

# Disodium Cromoglycate (Lomudal) in Asthma with Emphasis on Lung Function Tests\*

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## SUMMARY

Twenty allergic asthmatics were treated with inhaled disodium cromoglycate (Lomudal)† in addition to extant therapy. Improvement was assessed by the patient, clinically by the physician, by analysis of the patients' diary cards and by a battery of pulmonary function tests, after 3 months' treatment. Eighteen patients were improved. At the end of 1 year's treatment, only 1 failed to maintain improvement. No serious side-effects were encountered.

Lung function tests demonstrated less hyperinflation in 9 out of 11 patients tested, less airway obstruction in 14 out of 20, no change in a standardized exercise test and an improvement in acid-base balance from compensated respiratory alkalosis to normal. The results in this trial are discussed in relation to others in this literature. The value of DSCG in facilitating reduction of corticosteroid and sympathomimetic therapy for asthma is emphasized. Some practical points in the use of DSCG are listed.

Disodium cromoglycate is safe and efficacious in allergic bronchial asthma and is a very useful adjunct in the therapy of this common, potentially serious condition.

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Extrinsic bronchial asthma may be defined as a condition of usually intermittent episodes of bronchospasm with symptom-free periods, in a subject with a personal or family history of an allergic condition. Intrinsic asthma is similar but there is no overt allergic factor. Though often very mild, asthma is potentially very serious and is an important cause of death especially among the young.<sup>22</sup> Of the 10 major causes of death in England and Wales in children aged 10-14 years in 1965 asthma was ranked sixth.<sup>26</sup> Any advance in the treatment of this condition must therefore be welcomed.

Disodium cromoglycate (DSCG) was recently introduced as a therapeutic agent for asthma, the first clinical reports having been published in 1967.<sup>1,25</sup> DSCG is a member of the chromone class of compounds and has been found to inhibit specifically the liberation of the mediators of anaphylaxis initiated by the interaction of antigen with reagent type antibodies. It is neither a bronchodilator nor an anti-inflammatory agent and its action is distinct from that of corticosteroids.<sup>6</sup> It inhibits mast cell degranulation.<sup>7</sup>

Since 1967, many clinical trials of DSCG have been made<sup>5,9,17,19,23,26-28,31</sup> and favourable responses of variable de-

grees have been reported in a substantial proportion of patients. There are, however, a few publications<sup>12,14</sup> which do not support the claims of other investigators.

In some of the earlier studies it was observed that there was more often subjective improvement than improvement of forced expiratory volume in 1 second.<sup>27,28</sup> One of the objectives of this study was to attempt to determine why patients were symptomatically improved, by applying a full battery of pulmonary function tests. Therefore the patients selected for the trial were predominantly young allergic asthmatics who were likely to be symptomatically improved by DSCG.<sup>2</sup>

## MATERIAL AND METHODS

Twenty subjects (11 females and 9 males) aged 7-40 years (mean 25.2 years) were included in the study. All had a personal or family history of allergy and eosinophils were demonstrated in their sputum.

DSCG was added to extant therapy in a dosage of 4 capsules daily throughout the 3 months' trial period. The drug was administered by inhalation, using the Spinhaler<sup>®</sup>, a turbo-vibratory device available from any pharmacist. Other therapy was altered if warranted by the patients' condition as assessed at their regular fortnightly visits. At the end of the trial period each patient made an over-all assessment and stated his own opinion of whether his condition was much better, better, the same, or worse, as a result of DSCG therapy. We assessed the response to DSCG by taking into account the symptoms, physical signs and total medication at the end of 3 months and again after completion of 1 year's therapy.

On introduction to the study, the patients were required to commence recording the severity of their symptoms and drug usage 12-hourly on diary cards. Symptoms recorded were breathlessness, chest tightness, wheeze, cough, sputum volume and interruptions of sleep. We examined these cards and assessed from them the effect of the DSCG therapy on the patients' condition and on their concomitant medication.

Subjects underwent tests of ventilatory capacity before commencing therapy with DSCG, and monthly during 3 months' treatment. The tests performed monthly on 20 subjects included measurement (before and after inhalation of a bronchodilator aerosol\*) of: (i) Vital capacity (VC), (ii) maximal voluntary ventilation (free) (MVV<sub>f</sub>), (iii) maximal mid-expiratory flow rate (MMF), (iv) forced

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†Fisons Chemicals (S.A.) (Pty) Ltd, Johannesburg.

\*Prenomiser Plus, Fisons Chemicals, Johannesburg.

expiratory volume in 1 second (FEV<sub>1</sub>) and (v) forced vital capacity (FVC).

However, the results of the final tests at the end of 3 months' therapy were available in 16 subjects and only these are included in the statistical analysis. In addition, before and after 3 months' DSCG therapy the following measurements were made:

1. Subdivisions of lung volume—functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC) in 11 subjects.
2. Lung clearance index (LCI) in 11 subjects.
3. Standardized exercise test including minute ventilation, heart rate, respiratory rate and arterial oxygen saturation in 12 subjects.
4. pH, carbon dioxide tension (PCO<sub>2</sub>), standard bicarbonate and base excess by the Astrup micromethod<sup>35</sup> on arterialized capillary blood from the earlobe in 13 subjects.
5. End-tidal carbon dioxide concentration in 13 subjects.

Techniques and predicted values used have been described in previous publications from this laboratory.<sup>30,31,39,40</sup>

## RESULTS

### Clinical Assessment

After 3 months' DSCG therapy, 5 patients stated they felt much better, 13 better, 2 the same and none worse.

TABLE I. CLINICAL ASSESSMENT OF RESULTS OF DSCG THERAPY

Method of assessment	Number of patients whose symptoms are:		
	The same	Better	Much better
Patient	2	13	5
Doctor	1	13	6
Diary card	2	8	10
Doctor (after 1 yr therapy)	3	12	5

The physician's assessments were almost identical but analysis of the diary cards suggested that half the patients were much better. After 1 year of DSCG therapy 5 patients were considered to be much better, 12 better, 3 the same and none worse (Table I).

Patients reported less breathlessness, chest tightness, wheezing and coughing and better sleep as well as fewer attacks of chest involvement complicating 'colds'. A number of patients reported that DSCG had allowed them to 'return to a normal life' and some stated that they could indulge in physical activity which was previously beyond their capabilities. No adverse side-effects were encountered after 1 year's therapy except for occasional soreness or irritation of the throat and transient bronchospasm.

Nearly every patient was able to decrease the use of other drugs for asthma after the introduction of DSCG therapy. Thus of 13 subjects who had been on steroids, dosage was reduced in 7 and withdrawn in 4. Sympathomimetics (including aerosols) were reduced in 11 and withdrawn in 5 out of 18 patients. Similar changes occurred in regard to the xanthine group of drugs (Table II).

TABLE II. CHANGES IN CONCOMITANT DRUG THERAPY DURING DSCG THERAPY

Drug	Number of patients in each group			
	None during trial	No change	Reduction	Withdrawal
Steroid	7	2	7	4
Sympathomimetic	2	2	11	5
Xanthine	7	0	8	5

### Pulmonary Function Tests

The results of the pulmonary function tests performed before and after 3 months' DSCG therapy are tabulated as mean values and standard deviations for the number of patients undergoing the various tests (Tables III to VI). Results after 1 or 2 months' therapy were in no way

TABLE III. SUBDIVISIONS OF LUNG VOLUME AND LUNG CLEARANCE INDEX

	No. of patients	Pre-DSCG		Post-DSCG		Probability
		Mean	SD	Mean	SD	
VC litres measured (B)	16	3.4	1.3	3.7	0.9	P>0.05
VC litres measured (A)	15	4.0	1.1	4.2	1.0	P>0.05
VC % predicted (B)	16	86.8	19.0	97.2	18.8	0.05> P>0.01
VC % predicted (A)	15	93.2	13.7	101.7	13.5	0.05> P>0.01
FRC litres measured	11	3.9	1.2	3.6	1.1	P>0.05
FRC % predicted	11	118.8	30.0	106.9	18.5	P>0.05
RV litres measured	11	2.3	0.8	2.0	1.0	P>0.05
RV % predicted	11	150.5	53.2	120.5	44.7	P>0.05
TLC litres measured	11	6.5	1.6	6.3	1.8	P>0.05
TLC % predicted	11	111.0	17.3	106.9	14.8	P>0.05
FRC/TLC % measured	11	60.5	5.9	56.3	6.6	P>0.05
RV/TLC % measured	11	36.4	7.2	30.8	8.7	P>0.05
LCI litre/litre FRC	11	2.5	1.0	2.7	0.8	P>0.05

VC = vital capacity; FRC = functional residual capacity; LCI = lung clearance index; RV = residual volume; TLC = total lung capacity; B = before, A = after bronchodilator.

TABLE IV. VENTILATORY CAPACITY

	No. of patients	Pre-DSCG		Post-DSCG		Probability
		Mean	SD	Mean	SD	
MVV <sub>F</sub> litre/min measured (B)	15	71.7	33.9	87.9	33.4	0.05 > P > 0.01
MVV <sub>F</sub> litre/min measured (A)	15	89.1	35.2	107.5	33.6	0.01 > P > 0.001
MVV <sub>F</sub> % predicted (B)	12	55.8	17.3	70.4	21.6	0.05 > P > 0.01
MVV <sub>F</sub> % predicted (A)	13	69.2	21.2	83.0	22.3	0.01 > P > 0.001
MMF litre/sec measured (B)	16	1.1	0.7	1.4	0.7	0.05 > P > 0.01
MMF litre/sec measured (A)	15	1.6	1.0	2.0	1.0	0.05 > P > 0.01
FEV <sub>1</sub> litres measured (B)	16	1.8	0.8	2.2	0.8	P > 0.05
FEV <sub>1</sub> litres measured (A)	14	2.2	0.9	2.6	0.8	0.01 > P > 0.001
FEV <sub>1</sub> /FVC % (B)	16	58.6	10.1	61.8	12.3	P > 0.05
FEV <sub>1</sub> /FVC % (A)	15	62.8	14.2	66.7	14.5	P > 0.05

MVV<sub>F</sub> = maximal voluntary ventilation (free); MMF = maximal mid-expiratory flow; FEV<sub>1</sub> = forced expiratory volume in 1 second; FVC = forced vital capacity.

TABLE V. VENTILATION, OXIMETRY, HEART AND RESPIRATORY RATES AT REST AND DURING EXERCISE

	No. of patients	Pre-DSCG		Post-DSCG		Probability
		Mean	SD	Mean	SD	
Rest vent. litre/min	12	10.4	2.0	9.7	1.8	P > 0.05
Ex. vent. litre/min	8	33.0	5.2	31.8	3.0	P > 0.05
Heart rate per min Rest	12	85.0	10.5	80.0	11.4	0.05 > P > 0.01
Heart rate per min Ex.	8	126.2	12.5	126.5	23.5	P > 0.05
Resp. rate per min Rest	12	18.0	4.3	17.3	4.5	P > 0.05
Resp. rate per min Ex.	8	24.8	4.3	27.5	5.4	0.05 > P > 0.01
Art. O <sub>2</sub> sat. % Rest	11	92.3	1.6	91.9	1.7	P > 0.05
Art. O <sub>2</sub> sat. % Ex.	8	89.8	2.3	90.7	1.3	P > 0.05

Vent. = ventilation; Resp. = respiratory; Ex. = 300 kg.-m/min exercise; Art. O<sub>2</sub> sat. % = percentage arterial oxygen saturation.

TABLE VI. ACID BASE AND CARBON DIOXIDE

	No. of patients	Pre-DSCG		Post-DSCG		Probability
		Mean	SD	Mean	SD	
Blood pH	13	7.4	0.0	7.4	0.0	P > 0.05
Blood Pco <sub>2</sub> mmHg	13	29.5	3.4	35.3	3.9	0.01 > P > 0.001
Standard bicarbonate mEq/litre	13	20.6	1.7	22.2	1.3	0.05 > P > 0.01
Base excess mEq/litre	13	-4.4	2.2	-2.1	1.9	0.05 > P > 0.01
End-tidal Pco <sub>2</sub> mmHg	13	28.5	2.9	31.9	4.4	0.05 > P > 0.01

different from those after 3 months, and are not considered further. The probability that the difference between pre- and post-DSCG results is due to the drug therapy, is indicated in the last column of these tables: if P is less than 0.05 the difference may be regarded as statistically significant.

The vital capacity was measured in 15 subjects before and after a bronchodilator aerosol. One subject was known to develop distressing symptoms after isoprenaline inhalation

and was, therefore, not given any bronchodilator aerosol. The VC increased but the change did not quite reach statistically significant levels. However, when the VC is expressed as a percentage of the predicted value for each subject the improvement was statistically significant (Table III).

The subdivisions of lung volume were estimated in 11 patients. Functional residual capacity, residual volume and total lung capacity all became smaller indicating less hyper-

inflation post-DSCG, but the change is not statistically significant. The mean FRC was reduced from 119% to 107% of the predicted value and the RV from 151% to 121%. Nine of the 11 patients with these measurements improved towards normal. The lung clearance index, which is a measure of the intrapulmonary distribution of inspired gas, was measured on the same 11 patients and showed no statistically significant change (Table III).

Most of the tests of ventilatory capacity (Table IV) showed a statistically significant improvement after 3 months' treatment with DSCG. Maximum voluntary ventilation improved from 72 to 88 litre/min after 3 months' of therapy. Before DSCG therapy a bronchodilator aerosol improved the mean maximum voluntary ventilation from 72 to 89 litre/min. After 3 months' therapy the maximum voluntary ventilation was 88 litre/min before a bronchodilator aerosol had been inhaled, and further improvement with the use of the aerosol was obtained. The mean level for maximum voluntary ventilation rose to within normal limits after 3 months' therapy with DSCG and inhalation of a bronchodilator aerosol. The MMF and FEV<sub>1</sub> (as well as the VC) show a similar pattern, suggesting that the action of the bronchodilator aerosol is enhanced by the DSCG. The ratio FEV<sub>1</sub>/FVC improves after DSCG but the levels do not reach statistical significance because there is improvement in both components of the ratio. Nevertheless, after 3 months' DSCG therapy and inhalation of a bronchodilator aerosol this ratio is considerably better than in the control period and is close to normal levels.

Assessing the results of all these tests which are indirect measures of airway resistance, it was noted that there was less airway obstruction in 14 out of the 20 cases in the trial.

In an attempt to measure exercise tolerance we performed a standardized exercise test<sup>20</sup> during which we measured minute ventilation, heart rate, respiratory rate and arterial oxygen saturation. Twelve patients had such a test before and after DSCG therapy; 4 were probably improved and 8 unchanged. The mean results of each parameter are tabulated in Table V, which includes the exercise data on the 8 patients who were capable of performing the 300 kg-m/min load of exercise. The only statistically significant changes were a fall in the resting heart-rate and an increase in the respiratory rate per minute during exercise after 3 months' DSCG therapy.

Arterialized capillary blood was analysed in 13 patients. The pH was unaltered after 3 months' DSCG therapy but the carbon dioxide tension rose from a low level to normal. This reduction in alveolar hyperventilation is mirrored by the change in the standard bicarbonate of plasma and the base excess of blood so that normal levels for this altitude<sup>21</sup> (approximately 1 725 m above sea level) are attained. This diminution of hyperventilation is confirmed by the measurements of end-tidal (alveolar) carbon dioxide tension which rise to near normal levels after 3 months' DSCG therapy. During the control period there was a compensated respiratory alkalosis which became normal at the end of the trial period.

## DISCUSSION

Apart from measurements of ventilatory capacity, pulmonary function in asthma has been little studied until recently.<sup>25</sup> Hyperinflation of the lung is a feature of asthma, just as it is of chronic bronchitis and emphysema.<sup>25</sup> After 3 months' therapy with DSCG, the degree of hyperinflation in this series was reduced to normal (Table III) as has been noted in other trials.<sup>21,23</sup> This may help explain symptomatic improvement in patients in whom the FEV<sub>1</sub> remains relatively unaltered<sup>21,25,26</sup> and is an important argument against Grant *et al.* who were unimpressed with the value of DSCG because they placed great emphasis on the FEV<sub>1</sub> as an index of improvement.<sup>22</sup> In fact, in the present series also, the FEV<sub>1</sub> is not significantly different after DSCG unless it is measured after the use of a bronchodilator aerosol (Table IV). However, both the other tests of ventilatory capacity performed, the maximal voluntary ventilation and the maximal mid-expiratory flow rate, were significantly improved with or without prior inhalation of a bronchodilator.

In contrast to most investigators, Herxheimer and Bewersdorff<sup>24</sup> concluded that DSCG was of little value, but they did not administer the drug in the recommended manner or dosage and their contentions have been refuted.<sup>7,15</sup> Many patients state that dyspnoea is lessened by DSCG therapy. However, measurements of exercise tolerance and capacity showed no improvement in this series (Table V) or in others.<sup>20</sup> The exercise test which we employed completely failed to explain why patients experienced less breathlessness on exertion after DSCG therapy, but dyspnoea cannot readily be correlated with any specific measurements. Nevertheless, lessening of this symptom is a desirable therapeutic goal and one of the advantages of DSCG.

Hypoxaemia, due to altered ventilation-perfusion ratios is frequent during asthmatic attacks.<sup>24</sup> Reduced arterial carbon dioxide tension is the usual associated blood gas abnormality except in the presence of very severe airway obstruction.<sup>24</sup> Therefore, hypercapnia in the asthmatic is an important sign of deterioration<sup>30</sup> and an indication for urgent active treatment. Patients in this series were not studied during acute attacks and none were hypoxaemic at rest or during exercise (Table V). However, many were hypocapnic and in a state of compensated respiratory alkalosis. After DSCG therapy, acid-base balance and arterial PCO<sub>2</sub> returned to normal for this altitude (Table VI).<sup>21</sup>

It is difficult to assess objectively improvement in a condition like asthma which fluctuates in severity from day to day and even from hour to hour, with or without treatment. One way of overcoming this difficulty is to apply very frequent tests.<sup>4</sup> The patients of Robertson *et al.* recorded the peak-flow rate 3 times each morning and evening: the results provided useful confirmation of symptomatic benefit from DSCG.<sup>33</sup>

We decided to assess patient improvement after DSCG therapy in a number of different ways. Firstly, each patient made his own over-all assessment. Secondly, the physicians made a clinical judgement based on symptoms, physical signs and total drug usage. Thirdly, the physicians analysed

the diary cards kept by each patient who recorded 12-hourly symptoms and medication used throughout the trial. Fourthly, a battery of pulmonary function tests was applied. In general, there was a good correlation between these various assessments (Table I). The two patients who experienced no benefit from DSCG had unaltered tests, while the others all improved in some of the tests performed.

Until the advent of DSCG, there were 3 main groups of drugs used in asthma, viz. corticosteroids, sympathomimetics and xanthines. They have important side-effects and reduction in the quantity of these drugs used by asthmatics may be regarded as beneficial. Nearly every patient in this series was able to decrease his use of one or more of these drugs since commencing DSCG. Similar observations have been reported.<sup>34</sup> Its steroid-sparing property has been repeatedly demonstrated<sup>35,36</sup> and recently emphasized.<sup>3</sup> Decrease in the use of sympathomimetics, including aerosol inhalers may be equally important. Speizer *et al.*<sup>36</sup> suggested that the increasing death rate from asthma might be related to the increased use of sympathomimetic aerosols. Inman and Adelstein<sup>36</sup> reported a parallel rise in such aerosol sales and deaths attributed to asthma with a peak in 1967, followed by a parallel fall possibly due to the fact that the dangers of excessive use of sympathomimetic aerosols had been widely publicized in that year.<sup>8</sup> The propellant in aerosols ('freon') may be a cause of cardiac toxicity and death.<sup>37</sup> DSCG is not administered with a propellant and thus obviates this potential danger.

### PRACTICAL POINTS IN USE OF DSCG

1. As the action is prophylactic and lasts approximately 6 hours, it should initially be used on a regular basis 4 times per day (eg. on waking, before lunch and supper and on retiring). Dosage may be increased or decreased later as required.

2. Occasionally inhalation of the powder produces transient bronchospasm or a feeling of tightness in the chest. If troublesome, this symptom can be avoided by prior inhalation of a bronchodilator aerosol but excessive use must be prohibited.

3. DSCG is compatible and possibly synergistic with other drug therapy in asthma and should be introduced as additional medication. If and when improvement occurs, the other drugs may be reduced or stopped, but in the case of corticosteroids reduction of dosage must be gradual, to prevent acute adrenal insufficiency and/or pseudo-rheumatism.<sup>38</sup>

4. Patients must be warned not to stop DSCG therapy suddenly as severe relapse of asthma may occur.

5. Most patients responding favourably to DSCG do so within 2 weeks, though occasionally patients may respond only after 3 months' therapy. If no benefit is obtained, the method of administration should be checked in detail with the patient, as this is often faulty.

6. Sputum prevents DSCG reaching the bronchial mucosa and must be reduced as much as possible.

7. Young allergic patients who have not previously had therapy for asthma should use DSCG first. If asthma develops only on exposure to seasonal antigens, adequate protection may be obtained with DSCG used only during the relevant season.

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