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THE EFFECT OF
DISODIUM CROMOGLYCATE ON
ALLERGEN CHALLENGE
IN CHILDREN WITH BRONCHIAL ASTHMA

By

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Experimental studies involving different immunological systems have shown that Disodium Cromoglycate (DSCG)* interferes in some way with the release of chemical mediators following the antigen-reaginic antibody reaction (3). The first experimental study in man was performed by *Altounyan* who, in 1967, reported that DSCG could inhibit the asthmatic response to inhaled allergen in an asthmatic subject (1). This observation was confirmed by *Pepys et al.* in 1968 in 5 asthmatic patients with immediate allergic reactions as well as in a further 5 patients with late asthmatic or systemic reactions (13). *Herxheimer et al.* (12) could not report equally favourable results, however, using a different inhalation technique they found the inhibitory effect of DSCG only applied in a few of their patients.

As the ability of DSCG to inhibit induced allergic reactions is of primary importance in understanding the clinical effectiveness reported, we considered further documentation would be of interest in view of the differences in results in the few experimental studies published so far.

This report deals with the prophylactic effect of DSCG

* Trade mark, "Intal", "Lomudal", Fisons Limited—Pharmaceutical Division, Loughborough, England.

TABLE 1.
Clinical data on children studied.

Patients	Age years	Duration of asthma years	Main season of symptomatology	Allergen used for provocation	
1. A. Lj.	9	7	May	Birchpollen	10^{-3}
2. C. W.	10	7	June, July*	Cocksfoot	10^{-2}
3. A. L.	9	8	June-August	Cocksfoot	10^{-1}
4. S. O. J.	13	11	May*	Birchpollen	10^{-3}
5. T. L.	15	7	June-July	Cocksfoot	10^{-2}
6. C. S.	14	11	May-July	Birchpollen	10^{-3}
7. M. R.	13	11	June, July*	Meadow fescue	10^{-2}
8. O. C.	11	9	May-August*	Birchpollen	10^{-2}
9. E. M.	10	2	May	Birchpollen	10^{-3}
10. B. R.	15	10	June-August	Cocksfoot	10^{-1}
11. J. P. Q.	12	5	May	Birchpollen	10^{-3}
12. G. S.	11	6	May-July	Birchpollen	10^{-2}

* Occasional symptoms also other seasons.

on the bronchial reaction induced by allergen challenge in a group of children with seasonal allergy. The degree of bronchial reaction was assessed by measurement of the airway resistance.

MATERIAL

Twelve children with bronchial asthma were admitted to the study during a symptom free period when no medication was required (Table 1). Two were girls and 10 were boys. The age range was 9-15 years. The average duration of disease was 8 years ranging from 2-11 years. Eight children had a history of purely seasonal asthma with symptoms occurring only during spring and/or summer. In four children asthmatic symptoms could appear also during other seasons but always with an exacerbation during spring and/or summer. None of the children had constant symptoms and all of them had well defined symptom free periods. Allergy against one or several pollen allergens was demonstrated in all children by skin and provocation tests.

METHODS

Airway resistance was measured by means of a pressure body plethysmograph according to DuBois (5), modified by Geubelle & Senterre (9). The modifica-

tion consists of a Krogh spirograph mounted in the plethysmograph for measurement of the tidal air at BTPS, which allows measurement of the tidal air during breathing at normal rate and depth, thus making panting unnecessary and making it easier for the child to keep a constant end expiratory level. For further description of the method reference is made to *Grubelle & Senterre* (9).

Spirographic tidal volume, airflow, mouth and plethysmographic pressure were recorded simultaneously on an Elema direct writing recorder. The airway resistance was calculated during quiet breathing at points of equal volume, i.e. around the middle of inspiration and expiration. The ten middle breaths in a series of 20 breaths with constant end expiratory level were measured. The data of tidal volume, airflow, mouth- and plethysmographic pressure as well as the calibration factors were fed into a computer and the mean of ten breaths was used as the airway resistance, expressed in $\text{cm H}_2\text{O/l/sec}$. The random error of the method was calculated from the linear regression between the mean of 10 breaths and the SD of the mean for each child at each measurement at symptom free state, 68 observations in all. This gave the equation $\text{SD} = 0.22 \times \text{AR} + 0.059$. From this equation the coefficient of variation was derived as being ± 7.9 per cent when using 10 breaths.

PROCEDURE

The study was performed during the winter 1968–1969 when the children were not exposed to the pollen allergens to which they were sensitive and were thus in a stable symptom free period.

Three different pollen allergens were used, birch pollen (*Betula verrucosa*) in 7 children, cocksfoot (*Dactylis glomerata*) in 4 children and meadow fescue (*Festuca pratensis*) in one child (Table 1). The test dose of allergen was always one ml. inhaled through a nebulizer (PariOptimal) which administered, as an aerosol, drops of 0.5 – 5 microns. The concentration was determined by previous inhalation tests as being the one which had produced evident but mild clinical symptoms of asthma.

The procedures were always performed in the morning. The asthmatic response was clinically evident, on average, 7 minutes after allergen inhalation (range 5–10 minutes). DSCG was inhaled from capsules containing 20 mg of a micronised powder and 20 mg lactose through a "Spinhaler".

Isoprenaline was inhaled as an aerosol for 30 seconds through a PariOptimal nebulizer.

The tests were performed as follows:

- I. Control measurement of the airway resistance, without symptoms, without drugs.
- II. Measurement at time of clinical response to allergen inhalation, average 7 minutes.
- III. Measurement 10 minutes after Isoprenaline inhalation, given to relieve the bronchial obstruction.
- IV. Measurement 10–15 minutes after DSCG inhalation.
- V. Measurement after allergen inhalation performed 25 minutes after DSCG inhalation. The same individual time interval between allergen inhalation and measurement as in II was used.
- VI. Measurement 10 minutes after Isoprenaline inhalation.

Procedures I, II and III were performed in a series and I, IV, V and VI in another series on three different occasions each on an alternate basis, DSCG being given every second time. The time interval between the different experiments was never less than 2 days.

RESULTS

Table 2 gives the control airway resistance, airway resistance after allergen challenge and airway resistance after allergen challenge preceded by inhalation of DSCG.

The mean airway resistance from all the observations on different days, using 10 breaths from every tracing, for each treatment procedure I–VI, was used for calculation of the group analyses.

Table 3 gives the means of the airway resistance for each treatment for every child as well as the treatment means.

The data in Table 3 was analysed by analysis of variance (randomised blocks). This showed significant differences ($p < 0.01$) between patients and between treatments.

Further comparison of the treatment means were carried out using Duncans multiple range test (6). This showed that

TABLE 2.

Airway resistance in cm H₂O/l/sec before and after allergen challenge.

Patient number	Control	After allergen challenge	Control	After allergen challenge after DSCG
1	2.6	11.9	5.4	4.8
	2.7	5.7	4.4	5.8
	4.9	13.6	1.9	5.5
2	3.2	15.1	3.0	3.1
	3.2	15.7	3.0	6.6
	2.9	6.8	2.8	2.8
3	3.8	14.6	3.6	3.6
	4.0	11.4	3.9	4.1
	2.9	15.2	2.9	3.4
4	2.5	4.6	1.7	1.6
	2.7	9.5	2.0	2.3
	2.0	7.2	2.0	1.7
5	1.3	10.7	3.0	3.1
	2.0	18.7	3.2	7.1
	1.5	9.3	1.7	1.6
6	2.0	15.8	3.3	13.4
	3.1	9.5	2.5	6.1
7	4.8	8.6	3.3	2.9
	2.3	4.5	2.5	2.5
	3.8	9.6	3.3	2.9
8	3.4	20.4	4.4	4.4
	4.8	23.3	5.7	13.7
	4.8	27.8	4.5	3.4
9	3.6	10.9	4.1	8.4
	4.4	15.2	6.7	15.3
10	2.6	11.0	2.7	3.4
	2.2	13.9	4.6	5.7
	4.1	11.9	3.7	20.4
11	2.1	8.8	1.4	1.7
	1.8	11.7	1.5	2.3
	2.1	6.4	1.3	2.3
12	3.2	17.6	3.1	3.1
	4.0	11.7	3.4	3.8
	3.3	4.3	3.7	4.2

TABLE 3.

Mean values of airway resistance in cm H₂O/l/sec for each treatment procedure for individual children.

Patient number	I Control	II After allergen challenge	III After Isoprenaline after II	IV After DSCG	V After allergen challenge after IV	VI After Isoprenaline after V	Protection of DSCG
1	3.7	10.4	3.1	3.7	5.4	2.5	partial
2	3.0	12.5	5.8	3.4	4.2	3.0	partial
3	3.5	13.7	6.5	4.3	3.7	3.4	complete
4	2.2	7.1	2.4	2.6	1.9	2.0	complete
5	2.1	12.9	2.3	2.0	3.9	1.5	partial
6	2.7	12.7	2.5	2.3	9.8	2.5	no
7	3.3	7.6	2.1	2.7	2.8	1.9	complete
8	4.6	23.8	6.3	4.8	7.2	2.9	partial
9	4.7	13.1	5.2	5.3	11.9	5.2	no
10	3.3	12.3	3.1	4.2	9.8	2.4	partial
11	1.7	9.0	3.7	2.0	2.1	2.3	complete
12	3.5	11.3	5.3	5.3	3.7	3.2	complete
means	3.2	12.2	4.0	3.6	5.5	2.7	
± SE*	0.58	0.58	0.58	0.58	0.58	0.58	

* Calculated during analysis of variance.

at $P = 0.01$ the mean value of airway resistance after a non protected allergen challenge was significantly higher than all the other readings. This also showed that there was no significant difference between control airway resistance, airway resistance after DSCG inhalation and airway resistance after allergen challenge preceded by DSCG inhalation.

Thus the group analyses demonstrate that prior inhalation of DSCG exerts a significant protection against an increase in airway resistance induced by allergen challenge.

However, the degree of protection differed among the individual children, and this is obvious from Tables 2 and 3. In five children, Nos. 3, 4, 7, 11 and 12, DSCG exerted complete protection each time. The difference between control airway resistance and airway resistance after protected

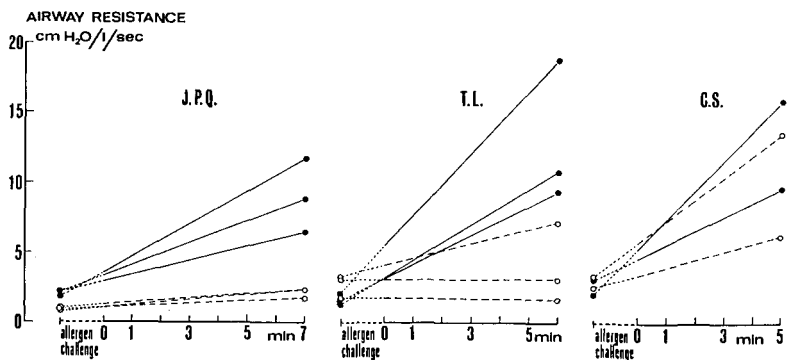


Fig. 1.

Effect of allergen challenge on airway resistance in 3 children.

- ——— ● without prior inhalation of DSCG
 ○ ——— ○ with prior inhalation of DSCG

allergen challenge ranged between -0.4 and $+1.0$ cm H₂O/l/sec., with a mean value of $+0.1$, which is less than the difference between control airway resistance on different days. In a further 5 children, Nos. 1, 2, 5, 8 and 9 partial protection was experienced, i.e. on one of the three occasions, DSCG inhalation failed to exert significant protection against an increase in airway resistance. In two children, Nos. 6 and 9, no protection of the DSCG inhalation on the provocation reaction could be demonstrated. Fig. 1 gives examples of the three patterns, which are consistent within the three groups.

DISCUSSION

An accurate assessment of the degree of bronchial reaction following allergen challenge requires a method that does not involve any voluntary effort by the patient and does not, by itself, induce bronchial spasm or airtrapping. The method must also be sensitive and easily reproducible. Those criteria are fulfilled by the measurement of airway resistance using the method we adopted.

The control airway resistance in the children differed little

from day to day and was always within the normal range found in symptom free asthmatic children (7, 9) as well as in healthy children of the same age range (7). This confirms that the children were in a stable phase during the period of study, this being a prerequisite for comparison between provocation reactions performed on different days.

In spite of this clinical stability, it is evident from the data that the dose of allergen administered did not always produce the same increase in airway resistance. The variations are sometimes fairly large and may in some children be explained by a temporary decrease in sensitivity induced by repeated provocations (2, 11). The reverse, an increase in sensitivity due to the fact that the effect of the previous provocation had not completely disappeared (8), is possible in one or two children. These are factors that must be taken into consideration when performing repeated provocations in the same child during a limited period of time. It was to reduce this effect upon the results that the time interval between provocations was never less than two days and DSCG was given on an alternate day basis.

The inhibitory effect of DSCG on the bronchial reaction ordinarily induced by allergen inhalations is indisputable, and was found in 10 out of 12 children. We can thus confirm the results reported by *Pepys et al.* (13) in their 5 patients with immediate bronchial reaction. Our results are more favourable than the ones reported by *Herxheimer et al.* (12). A comparison with their study, however, is rendered difficult because they used a different method of administration of DSCG at a lower dosage, facts which might have had an influence upon their results.

The difference in effect of DSCG found among our children, in whom complete inhibition was registered in 5, partial inhibition in 5 and no inhibition in 2, can not be attributed to any difference in the type of allergy, the degree of sensitivity or the clinical status of the child.

Goose & Blair (10) has shown that DSCG inhibits rat reagintype antibody-antigen reactions and that the degree of

inhibition varied with the dose of DSCG used. As an analogy to this observation, it is possible that the dose of DSCG administered was inadequate when partial or complete lack of protection was experienced following allergen challenge. It is unlikely that more than 20 mg. would have been necessary as the bronchial reaction was not stronger in the children in whom complete inhibition was achieved. A more probable explanation is that, due to poor inhalation technique, insufficient drug reached the bronchial tree to be effective. The dispersion of the powder in the respiratory tract must to a great extent be dependent upon a good inhalation technique which children can not always achieve. As DSCG probably acts topically at the site of the antigen-reaginic antibody reaction (4) it is thus desirable that a sufficiency of the particle land on the appropriate area of the airways to produce optimal effect.

At present, insufficient is known about the exact location in the airways where DSCG should act to give optimal effect, the dispersion properties of the drug in the bronchial tree after inhalation via the Spinhaler at different inspiratory flows, or the pathways of the drug to the site of the antigen-reaginic antibody reaction. Further studies to elucidate these problems are required before we can fully understand why the protective action of DSCG against the effect of allergen challenge sometimes fails.

S U M M A R Y

Twelve children with seasonal asthma were challenged with appropriate pollen allergens. The bronchial reaction was assessed by means of increase in airway resistance. When DSCG was inhaled, before the allergen challenge, inhibition of the reaction was observed in 10 children. The inhibition was complete in 5 children and partial in another 5 children. In 2 children no inhibition was observed. It is suggested that the differing response and effect may be dose dependent and that a deficient dispersion of the drug in the respiratory tract

due to poor inhalation technique contributed to the lack of positive response in a few children.

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REFERENCES

1. *Altounyan, R. E. C.*: Inhibition of experimental asthma by a new compound — disodium cromoglycate "Intal", *Acta Allergol.* 22, 485, 1967.
2. *Citron, K. M.*: The uses of bronchial sensitivity tests, *Acta Allergol. (Suppl. 8)* 22, 17, 1967.
3. *Cox, J. S. G.*: Disodium Cromoglycate (FPL 670) ("Intal"): A specific inhibitor of reaginic antibody-antigen mechanisms, *Nature* 216, 1328, 1967.
4. *Cox, J. S. G., Bell, J. H. & Hartley, P. S.*: Administration of Disodium Cromoglycate. *Brit. Med. Journal* 1, 634, 1969.
5. *DuBois, A. B., Botelho, S. Y. & Comroe, J. H. Jr.*: A new method for measuring airway resistance in man using a body plethysmograph. Values in normal subjects and in patients with respiratory disease. *J. Clin. Invest.*, 35, 327, 1956.
6. *Duncan, D. B.*: *Biometrics* 1955, 11, 1 Ph. No. 10216.
7. *Engström, I. & Fejmolova J.*: Unpublished data.
8. *Engström, I.*: Studies on airway obstruction provoked by diagnostic allergen inhalation in asthmatic children. *Acta Allergol. (Suppl. 8)* 22, 29, 1967.
9. *Geubelle, F. & Senterre, J.*: Lung tissue resistance in symptom-free asthmatic children. *Progr. Resp. Res.* 4, 236, 1969.
10. *Goose, J. & Blair, A. M. J. N.*: Passive cutaneous anaphylaxis in the rat, induced with two homologous reagin-like antibodies and its specific inhibition with disodium cromoglycate. *Immunology* 16, 749, 1969.
11. *Herxheimer, H.*: Bronchial hypersensitization and hyposensitization in man. *Int. Arch. Allerg.* 2, 40, 1951.
12. *Herxheimer, H. & Bewersdorff, H.*: Disodium cromoglycate in the prevention of induced asthma. *Brit. Med. J.* 2, 220, 1969.
13. *Pepys, J., Hargreave, F. E., Chan, M. & McCarthy, D. S.*: Inhibitory effects of disodium cromoglycate on allergen inhalation tests. *Lancet* 2, 134, 1968.

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