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 (V\textsubscript{50He}) to V\textsubscript{50air} 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 (FEV\textsubscript{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 FEV\textsubscript{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/mm\textsuperscript{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 (FEV1),
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 (MEVF) curves were pro-
duced using a heated pneumotachograph (calibrated
for air and helium (He)-oxygen (O2)) with integration
of flow, and recorded on a Hewlett-Packard 7041A
X-Y recorder. Another MEFV curve was then pro-
duced after the patient had been breathing a He-O2
mixture in concentrations of 79 % and 21 % respec-
tively 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-O2 matched were used for analysis. The expiratory
flows at 50 % VC breathing air (V50He) and He-O2
(V50He) were measured, and the degree of density
dependence was assessed as the ratio of V50He to
V50air. Responders were those patients in whom the
ratio V50He/V50air was over 1·20. Where necessary,
volumes were corrected to BTPS. Predicted normal
values were taken from Cotes (1975) for FEV1, 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 adminis-
tered 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
FEV1, FVC, MMEF, and MEFV curves breathing
air and He-O2, 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-O2 were also recorded between
5 and 10 minutes post exercise. A positive response
was defined as one in which there was a decrease in
FEV1 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
V50He/V50air 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
FEV1, FVC, or MMEF, before aerosol adminis-
tration on the four days. Mean baseline MMEF was
significantly lower in non-responders (p<0·02), but
there were no significant differences in FEV1 or FVC.

SCG (p<0·02), IB (p<0·01), and IB plus SCG
(p<0·01) all significantly inhibited the percentage
fall in FEV1 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 FEV1 and MMEF. In the non-
responders SCG was superior to IB in preventing the
percentage fall in FEV1 (p<0·05) and MMEF
(p<0·02) but not FVC. The combination of SCG
plus IB also reduced the percentage fall in FEV1
(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 FEV1 and MMEF in both responders and
non-responders.

In the three patients in whom V50He/V50air 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 (respon-
ders), while in those showing no such increase the
Table 1  Baseline FEV₁ and maximum percentage fall after exercise (mean ± SEM)

<table>
<thead>
<tr>
<th>Control</th>
<th>Sodium cromoglycate</th>
<th>Ipratropium bromide</th>
<th>Ipratropium bromide + sodium cromoglycate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline % fall</td>
<td>Baseline % fall</td>
<td>Baseline % fall</td>
<td>Baseline % fall</td>
</tr>
<tr>
<td>Responders 3.24 ± 0.24</td>
<td>3.23 ± 0.28</td>
<td>3.14 ± 0.27</td>
<td>3.15 ± 0.29</td>
</tr>
<tr>
<td>(94.3 ± 4.7)</td>
<td>(94.2 ± 5.2)</td>
<td>(92.2 ± 4.1)</td>
<td>(92.0 ± 6.0)</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.02</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Non-responders 2.69 ± 0.40</td>
<td>2.65 ± 0.40</td>
<td>2.54 ± 0.32</td>
<td>2.54 ± 0.38</td>
</tr>
<tr>
<td>(75.3 ± 13.4)</td>
<td>(74.3 ± 11.5)</td>
<td>(71.2 ± 10.5)</td>
<td>(71.4 ± 13.5)</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.05</td>
<td>NS</td>
<td>&lt; 0.02</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Control</th>
<th>Sodium cromoglycate</th>
<th>Ipratropium bromide</th>
<th>Ipratropium bromide + sodium cromoglycate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline % fall</td>
<td>Baseline % fall</td>
<td>Baseline % fall</td>
<td>Baseline % fall</td>
</tr>
<tr>
<td>FVC Responders 4.17 ± 0.30</td>
<td>4.08 ± 0.31</td>
<td>4.10 ± 0.29</td>
<td>4.09 ± 0.31</td>
</tr>
<tr>
<td>(102.4 ± 4.9)</td>
<td>(100.3 ± 5.2)</td>
<td>(100.8 ± 3.8)</td>
<td>(100.7 ± 6.3)</td>
</tr>
<tr>
<td>p Value</td>
<td>NS</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Non-responders 4.55 ± 0.46</td>
<td>4.46 ± 0.56</td>
<td>4.34 ± 0.48</td>
<td>4.27 ± 0.34</td>
</tr>
<tr>
<td>(105.5 ± 10.1)</td>
<td>(103.6 ± 10.3)</td>
<td>(100.7 ± 9.7)</td>
<td>(99.2 ± 9.8)</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.05</td>
<td>NS</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>MMEF Responders 2.85 ± 0.30</td>
<td>3.04 ± 0.36</td>
<td>2.81 ± 0.35</td>
<td>2.78 ± 0.35</td>
</tr>
<tr>
<td>(56.3 ± 4.1)</td>
<td>(60.2 ± 5.6)</td>
<td>(55.6 ± 5.8)</td>
<td>(55.1 ± 5.3)</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.02</td>
<td>NS</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Non-responders 1.73 ± 0.45</td>
<td>1.50 ± 0.36</td>
<td>1.34 ± 0.24</td>
<td>1.53 ± 0.43</td>
</tr>
<tr>
<td>(35.4 ± 8.6)</td>
<td>(30.9 ± 7.3)</td>
<td>(27.5 ± 5.7)</td>
<td>(31.5 ± 9.3)</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.05</td>
<td>NS</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Format is identical to Table 1 FVC (l) MMEF (l/s2).
Sodium cromoglycate and ipratropium bromide in exercise-induced asthma

Fig 1  Effect of exercise on absolute values for FEV₁ 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 FEV₁ 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 FEV₁, 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 helin response is not known.

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