

From the Department of Allergy, Sahlgrenska sjukhuset, Göteborg, Sweden.
(Head: Hans Arnoldsson, ass. prof., M.D.).

DISODIUM CROMOGLYCATÉ (INTAL[®], LOMUDAL[®]) IN INTRINSIC ASTHMA

By

BÖRJE ELGEFORS & HANS FORMGREN

INTRODUCTION

Since Howell and Altounyan in 1967 published their trial of disodium cromoglycate (DSCG) in the treatment of allergic bronchial asthma (7) about 80 reports have appeared. About 700 patients with asthma of different types and of varying severity have been treated and studied. Both open trials and studies with the double blind technique have been performed. The views on the effect of the drug differ from enthusiasm to skepticism.

In some studies *in vitro* methods have been used to investigate the mode of action of DSCG. Cox (2) showed that DSCG inhibits the immediate hypersensitivity reaction of allergy (type I) presumably by inhibiting the release of histamine from the mast cells (10). Furthermore, it has been demonstrated (2) that DSCG inhibits the passive cutaneous anaphylactic reaction in animals. In man, *Pepys et al.* (12) convincingly demonstrated that pretreatment with DSCG inhibits the airways obstruction induced by inhalation of specific allergen. They showed that immediate hypersensitivity reaction (type I) as well as the late type of reaction mediated by immune complexes (type III) were suppressed by the drug. Other investigators have confirmed their findings (5). Also in exercise-induced asthma the prophylactic effect has been

documented (4, 11, 14). In long-term studies the best results have been achieved in patients with extrinsic asthma. On the other hand some investigators have got less striking results or have not been able to demonstrate any obvious effect of the drug (6, 8).

We intended to test the usefulness of DSCG in intrinsic asthma, i.e. in patients where no allergy can be proven by skin tests and inhalation tests.

MATERIAL AND METHODS

Nineteen patients (nine women and ten men) took part in the study. The mean age was forty-two with a range of 25-58 years. All had regularly been seen by us at the out-patient clinic for more than one year. They fulfilled the criteria of intrinsic asthma, based on case history, skin tests and inhalation tests. All of them had daily moderate symptoms of asthma with demonstrable reversibility of the airway obstruction. None had detectable symptoms of chronic bronchitis or emphysema. The mean duration of the asthmatic symptoms was 15 years and all had received longterm (more than one year) treatment with steroids. The daily mean maintenance dose of steroids was 10 mg of prednisolone. Beside the steroids the patients were regularly treated with oral bronchodilating drugs containing ephedrine and theophyllamine. When needed, isoprenaline or orciprenaline dose aerosols were used. Before the trial the patients were informed of the presumed effect of the new drug. They were all carefully instructed how to use the special device for powder inhalations (Spinhaler) and were ordered 4 capsules (20 mg DSCG) daily. Twelve patients received DSCG with 0.1 mg isoprenaline¹ and seven patients DSCG plain. They were told to record their symptoms and daily medications on a special card.

The card used is described in detail by Morrison Smith & Devey (9). For example the score for optimal condition was 6 for asthmatic symptoms, 7 for expectoration, and 4 for cough, and decreasing scores for increasing severity. The patients started record-keeping 2-6 weeks before they received the drug.

The patients were investigated in the out-patient ward every 4th week after institution of DSCG, and the cards were also checked. Spirometry was recorded with Vitalograph.² The highest values of three measurements of forced vital capacity (FVC) and forced expiratory volume during the first second (FEV₁) at each examination were used in the calculations.

¹ Intal compound. Fisons pharm. ltd., England.

² Vitalograph Ltd., Maids Moreton House, Buckingham, England.

TABLE 1
*Spirometry Values in Liters, for Forced Vital Capacity (FVC) and
 Forced Expiratory Volume/Second (FEV₁).*

	Predicted normal value		Before treatment		Mean increase during treatment		
	Mean	S.D.	Mean	S.D.	4th week	8th week	12th week
FVC	4.10	0.88	3.80	1.10	0.17	0.12	0.08
FEV ₁	3.20	0.62	2.20***	0.83	0.37**	0.16	0.05
Number of patients			18		18	18	13

** Statistically significant $p < 0.01$.

*** Statistically significant $p < 0.001$.

S.D. Standard deviation.

The subjective scores were separated day and night and weekly total scores for each variable (asthma, expectoration, cough and medication) were made for the pretreatment, 4th, 8th and 12th weeks. The variables were kept separate, and no overall score was made. The calculations were done with an Olivetti Programma 101 computer. Mean differences between the pretrial scores and the total scores for the 4th, 8th and 12th weeks during treatment were tested for significance with Student's t-test.

RESULTS

Compared with the predicted normal values, there was a significant reduction of FEV₁ before the trial ($p < 0.001$). After four weeks of treatment the FEV₁ increased by 0.37 liter ($p < 0.01$), but during the remaining period the FEV₁ returned to the pretreatment level (Table 1). The mean asthma score increased slightly during the first four weeks and did not differ significantly between the DSCG compound and plain groups (Fig. 1). Although, this improvement is statistically significant, it means only half a score per day. During the remaining 8 weeks the asthma score declined. Concerning the frequency of isoprenaline inhalations (Fig. 1), there was an initial striking decrease. This decrease was only observed in the DSCG compound group. The use of oral bronchodilating drugs could also be reduced a little in the beginning of the trial (Fig. 2). The daily maintenance dose

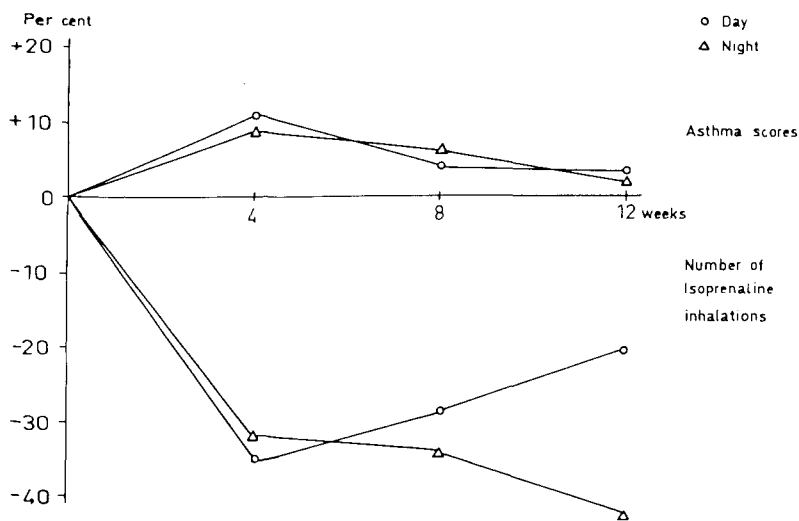


Fig. 1.

Changes of mean asthma scores and mean use of isoprenaline during treatment with disodium cromoglycate expressed in relation to figures for the pretreatment week.

of prednisolone could be reduced by 2.5 mg during the first 8 weeks, but then it returned to the initial level. The scores for cough and sputum did not show any appreciable changes.

One patient with concomitant rhinitis who improved subjectively and objectively (increase of FEV_1) made several attempts to reduce his daily prednisolone dosage but each time nasal congestion and anosmia returned to the same degree as he had had 8 years earlier. Two patients wanted to continue the medication because of subjective improvement. In the remaining cases the drug was withdrawn without increased asthmatic symptoms.

SIDE EFFECTS

No serious side effects have been noted. Some patients were uncertain whether or not the proper amount of the drug reached the bronchi, since they noted that the biggest particles

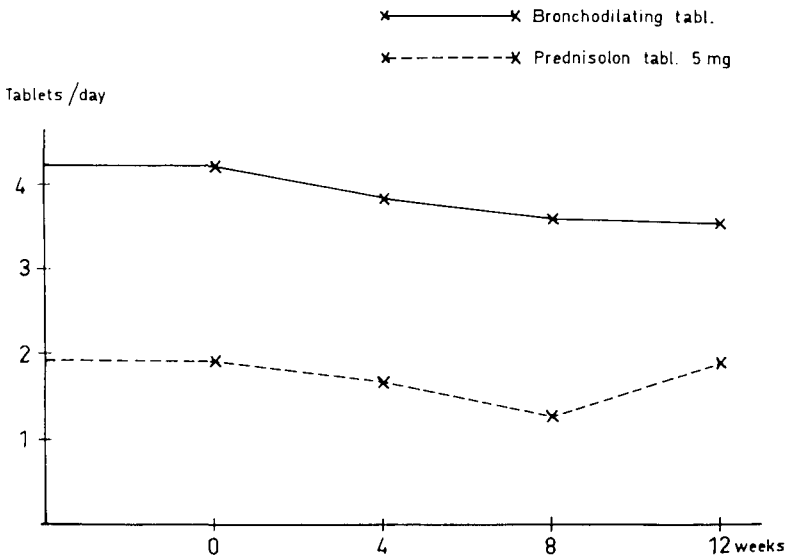


Fig. 2.

Changes in supplementary oral therapy during treatment with disodium cromoglycate expressed in number of tablets per day.

stayed in the oropharynx. According to Cox (3) the bigger particles consist mainly of the inert carrier substance (lactose). Occasionally gelatin particles have been inhaled after too vigorous perforations of the capsules. Temporary cough was observed after the inhalation.

DISCUSSION

Many of the reported good results are difficult to compare because of the sparse descriptions of the patients and the failure to separate extrinsic from intrinsic asthma. Daily exposure to undetected allergens may mimic the intrinsic form of asthma. Patients with chronic bronchitis and emphysema may sometimes have been included. Another obstacle in the evaluation of the effect of a drug is the lack of objective methods to judge the response to therapy. This is especially

TABLE 2

Changes of the Different Variables as Compared to the Pretreatment Figures.

		Weekly mean before DSCG	Mean paired difference during DSCG medication		
			12th week	8th week	4th week
Asthma score	day	28.6	3.1*	1.3	0.8
	night	30.4	2.9*	1.8	0.4
Cough score	day	20.3	1.0	0.8	0.8
	night	21.2	1.6	1.2	1.3
Sputum score	day	36.9	0.2	0.1	—2.3
	night	38.5	—0.7	—1.4	—3.4
Adrenaline	day	56.4	—19.6*	—16.1†	—11.3
	night	31.0	—9.9*	—10.6*	—12.9
Bronchodilating tablets		29.8	—2.9**	—4.6*	—4.8*
Prednisolone tablets à 5 mg		13.6	—1.6	—4.6†	—0.3
Number of patients		18	18	18	13

* Statistically significant $p < 0.05$.** Statistically significant $p < 0.01$.

true with asthma, in which the appearance of symptoms changes spontaneously from one time to another. Furthermore, the methods of treatment are different in different countries and climates also vary.

We have selected the patients with asthma according to the definitions proposed at the Congress of Allergology in Oslo 1966. Asthma is defined as a disease in the airways characterized by a reversible dyspnoea of obstructive type with varying duration and severity. Extrinsic asthma, as proved by positive intracutaneous and inhalation tests, is differentiated from intrinsic asthma, where these tests are negative. At present there exists no other objective method to separate these two types of asthma. Quantitative IgE determination may be of value, but it is not yet available for clinical use (15). In the intrinsic type of asthma based on the previously mentioned diagnostic principles we have not been able to show that DSCG has any obvious clinical effect.

The observed initial improvement may be a placebo effect. The decrease in the frequency of isoprenaline inhalations is to some extent due to better awareness of misuse of the drug in some patients. The daily dose of DSCG compound means a hidden administration of isoprenaline equivalent to five isoprenaline inhalations per day and thus decreases the spray consumption.

It has been reported (1, 13) that steroid medication has been reduced and even terminated in relation to treatment with DSCG. The patients were not selected however in regard to allergy, therefore they may have had allergy of pathogenetic importance.

In conclusion, the negative results of our open study indicate that DSCG seems to be of little if any value in the treatment of patients with *intrinsic* asthma.

S U M M A R Y

Nineteen adult patients with intrinsic asthma were treated with DSCG in an open assessment. No significant changes in symptoms, steroid dosage or FEV₁ persisted after three months. The importance of classifying asthma as extrinsic or intrinsic is stressed.

R E F E R E N C E S

1. Campbell, A. H. & Tandon, M. K.: A trial of disodium cromoglycate in older asthmatics. *Med. J. Aust.* 56: 2, 535-537, 1969.
2. Cox, J. S. G.: Disodium cromoglycate: a specific inhibitor of reaginic antibody-antigen mechanisms. *Nature* 216, 1328-1329, 1967.
3. Cox, J. S. G.: Letter to the editor. *Brit. Med. J.* 3, 176, 1969.
4. Davies, S. E.: Effect of disodium cromoglycate on exercise induced asthma. *Brit. Med. J.* 3, 593-594, 1969.
5. Engström, I. & Vejmola, J.: Medicinsk riksstämma, Stockholm, 1969.
6. Grant, I. W. B., Channel, S. & Drever, J. C.: Disodium cromoglycate in asthma. *Lancet* II, 673, 1967.
7. Howell, J. B. L. & Altounyan, R. E. C.: A double-blind trial of disodium cromoglycate in the treatment of allergic bronchial asthma. *Lancet* II, 539-542, 1967.

8. *Kidner, P. H., Meisner, P., Pride, N. B. & Pearson, R. S. B.*: Disodium cromoglycate in the treatment of bronchial asthma. *Lancet II*, 655-657, 1968.
9. *Morrison Smith, J. & Dewey, G. F.*: A clinical trial of disodium cromoglycate in the treatment of asthma in children. *Brit. Med. J.* 2, 340-344, 1968.
10. *Orange, R. P. & Austen, K. F.*: Pharmacologic dissociation of immunologic release of histamine and slow reacting substances of anaphylaxis in rats. *Proc. Soc. Exptl. Biol. Med.* 129, 836-841, 1968.
11. *Palmer, K. N. F. & Legge, J. S.*: Disodium cromoglycate in exercise induced asthma. *Lancet II*, 219, 1969.
12. *Pepys, J., Hargreave, F. E., Chan, M. & McCarthy, D. S.*: Inhibitory effects of disodium cromoglycate on allergen-inhalation tests. *Lancet II*, 134-137, 1968.
13. *Read, J. & Rebuck, A. S.*: Steroid-sparing effect of disodium cromoglycate in chronic asthma. *Med. J. Aust.* 1, 566-569, 1969.
14. *Ward, F. G., Gomes, S. & McNeill, R. S.*: Disodium cromoglycate in exercise induced asthma. *Brit. Med. J.* 3, 176, 1969.
15. *Wide, L., Bennich, H. & Johansson, S. G. O.*: Diagnosis of allergy by an *in vitro* test for allergen antibodies. *Lancet II*, 1105-1107, 1967.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.