentils, beans or meat substitutes made of soy, and he had regular attacks of asthma 4-5 h after meals containing these substances. He is still intolerant only to this group of food substances and his condition has improved considerably since he has avoided eating them. He does not suffer

from rhinitis, nasal polyposis or urticaria and he has no abdominal symptoms in connection with the asthmatic reactions. He tolerates aspirin, tartrazin and sodium benzoate. Laboratory investigations showed: blood eosinophil count varied from 230 to 580/ μ l and total serum IgE of 5500 U/ml with the PRIST technique (normal range: 1.6-122 U/ml). Prick test gave the following positive reactions: timothy grass 2 histamin equivalent prick (HEP), *Aspergillus fum.* 2 HEP and soy bean 1 HEP. No late cutaneous reactions were seen, but no intracutaneous tests were performed. All extracts used were products from Allergologisk Laboratorium, Copenhagen. IgE-RAST test by the Radioallergosorbent test (Phadebas® Rast, Pharmacia, Sweden) gave a class 2 reaction for timothy grass, a class 3 reaction for *Aspergillus fum.* and a class 2 reaction for pea. An aquas extract, containing 6 g% protein, was made from the soy flour used in the oral challenge test (Dan-pro H, Århus Oliemølle, Århus, Denmark). This extract was coupled to CNBr-activated cellulose particles as described by Wide et al. (17). An IgE-RAST was performed (18) and the patient's serum

was slightly more than background but his high total S-IgE level could have contributed to that. It seems that RAST must be performed using different soy-extracts as their protein composition differs because of different procedures in manufacturing.

During a period when the patient was not subjected to seasonal exacerbations of his asthma a series of challenges were performed by administering 10 g soy flour, through a duodenal sond, as the provoking agent. The challenges were carried out with at least 7-day intervals, all challenges commencing at 0900. DCG was administered by different routes and by using different dosages before challenge. During challenge venous blood samples were taken at regular intervals and the blood eosinophils were counted using Rud's modification (12) of Dunger's method (5). At the same time serum was collected and stored at -17°C until assayed for eosinophil cationic protein (ECP) by the radioimmunosorbent test described elsewhere (15).

Prausnitz-Küstner tests were performed by injecting 0.1 ml of the patient's serum intracutaneously on the forearms of four normals and four asthmatic persons. Sensitization was allowed for 2 days and the sensitized area on one arm was challenged by intracutaneous test with soy bean extract. 10–50 g of soy flour was given orally to challenge the other arm's sensitized area. To evaluate whether the soy flour would be more allergenic if further denatured, all the skin-sensitized persons were given a piece of pastry containing 10 g of soy flour.

In two persons P-K test was carried out by intracutaneous injections of 0.1 ml of the patient's serum preheated to 56°C for 2 h.

RESULTS

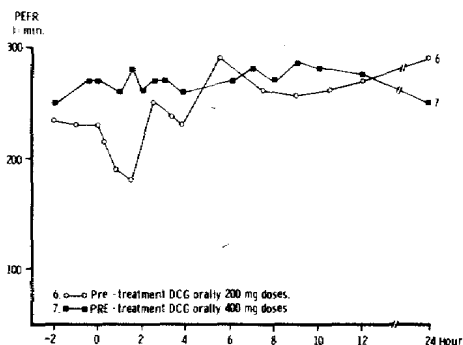
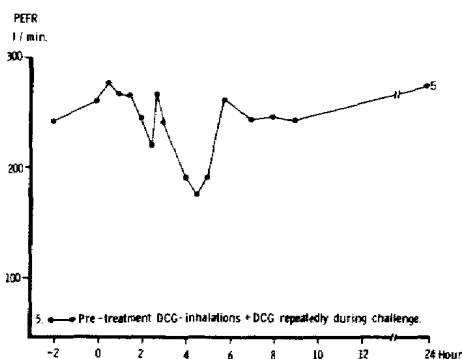
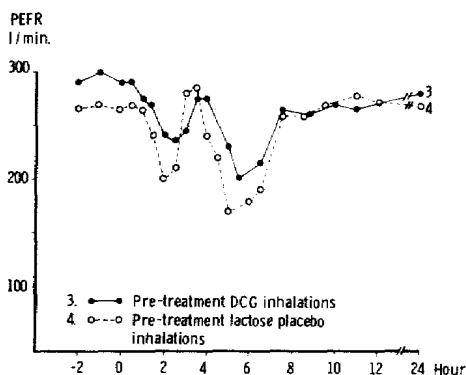
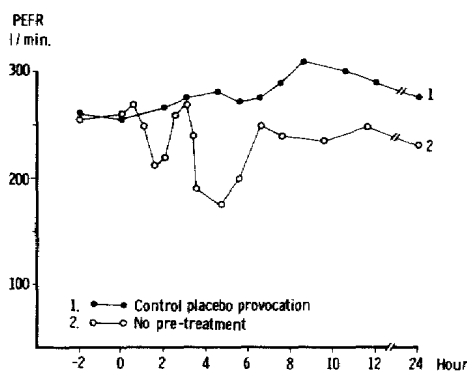
The results of the challenges are shown in Figs. 1–4. Without pretreatment an immediate asthmatic reaction developed, the onset of which was about 60 min after ingestion of the soy followed by a late reaction which began about 3 h after

challenge (test No. 2, Fig. 1). In test No. 3 (Fig. 2) DCG was given by inhalation $20\text{ mg} \times 4$ the day before plus 20 mg 2 h and again 15 min before challenge, but no protection was observed. This was also the case when these pretreatment DCG inhalations were followed by inhalations of DCG 20 mg every 15 min during the initial 3 h of the challenge (test No. 5, Fig. 3). Pretreatment with oral administration of DCG $200\text{ mg} \times 4$ the day before plus 200 mg 2 h and again 15 min before challenge could completely block the late reaction but had no effect on the immediate reaction (test No. 6, Fig. 4). When the oral doses were raised from 200 mg to 400 mg in the pretreatment schedule complete protection was achieved (test No. 7, Fig. 4). Pretreatment by oral administration of 400 mg DCG 30 min before challenge gave no protection. In the P-K tests challenge of the sensitized skin areas by prick test with soy extract gave positive weal and flare reaction equivalent to $1/2$ HEP, except on the skin sites sensitized with heat inactivated serum, where no reaction was seen. Late cutaneous reactions were not seen. These results point to an IgE-mediated pathogenesis.

The blood eosinophil count showed a rise during the time of the late asthmatic reaction (Fig. 5). S-ECP concentration, on the other hand, showed a marked decrease and the lowest concentration was measured during the time of the late asthmatic reaction.

DISCUSSION

The patient's reaction to pea, lentils, bean and soy is in agreement with the known existence of common antigens in these vegetables (8) which all belong to the *Leguminosae* family. The studies made show for the first time that the administration of a food allergen can initiate an asthmatic reaction which has both an immediate and a late component with a return to baseline PEFR-values in between. The timing of these reactions is equivalent to that ascribed to inhaled allergens (1). The inhalation of DCG did not inhibit either of



Figs 1-4. The effect of different pretreatments with disodium cromoglycate (DCG) on the responses to oral soy allergen challenges.

Abscissa: time.

Ordinate: peak expiratory flow rate (PEFR).

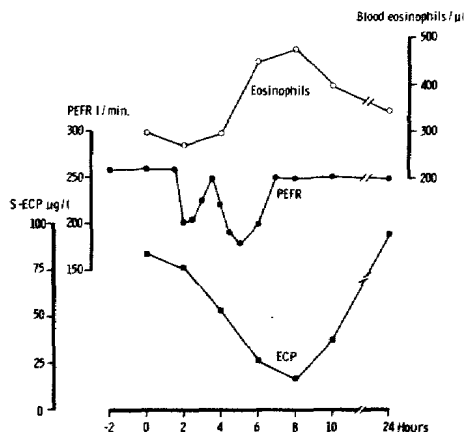


Fig. 5. Variation of blood eosinophils, eosinophil cationic protein (ECP) and peak expiratory flow rate (PEFR) during oral challenge with 10 g soy.

these reactions in the present case. The administration of DCG orally inhibits either the delayed reaction alone or both reactions, depending on the size of the dose given before the challenge. It also appears that several doses are required, as a single dose does not inhibit the reactions.

When DCG is administered orally the systemic absorption is reported to be 0.8 to 1.0% (9), and with an inhaled dose 7.6%. The total absorbed from 200 mg and 400 mg given orally will therefore be 2 mg and 4 mg respectively. Systemic absorption from 20 mg by inhalation is 1.5 mg. It therefore seems unlikely that it is the drug, which is systemically absorbed, that is active in this case. More likely the soy allergen is causing a reaction in the gastrointestinal tract. This can

be blocked by a suitable dose of DCG applied locally, which possibly inhibits release of bio-active substances. The negative P-K tests after oral challenge of the recipients speaks in favour of this as no soy allergen able to elicit a reaction seems to have been absorbed.

The permeability of the gastrointestinal mucosa for proteins differs greatly among individuals (4) and in the same person at different times. DCG given orally might reduce an abnormally high protein permeability in the mucosa. If absorbed protein alone had caused the asthmatic reaction then inhaled DCG should have had an inhibitory effect, but this was not the case.

ECP is a major protein in the eosinophil granules (10). Venge et al. (16) have recently reported on the low serum levels of this protein in patients with bronchial asthma. The late asthmatic reaction seen in challenge tests is the reaction which most resembles asthmatic disease. As increasingly low concentration of S-ECP was seen during the late reaction this may correspond to the low levels found in some asthmatics. Possibly ECP is consumed as it seems to take part in the allergic inflammatory reaction.

Late asthmatic reactions, have been regarded as arthus-like reactions mediated through IgG antibodies (11). Recent work, however, has shown that skin responses with a late component can be seen after challenge with pure anti-IgE (14). In allergic persons Zetterström found that late reactions after allergen challenge were dependent on the height of the se-IgE concentration (19). Dual reactions seem to be a universal biological phenomenon after different kinds of tissue injury (13).

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