

# Sodium cromoglycate and ipratropium bromide in exercise-induced asthma

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**Thomson, N C, Patel, K R, and Kerr, J W (1978).** *Thorax*, 33, 694-699. **Sodium cromoglycate and ipratropium bromide in exercise-induced asthma.** In thirteen patients with extrinsic asthma the effects of placebo, sodium cromoglycate, ipratropium bromide, and ipratropium bromide plus sodium cromoglycate were studied in a random double-blind fashion to assess their inhibitory action in exercise-induced asthma (EIA). Exercise testing consisted of steady state running on an inclined treadmill for up to eight minutes. In eight of the 13 patients studied the baseline ratio of expiratory flow at 50% vital capacity (VC) breathing helium-oxygen ( $\dot{V}_{50\text{He}}$ ) to  $\dot{V}_{50\text{air}}$  was over 1.20 and they were called responders; the remaining five patients were called non-responders. There was a significantly lower baseline maximum mid-expiratory flow rate (MMEF) in non-responders ( $P < 0.02$ ) as compared to responders but no difference in forced expiratory volume in one second ( $\text{FEV}_1$ ) or forced vital capacity (FVC).

Sodium cromoglycate ( $P < 0.02$ ), ipratropium bromide ( $P < 0.01$ ), and ipratropium bromide plus sodium cromoglycate ( $P < 0.01$ ) all significantly inhibited the percentage fall in  $\text{FEV}_1$  after exercise in the responders. Ipratropium bromide had no preventive action in non-responders, unlike sodium cromoglycate ( $P < 0.05$ ) and ipratropium bromide plus sodium cromoglycate ( $P < 0.02$ ).

It is postulated that mediator release is an important factor in development of EIA in most extrinsic asthmatics, whereas cholinergic mechanisms are relevant only in those patients in whom the main site of airflow obstruction is in the large central airways.

Although the mechanisms involved in exercise-induced asthma (EIA) are unknown, both the release of bronchoconstrictor mediators (*Lancet*, 1976) and reflex bronchoconstriction secondary to stimulation of vagal receptors (Gold, 1975) have been postulated. Sodium cromoglycate (SCG), which inhibits the release of mediators from mast cells (Orr *et al*, 1970), may have a preventive effect in EIA through a similar mechanism (Davies, 1968). The inhibitory action of anticholinergic agents is more variable (Godfrey and König, 1976; Tinkelman *et al*, 1976), although any lack of effect does not appear to be due to inadequate cholinergic blockade (personal observations) as had been previously suggested (Tinkelman *et al*, 1976). In an uncontrolled study reported by McFadden *et al* (1977) the combination of SCG and the anticholinergic drug ipratropium bromide (IB) inhibited EIA in all patients studied, whereas IB alone inhibited only those patients with mainly large airways obstruction as assessed by changes in density dependence of maximal expiratory flow rates. SCG was not given alone. They concluded that the airway response to

exercise in asthmatics is heterogenous in terms of predominant site of flow limitation and with regard to mechanism.

The purpose of this study was to investigate in a double-blind manner the effects of SCG, IB, and IB plus SCG in the prevention of EIA in patients whose main site of airflow obstruction was in small and large airways as assessed by maximal expiratory flow rate response to low density gas breathing. It was hoped that these results might further define the role of mediator release and vagal action in EIA.

## Methods

Seven men and six women (age 17-33 years) with extrinsic bronchial asthma and reversible airflow obstruction gave informed consent to be studied. All patients had positive skin tests to inhalant allergens, a blood eosinophilia ( $>450/\text{mm}^3$ ) and a total blood IgE level above 200 u/ml. SCG and bronchodilators were discontinued 24 hours before each test was carried out. Patients on oral or aerosol corticosteroids

were excluded from the study. All were non-smokers.

Forced expiratory volume in one second (FEV<sub>1</sub>), forced vital capacity (FVC), and maximum mid-expiratory flow rates (MMEF) were measured in triplicate on a water-sealed spirometer (Godart), the best recording being used for analysis. Maximal expiratory flow volume (MEFV) curves were produced using a heated pneumotachograph (calibrated for air and helium (He)-oxygen (O<sub>2</sub>)) with integration of flow, and recorded on a Hewlett-Packard 7041A X-Y recorder. Another MEFV curve was then produced after the patient had been breathing a He-O<sub>2</sub> mixture in concentrations of 79% and 21% respectively for at least one minute, which included three deep inspirations. The curves with the highest maximal flows whose vital capacities (VC) on air and He-O<sub>2</sub> matched were used for analysis. The expiratory flows at 50% VC breathing air ( $\dot{V}_{50\text{air}}$ ) and He-O<sub>2</sub> ( $\dot{V}_{50\text{He}}$ ) were measured, and the degree of density dependence was assessed as the ratio of  $\dot{V}_{50\text{He}}$  to  $\dot{V}_{50\text{air}}$ . Responders were those patients in whom the ratio  $\dot{V}_{50\text{He}}$  to  $\dot{V}_{50\text{air}}$  was over 1.20. Where necessary, volumes were corrected to BTPS. Predicted normal values were taken from Cotes (1975) for FEV<sub>1</sub> and FVC and from Cherniak and Raber (1972) for MMEF.

Exercise testing consisted of steady state running on an inclined treadmill (10°) for between five and eight minutes. The speed of the treadmill was adjusted so that the patient's pulse rate at the end of the exercise was at least 170–180 beats/min. The same setting and duration was used for each test in any one patient. The four exercise tests performed on each patient were all completed within 10 days.

The studies were carried out in a random double-blind fashion using the following agents administered by Wright's nebuliser during 10 minutes' tidal breathing, flow rate 8 l/min: (1) SCG nebuliser solution (10G/l)—estimated dose nebulised 20 mg; (2) IB (1G/l)—estimated dose nebulised 2.0 mg; (3) SCG (10G/l)+IB (1G/l) solutions; and (4) saline solution (9G/l). Following baseline measurements of FEV<sub>1</sub>, FVC, MMEF, and MEFV curves breathing air and He-O<sub>2</sub>, the drug solution was inhaled for two periods of five minutes separated by an interval of one minute. After 20 minutes spirometry was repeated, and then at 2, 5, 10, 15, and 20 minutes after the exercise test. In three subjects MEFV curves breathing air and He-O<sub>2</sub> were also recorded between 5 and 10 minutes post exercise. A positive response was defined as one in which there was a decrease in FEV<sub>1</sub> of more than 20%. Results of exercise tests were expressed as the maximum post-exercise fall in pulmonary function recording as a percentage of post-drug or placebo baseline. Statistical analysis was performed using Student's paired and unpaired *t* tests.

## Results

In eight of the 13 patients studied, the baseline ratio  $\dot{V}_{50\text{He}}/\dot{V}_{50\text{air}}$  was over 1.20, and these were called responders; the remaining five patients were called non-responders. Hereafter, we refer to the results in these two groups.

The results of the tests are given in tables 1 and 2. There was no significant difference between the mean baseline values, expressed as percentage of predicted FEV<sub>1</sub>, FVC, or MMEF, before aerosol administration on the four days. Mean baseline MMEF was significantly lower in non-responders ( $P < 0.02$ ), but there were no significant differences in FEV<sub>1</sub> or FVC.

SCG ( $P < 0.02$ ), IB ( $P < 0.01$ ), and IB plus SCG ( $P < 0.01$ ) all significantly inhibited the percentage fall in FEV<sub>1</sub> after exercise in the responders. IB, however, had no preventive action in the non-responders, unlike both SCG ( $P < 0.05$ ) and IB plus SCG ( $P < 0.02$ ). IB had no significant effect on FVC in non-responders. SCG significantly prevented the fall in MMEF in both responders ( $P < 0.02$ ) and non-responders ( $P < 0.05$ ), while IB had no preventive action in either group.

In responders the drugs shown to have a significant inhibitory action were equally effective in preventing the percentage fall in FEV<sub>1</sub> and MMEF. In the non-responders SCG was superior to IB in preventing the percentage fall in FEV<sub>1</sub> ( $P < 0.05$ ) and MMEF ( $P < 0.02$ ) but not FVC. The combination of SCG plus IB also reduced the percentage fall in FEV<sub>1</sub> ( $P < 0.02$ ), MMEF ( $P < 0.01$ ), and FVC ( $P < 0.05$ ) compared with IB. There was no difference, however, between SCG and SCG plus IB in the non-responders.

There were no differences between the falls in ventilatory capacity after the control exercise in the two groups. Figures 1 and 2 show the individual values for FEV<sub>1</sub> and MMEF in both responders and non-responders.

In the three patients in whom  $\dot{V}_{50\text{He}}/\dot{V}_{50\text{air}}$  was measured after exercise, the ratio increased in one from 1.29 to 1.35, in another it fell from 1.57 to 1.00, while in the third it remained 1.00. These post-exercise values all refer to post-IB exercise.

No side effects were noted during the study after any of the drugs used.

## Discussion

Patients with asthma have been separated into two groups by measuring the MMEF response to low density gas breathing (Despas *et al*, 1972). Those showing an increase in flow rates on breathing helium are thought to have the major site of resistance to expiratory flow in the large central airways (responders), while in those showing no such increase the

Table 1 Baseline FEV<sub>1</sub> and maximum percentage fall after exercise (mean ± SEM)

	Control		Sodium cromoglycate		Ipratropium bromide		Ipratropium bromide + sodium cromoglycate	
	Baseline	% fall	Baseline	% fall	Baseline B	A	Baseline B	A
Responders	3.24 ± 0.24 (94.3 ± 4.7)	38.7 ± 6.2	3.23 ± 0.28 (94.2 ± 5.2)	17.5 ± 6.0 < 0.02	3.14 ± 0.27 (92.2 ± 4.1)	3.42 ± 0.27 (99.7 ± 3.8)	3.15 ± 0.29 (92.0 ± 6.0)	3.44 ± 0.26 (100.5 ± 4.4)
P Value								
Non-responders	2.69 ± 0.40 (75.3 ± 13.4)	37.1 ± 5.5	2.65 ± 0.40 (74.3 ± 11.5)	9.9 ± 5.6 < 0.05	2.54 ± 0.32 (71.2 ± 10.5)	3.00 ± 0.45 (84.2 ± 13.1)	2.54 ± 0.38 (71.4 ± 13.5)	3.03 ± 0.48 (85.0 ± 14.7)
P Value								

Baseline data are expressed as absolute values (l) and percentage of predicted (in brackets).

B = Before drug, A = After drug.

P values refer to the difference between results after control exercise and those after sodium cromoglycate or ipratropium bromide or ipratropium bromide plus sodium cromoglycate.

Table 2 Baseline FVC and MMEF and maximum fall after exercise (mean ± SEM)

	Control		Sodium cromoglycate		Ipratropium bromide		Ipratropium bromide + sodium cromoglycate	
	Baseline	% fall	Baseline	% fall	Baseline B	A	Baseline B	A
FVC								
Responders	4.17 ± 0.30 (102.4 ± 4.9)	26.6 ± 6.8	4.08 ± 0.31 (100.3 ± 5.2)	13.0 ± 4.8 NS	4.10 ± 0.29 (100.8 ± 3.8)	4.09 ± 0.31 (100.6 ± 3.5)	4.09 ± 0.34 (100.7 ± 6.3)	4.26 ± 0.31 (104.7 ± 5.4)
P Value								
Non-responders	4.55 ± 0.46 (105.5 ± 10.1)	29.8 ± 4.0	4.46 ± 0.56 (103.6 ± 10.3)	7.6 ± 5.4 < 0.05	4.34 ± 0.48 (100.7 ± 9.7)	4.71 ± 0.56 (109.3 ± 9.0)	4.27 ± 0.34 (99.2 ± 9.8)	4.63 ± 0.54 (107.6 ± 10.0)
P Value								
MMEF								
Responders	2.85 ± 0.30 (56.3 ± 4.1)	50.8 ± 5.7	3.04 ± 0.36 (60.2 ± 5.6)	25.8 ± 9.1 < 0.02	2.81 ± 0.35 (55.6 ± 5.8)	3.59 ± 0.30 (71.0 ± 3.7)	2.78 ± 0.35 (55.1 ± 5.3)	3.77 ± 0.25 (74.7 ± 4.3)
P Value								
Non-responders	1.73 ± 0.45 (35.4 ± 8.6)	42.3 ± 8.5	1.50 ± 0.36 (30.9 ± 7.3)	10.8 ± 6.1 < 0.05	1.34 ± 0.24 (27.5 ± 5.7)	1.74 ± 0.43 (35.8 ± 8.5)	1.53 ± 0.43 (31.5 ± 9.3)	2.09 ± 0.54 (42.9 ± 11.6)
P Value								

Format is identical to Table 1 FVC (l) MMEF (l/s<sup>-1</sup>).

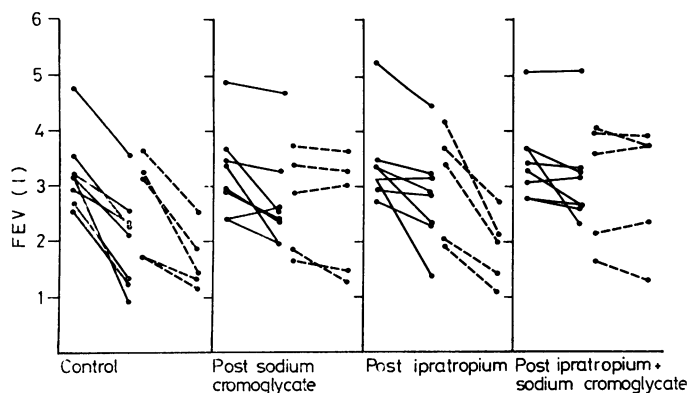


Fig 1 Effect of exercise on absolute values for  $FEV_1$  in responders (—) and non-responders (-----) after control exercise, post sodium cromoglycate, post ipratropium bromide, and post ipratropium bromide plus sodium cromoglycate.

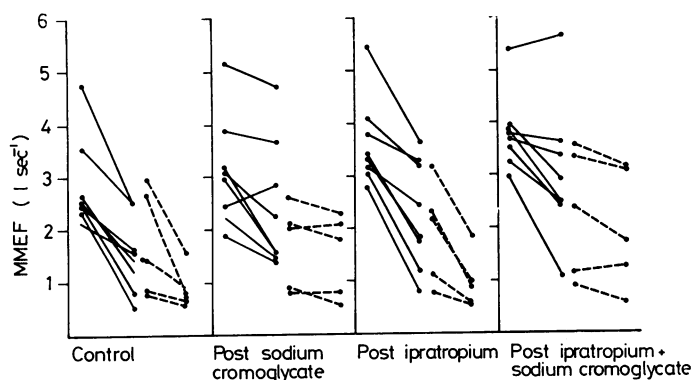


Fig 2 Effect of exercise on absolute values for MMEF in responders (—) and non-responders (-----) after control exercise, post sodium cromoglycate, post ipratropium bromide, and post ipratropium bromide plus sodium cromoglycate.

major site is thought to be in the small peripheral airways (non-responders). Other factors affecting the major site of obstruction may be cigarette smoking and the presence of chronic bronchitis or recurrent respiratory infections (Antic and Macklem, 1976). Using this classification, eight patients in our study were responders while five were non-responders. The predicted baseline values of  $FEV_1$  and FVC did not differ between the two groups. Non-responders had, however, significantly lower flow rates in small airways as assessed by baseline MMEF rates (McFadden and Linden, 1972).

In this study both SCG alone and in combination with IB inhibited EIA, as measured by fall in  $FEV_1$ , in both responders and non-responders, while IB had a preventive action only in responders. IB had no inhibitory activity, however, in either responders or non-responders when assessed by the change in MMEF, while SCG was significantly inhibitory in both these groups. If MMEF is a test of small airways calibre then IB unlike SCG would appear to have no inhibitory action on these airways. In both responders and non-responders there was no difference in the effectiveness of the drugs shown to have a preventive

action on EIA. SCG, although given in nebulised form which is likely to have increased its penetration into the lungs, was given in the dose normally used from a spinhaler. Our findings, therefore, confirm its effect in EIA reported by others (Davies, 1968; Godfrey and König, 1976). The estimated dose of IB nebulised was 2.0 mg, which is 50 times the normal therapeutic dose. Higher doses of anticholinergic agents are required to block reflex vagal bronchoconstriction in animals (Widdicombe and Stirling, 1970), but from our unreported sources this did not appear to be the case in our previous study in which the EIA of four of nine subjects was not prevented by 0.5 mg of IB or 10 mg of atropine. In previous studies comparing SCG and IB in extrinsic asthmatics Chan-Yeung (1977) reported the prevention of EIA in three out of four patients by IB and in all by SCG, while Godfrey and König (1976) prevented EIA in three out of seven patients with atropine methonitrate and six out of seven with SCG. These authors did not, however, identify any differences between their patients and the therapeutic responses observed.

McFadden *et al* (1977) studied 12 patients with

EIA who were all responders before exercise. IB inhibited those in whom density dependence increased after exercise indicating predominantly large airways obstruction but had no effect in those with predominantly small airways obstruction as assessed by a decrease in density dependence. This latter group, however, showed diminution in EIA by the addition of SCG. Despite not giving SCG alone, they proposed that mediator release might serve to initiate reflex bronchoconstriction. In our study post-exercise density dependence was measured in two responders, one showing an increase and the other a decrease in density dependence. The response to IB in these two patients was similar to that predicted by McFadden *et al* (1977). The non-responder before exercise remained so after exercise as has been found by others (Chang Yeung *et al*, 1976).

Our results are in keeping with IB acting mainly in the large airways and SCG acting in both small and large airways. In addition, SCG by nebuliser appears to be equally effective in both responders and non-responders. SCG inhibits mediator release from mast cells (Orr *et al*, 1970) while IB could have two sites of action, either directly on cholinergic receptors in bronchial smooth muscle or on mast cells preventing mediator release (Kaliner *et al*, 1972). This latter action of IB seems unlikely since SCG was effective in patients in whom IB was not. We propose, therefore, that mediator release is important in most extrinsic asthmatics with EIA. In those in whom the main site of airflow obstruction is in the large central airways, which are predominantly under vagal control, mediator release results in bronchoconstriction due to cholinergic mechanisms and direct smooth muscle action. When the main site of airflow obstruction is in the smaller airways under lesser vagal control, mediator release causes bronchoconstriction due to its direct action on smooth muscle, cholinergic activity being of little importance to overall airways calibre. In support of our findings the vagus nerve predominantly effects bronchomotor tone in the large airways (Vincent *et al*, 1970; Simonsson, 1972), and atropine has proportionally greater activity in these airways (Cavanaugh and Cooper, 1976; Ingram *et al*, 1977). It would appear, however, that this proposed mechanism may not be relevant in all patients as the post-exercise fall in two of our subjects was not inhibited by any of the drugs used. In addition, from a practical therapeutic standpoint, SCG is likely to be superior to IB in the prevention of EIA in extrinsic asthmatics in whom helium response is not known.

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