Effect of Disodium Cromoglycate on Exacerbations of Asthma produced by Hyperventilation

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Summary

The prophylactic inhalation of disodium cromoglycate lessens the exacerbations which occur in some asthmatic patients after voluntary hyperventilation. Reasons are given for considering this to be a possible mechanism for certain types of emotional exacerbation of the disease and for disodium cromoglycate giving symptomatic relief of asthma disproportionate to the improvement in routine measurements of ventilatory capacity. It is suggested that one clinical indication for giving disodium cromoglycate is to observe whether a fall in FEV₁ occurs after two minutes hyperventilation.

Introduction

Disodium cromoglycate was originally described as a specific inhibitor of the results of reagenic antibody-antigen mechanisms *in vitro* (Cox, 1967). It does not appear to be a smooth-muscle relaxant or bronchodilator, nor does it neutralize any of the known chemical mediators of the anaphylactic type of reaction.

Altounyan (1967) showed that disodium cromoglycate previously inhaled as a powder had a prophylactic action in a subject known to have an attack of asthma on the inhalation of an aerosol of grass pollen solution. By use of a double-blind cross-over trial in 10 patients with severe asthma requiring high doses of corticosteroids and considered to have an allergic basis to their asthma because of the presence of eosinophils (Lendrum, 1944) in the sputum, Howell and Altounyan (1967) showed that symptomatic improvement was obtained in all 10 cases; but in only four were spirometric measures improved. This discrepancy between subjective improvement and improvement of objective indices of ventilatory capacity appears to be a characteristic of disodium cromoglycate.

Apparently quite separate from its antiallergic action, disodium cromoglycate has been shown to lessen post-exercise asthma (Davies, 1968). Normal subjects have an increase in airflow resistance of the bronchi on hyperventilation (Newhouse *et al.*, 1964; Sterling, 1968), and according to Curry (1947) bronchi of asthmatic subjects are hyperirritable and overreact to almost any stimulus. It therefore seemed reasonable to investigate whether hyperventilation produced an exacerbation of asthma. A demonstration that overbreathing can increase airways resistance would show one mechanism by which emotion can exacerbate the asthmatic state, since the latter is often accompanied by some degree of overbreathing. If disodium cromoglycate modified this effect the implication would be that it had an action against some types of emotional asthma, and that these have a common factor with post-exercise asthma. The mechanism in either case is at present obscure. It was therefore decided to investigate the prophylactic action of disodium cromoglycate on

any attacks of asthma that might be provoked by hyperventilation.

Patients and Methods

Nineteen asthmatic patients who were ambulant and thought to be co-operative volunteered to participate in the study. The forced expiratory volume in one second (FEV₁) was measured and repeated until consistent readings within $\pm 10\%$ were obtained. While seated the subjects were asked to breathe as hard as they could for exactly two minutes when the FEV₁ was immediately remeasured. Readings were then taken every minute for eight minutes, after which an isoprenaline aerosol was administered if any decrease in the FEV₁ remained. Five patients did not show a fall in the FEV₁. Of these five, three had had no asthma for over a year, one had had no attack of asthma while being treated with disodium cromoglycate during the previous three months, and one had never had spontaneous asthma but had allergic rhinitis. In him experimental asthma had been induced by the inhalation of a nebulized solution of the appropriate allergen on several occasions.

Fourteen patients showed a fall in the FEV₁. Six were males and eight were females. They were aged 11 to 59, with a mean of 33 years, the extremes of age being excluded by chance and not selection. None of them had previously been treated with disodium cromoglycate. Each of these 14 was shown how to inhale disodium cromoglycate powder, using a special apparatus supplied by the makers (Spinhalers-Fisons). A further appointment was made and they were instructed to inhale 20 mg of disodium cromoglycate every four hours, including during the night, for 24 hours before the next appointment. On arrival for the second test they inhaled a further 20 mg of disodium cromoglycate, irrespective of when the last inhalation had been taken. Ten minutes later the hyperventilation tests were repeated.

Results

In all 14 cases showing a fall of the FEV₁ on hyperventilation the fall was diminished but not prevented by the previous inhalation of disodium cromoglycate. The maximum fall usually occurred some minutes after hyperventilation, and this is similar to the pattern usually seen in post-exercise asthma. A typical series of readings with and without disodium cromoglycate is shown in Fig. 1.

The maximum falls in the FEV₁ with and without the prophylaxis of disodium cromoglycate during the eight minutes following the two minutes' hyperventilation are shown in the Table. Columns 1 and 4 are the control measurements before hyperventilation. Columns 2 and 5 set out the maximum fall achieved after hyperventilation. Though there was usually an interval of about a week between tests the control FEV₁ was similar in all patients except No. 7, who was in a better condition on the day of the experiment with disodium cromoglycate. There is a significant difference ($P < 0.005$) in the mean of the maximum fall in the two series of experiments with and without disodium cromoglycate. The results are shown in Fig. 2. The Table shows that not

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Effect of Two Minutes' Voluntary Hyperventilation in 14 Asthmatic Subjects Before and After the Inhalation of Disodium Cromoglycate

Before inhalation			After inhalation		
Control	Maximum Fall	Fall after 8 minutes	Control	Maximum Fall	Fall after 8 minutes
FEV ₁ (litres)			FEV ₁ (litres)		
3.8	-2.0	-1.8	3.7	-0.3	+0.1
2.2	-0.7	-0.6	2.2	-0.6	+0.2
2.3	-1.1	-1.1	1.7	-0.7	-0.3
2.0	-1.1	-1.1	2.4	-0.6	-0.4
2.2	-0.8	-0.7	2.1	-0.3	-0.2
0.5	-0.3	-0.1	0.5	-0.1	0.0
1.4	-0.9	-0.9	2.2	-1.3	-0.8
2.5	-1.2	-1.2	2.5	-0.3	-0.3
2.0	-0.6	-0.6	1.9	-0.3	0.0
2.0	-0.7	-0.6	2.1	-0.2	0.0
1.3	-0.8	0.0	1.5	-0.6	+0.8
2.6	-1.4	-1.1	2.5	-0.5	-0.1
2.2	-1.0	-0.6	2.8	-0.8	-0.6
1.4	-0.5	-0.4	1.5	-0.3	-0.1
Total	-13.1	-10.8	Total	-6.9	-1.7

Analysis by Student's test (one-tail test): Maximum fall, $t=3.397$ for 13 degrees of freedom ($P<0.005$); Fall after 8 minutes, $t=5.067$ for 13 degrees of freedom ($P<0.001$).

FIG. 1—Effect on FEV₁ following two minutes' hyperventilation in an asthmatic subject.

FIG. 2—Effect of disodium cromoglycate on exacerbations of asthma produced by hyperventilation. Maximum fall in FEV₁ during eight minutes following hyperventilation ($P<0.005$).

FIG. 3—Effect of disodium cromoglycate on duration of asthmatic exacerbations produced by hyperventilation. Comparison of fall in FEV₁ eight minutes after hyperventilation with and without the prophylactic inhalation of disodium cromoglycate. ($P<0.001$).

only is the extent of the fall lessened but the recovery is hastened by the previous inhalation of disodium cromoglycate powder. Columns 3 and 6 show the difference in the fall of the FEV₁ eight minutes after the cessation of hyperventilation (Fig. 3). The significance of the mean of the difference in the falls of the FEV₁ at eight minutes with and without disodium cromoglycate showed that P was <0.001 .

Discussion

Variation in the difficulty of breathing is the hallmark of asthma, the patient being subjected to variable degrees of airways obstruction. These fluctuations subjectively make the patient more aware of the dyspnoea. If the exacerbations are removed and the disability is constant, adaptation in the patient's mode of life can be made; this is preferable to suffering inconvenient and sometimes unexpected attacks of asthma, each of which in the patient's mind may be a potential danger. Should such exacerbations be removed, patients might be expected to report a considerable degree of subjective improvement, reflected in any diary of symptoms which they might keep; but this feeling of improvement would not necessarily give a corresponding improvement in periodical objective measurements of ventilatory capacity.

Emotion of any sort may cause overbreathing. Patients with chronic asthma showed a significant rise in the minute volume of expired air as compared with the relaxed state when asked to recall the memory of an asthmatic attack ($P<0.025$) (Clarke, unpublished data). Under hypnosis the suggestion of an attack of asthma causes hyperventilation and a fall in the FEV₁ (Clarke, 1970). This is evidence to show that a vicious circle can be set up as follows: the proprioceptive sensation of asthma causes overbreathing which leads to a rise in the airways resistance, which in turn increases the proprioceptive sensation of asthmatic distress. If this causes the patient to feel angry or frightened these emotions in themselves can further increase the airways resistance (Smith *et al.*, 1970). It is suggested that the present study gives evidence of a mechanism for the emotional exacerbation of asthma already started by such external stimuli as antigens and non-specific irritants; this is in addition to the exacerbation caused as a con-

ditioned reflex (Dekker and Groen, 1956; McFadden *et al.*, 1969).

There is some contradiction in the literature on the clinical effects of disodium cromoglycate (Pepys *et al.*, 1968; Herxheimer and Bewersdorff, 1969), but nearly all authors are agreed that it often gives useful subjective relief not always reflected by changes in the FEV₁, the most common index used. Improvements in asthma need not always be reflected in the FEV₁ (Woolcock and Read, 1965; Lane, 1969). Two authors state that the response to treatment by disodium cromoglycate cannot be predicted on allergic grounds alone (Campbell and Tandon, 1969; Ford, 1969). Its benefit in a specific case still appears to be unpredictable.

It is postulated that disodium cromoglycate can interfere with exacerbations of asthma which are emotional in nature brought about by hyperventilation consequent on the proprioceptive perception of asthma or other emotional cause, in addition to blocking the results of reagin-antigen union with its consequent asthma. Either mode of action may be at work separately or together at the same time. When an active allergic reaction is present both subjective and objective relief would be obtained. Otherwise the emotional exacerbations caused by hyperventilation together with the relief of post-exercise asthma would give considerable subjective symptomatic and functional relief not necessarily reflected in periodical measurements of ventilatory capacity in the outpatient department. Indications for the use of disodium cromoglycate are still not definite, and it is suggested that one simple test

indicating its use would be to observe whether a fall in the ventilatory capacity followed two minutes of maximum hyperventilation.

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Gross Oedema in the Nephrotic Syndrome Treated with Frusemide in High Dosage

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Summary

Five grossly oedematous patients with nephrotic syndrome required frusemide in doses of 250 mg/day or more. Two cases needed albumin infusions to initiate the diuresis. As oedema was removed renal function improved in four cases. There were no side effects. It is concluded that frusemide in the high doses used is a safe and effective diuretic.

Introduction

The safety and potency of frusemide has been established by more than five years' clinical experience throughout the world (Wertheimer *et al.*, 1967; Dollery, 1968). In the absence of severe renal failure a satisfactory diuretic response is usually obtained with daily doses of 40-200 mg, but occasionally much higher doses are required (Muth, 1968; Heiland *et al.*, 1969). The safety of administration of these larger amounts of frusemide has not been adequately established in patients without severe renal failure, and therefore a series of five

grossly oedematous nephrotic patients who were treated with more than 200 mg of frusemide per day were studied.

Patients and Methods

Two women and three men aged 16 to 50 who had failed to respond to conventional doses of frusemide were studied (Table I). All had the nephrotic syndrome with gross oedema and hypoalbuminaemia (less than 1.5 g/100 ml in four cases) and more than 5 g of urinary protein loss per 24 hours. In all cases the glomerular filtration rate was below normal at the onset of treatment. All subjects were normotensive. The study was mainly retrospective, the criterion for selection being that these patients needed over 250 mg of frusemide per day. All patients treated at this hospital in the past two years who satisfied this criterion were included.

Treatment was begun with 40-80 mg of frusemide daily, but as none of the patients responded the dose was doubled, usually at daily intervals until the diuresis began. The dose was then varied according to the diuretic response, requirements tending to decrease as the oedema was removed. In two patients (Cases 1 and 4) who were uraemic the diuresis was established only after plasma volume expansion with salt-poor albumin, 25 g of which was diluted in 500 ml of water in one case and in mannitol 10% in the other, and given daily for one week. Frusemide was added to the infusion. Spironolactone or triamterene was given largely for the potassium-sparing properties. Potassium requirements

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