THE POSSIBLE SITE OF ACTION OF SODIUM CROMOGLYCATE ASSESSED BY EXERCISE CHALLENGE

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SUMMARY

1. The protective effect of different particle sizes of sodium cromoglycate (SCG) was assessed by exercise challenge in nine asthmatic patients.

2. SCG particles of 11.7 μm or 2.0 μm mass median diameter were generated by a spinning disc and compared with lactose placebo particles. The drugs were given 10 min before a 6 min run on a treadmill.

3. The post-exercise bronchoconstriction caused a 48% fall in peak flow rate in the placebo test, a 41% fall after the large SCG particles and a 20% fall after the small particles.

4. It is concluded that the site of action of SCG is probably in the smallest airways.

Key words: sodium cromoglycate, exercise-induced asthma, particle size, distribution of particles.

A characteristic feature of most asthmatic patients is the way in which a typical brief attack of asthma may be induced by the inhalation of an appropriate antigen (Aas, 1970). Exercise also provokes a brief attack which has many similarities to this type 1 allergic reaction (Jones, Bustom & Wharton, 1962; Silverman & Anderson, 1972; Godfrey, 1973). The asthmatic reactions can often be prevented by premedication with sodium cromoglycate if this is given before antigen challenge (Pepys, Hargreave, Chan & McCarthy, 1968), or before exercise challenge (Davies, 1968; Godfrey, 1970; Silverman & Andrea, 1972).

Sodium cromoglycate (SCG) is inhaled in the form of a powder and when presented in the standard capsule (Intal) the particle size is mostly less than 6 μm in diameter; the inhaler used clinically (Spinhaler) is designed to break up aggregates into fine particles. When used by patients, about 25% by weight of the drug in the capsule is dispersed into particles below 6 μm in size (Bell, Hartley & Cox, 1971) and about 5% by weight of the drug is in particles less than 2 μm in size (personal observations).

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It has been shown that when particles of about 2 μm enter the airways, they have a good chance of reaching the smallest bronchioles while particles of about 10–12 μm will reach only the large, proximal bronchi (Hatch & Gross, 1964). It occurred to us that the site of action of SCG could be explored by investigating the protective effect of different particle sizes of the drug on exercise-induced asthma.

**METHOD**

Studies were carried out on nine asthmatic patients aged 10–44 years as part of the assessment of the effect of exercise. Some details of the patients are given in Table 1. All patients were studied at the same time of day when in a stable state and not during an exacerbation of their illness. Each patient was studied once on 3 consecutive days inhaling either lactose placebo, or small or large SCG particles in random order. No other drugs were taken for at least 6 h before the test.

Simple lung-function tests were carried out before and after inhalation of the particles. The peak expiratory flow rate (PEF) was measured with a Wright peak flow meter; the forced expired volume in the first second (FEV₁) and the forced vital capacity (FVC) were measured with a water spirometer. In each test the best individual value from three attempts was recorded.

Particles of lactose or SCG were produced by the apparatus illustrated in Fig. 1. The aerosols of sodium cromoglycate were generated from aqueous solutions by using a spinning top aerosol generator (May, 1966). The generator was placed at the top of the chamber, which was approximately 2 m high and 0·5 m in diameter. The wet aerosol droplets were dried during their passage down the chamber by a current of warm air, which was drawn in at the top of the chamber. The subjects thus inhaled aerosols consisting of solid particles. The size of particle was controlled by regulating the rotational speed of the disc and the concentration of SCG in the solution.
The lactose particles were generated from a dry powder composed of finely ground lactose by using the Wright dust feed mechanism (Wright, 1950). In contrast to the almost monosized aerosols of SCG, the lactose aerosol contained a spread of particle sizes which would be deposited in all portions of the airways. During each test, frequent checks were made on the particle size distribution of the aerosols by microscopic examination of a slide which had been exposed in the chamber. The mass median diameter and geometric standard deviation of the SCG particles were \(2.0 \mu m \pm 1.2\) and \(11.7 \mu m \pm 1.1\) respectively. The lactose particles were of all sizes between 1 and 20 \(\mu m\).

The concentration of SCG inhaled by the patient was 19.5–29.3 nmol/l (10–15 \(\mu g/l\)) for small particles and 156–195 nmol/l (80–100 \(\mu g/l\)) for large particles.

It was intended that each subject inhale 29.3 nmol (15 \(\mu g\)) of SCG per kg body weight. Knowing the concentration of drug in the chamber and the quantity usually deposited in tubing and mouth, the volume of each particle cloud to be inhaled was calculated for each
subject. This usually meant inhaling 2–3 vital capacities of large particles and 20–30 vital capacities of small particles. In the control experiments 10–15 vital capacities of the mixed sized lactose particles were inhaled. The quantity of drug presumably passing the larynx was calculated from the volume inhaled, the inspired concentration, the quantity deposited in the tubing of the apparatus, the quantity collected in a filter through which the subject exhaled and the quantity in a mouthwash performed by the subject immediately after completion of the inhalations. The SCG concentration of washings was determined spectrophotometrically. The inhaled dose is given in Table 1; the mean pulmonary dose was 24·2 nmol/kg \( \pm \) 2·0 (S.E.M.) for small particles and 18·7 nmol/kg \( \pm \) 2·3 (S.E.M.) for large particles.

As soon as the mouthwash was completed, lung function tests were performed and then the exercise test was begun. The delay between inhalation and exercise was 10 min and did not differ between different tests. Exercise testing was carried out on a motor-driven treadmill as described previously (Connolly & Godfrey, 1970; Silverman & Anderson, 1972). Essentially the subject ran (not walked) for 6 min at a slope of 10% and a speed adjusted to give a heart rate of 170 per min in children and 150 per min in adults. The PEF was measured before starting, every 2 min during exercise without stopping, and at frequent intervals for 20 min after the end of exercise. For the assessment of response in this study, the % fall in PEF was calculated as follows:

\[
\text{fall (\%)} = \frac{\text{resting PEF} - \text{lowest PEF after exercise}}{\text{resting PEF}} \times 100
\]

The expected values for pulmonary function were taken from Godfrey, Kamburoff & Nairn (1969) and Cotes (1968). Results were analysed by standard statistical procedures and differences between studies were assessed by paired \( t \) tests.

RESULTS

Resting measurements

The mean resting PEF and FEV\(_1\) were 55–60% of expected and FVC was 80–90% of expected, showing a moderate degree of airways obstruction to have been present. There were no significant differences between values before and after inhalation of any one type of particle, or between values for different types of particle (Table 2).

Exercise-induced asthma

After the inhalation of lactose placebo, all subjects developed post-exercise bronchoconstriction amounting to a fall in PEF of between 20% and 71%. There was a substantial reduction of exercise-induced asthma in all but one subject after premedication with small particles. After inhalation of large SCG particles two subjects showed more severe exercise-induced asthma than after lactose, three had a similar amount and four had less exercise-induced asthma (but in one of these cases there was much less protection than with small particles). The detailed results are illustrated for one subject in Fig. 2 and the % fall in PEF for each individual is shown in Fig. 3. The difference in % fall for the whole group (Table 2) was highly significant when comparing small particles with either lactose (\( P < 0.001 \)) or large particles (\( P < 0.01 \)). There was no significant difference in % fall between lactose and large particles (\( P > 0.5 \)).
Table 2. Resting pre- and post-drug FEV₁, and % fall in PEF due to exercise. Details of resting PEF and FVC can be supplied by the authors on request.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Lactose</th>
<th>Small particles</th>
<th>Large particles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-drug</td>
<td>Post-drug</td>
<td>Post-exercise</td>
</tr>
<tr>
<td></td>
<td>FEV₁</td>
<td>FEV₁ (resting)</td>
<td>FEV₁ (%)</td>
</tr>
<tr>
<td>S.A.</td>
<td>73</td>
<td>73</td>
<td>24</td>
</tr>
<tr>
<td>J.R.</td>
<td>48</td>
<td>46</td>
<td>71</td>
</tr>
<tr>
<td>S.N.</td>
<td>54</td>
<td>58</td>
<td>45</td>
</tr>
<tr>
<td>W.W.</td>
<td>106</td>
<td>104</td>
<td>47</td>
</tr>
<tr>
<td>I.E.</td>
<td>40</td>
<td>48</td>
<td>57</td>
</tr>
<tr>
<td>S.T.</td>
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<td>34</td>
<td>50</td>
</tr>
<tr>
<td>C.T.</td>
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<td>50</td>
<td>20</td>
</tr>
<tr>
<td>D.W.</td>
<td>63</td>
<td>68</td>
<td>67</td>
</tr>
<tr>
<td>D.S.</td>
<td>54</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>Mean</td>
<td>59</td>
<td>59</td>
<td>48</td>
</tr>
<tr>
<td>SEM</td>
<td>7</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>
FIG. 2. Exercise-induced asthma in one subject after inhaling different particles. ▲, Small particles; □, large particles; ○, lactose.

FIG. 3. Results for all subjects showing the exercise-induced asthma in relation to inhaled particles.
Site of action of cromoglycate

DISCUSSION

This study has shown that, for most asthmatic subjects, 2.0 μm particles of SCG cause substantially greater suppression of exercise-induced asthma than 11.7 μm particles. The obvious conclusion to be drawn is that SCG must act on a peripheral site in the lung, but there is another possibility which must be considered, namely a numerical or area-related effect. Since the weight of both particle sizes inhaled was kept similar, the actual number of small particles would be approximately 200 times the number of large particles, the volume of a sphere of radius \( r \) being \( \frac{4}{3} \pi r^3 \). By similar reasoning, the total surface area of this number of small particles would be some 6 times that of the large particles, since the area of a sphere is \( 4\pi r^2 \). Now it is possible that the larger number or area of the smaller particles was responsible for their greater effect either because they were able to saturate more receptor binding sites or because they dissolved more rapidly in the region of these sites. On the whole, these hypotheses seem unlikely because they would imply either that the small particles should be 200 times as effective as the large particles or possibly 6 times as effective. Looking at the results in Table 2, it can be seen that small particles reduced exercise-induced asthma by approximately 58% (from 48 to 20) while large particles reduced it 17% (from 48 to 41). This represents roughly a threefold difference on average and is less than predicted by the numerical or size-related hypotheses.

The commercially available form of SCG delivers approximately 7 mg of the compound in particles less than 6 μm in size when inhaled, and calculations based on data from the present experiments suggest that some 60–80% of this weight enters the lungs. The degree of suppression of exercise-induced asthma by the commercial preparation is usually of a similar order to that found here with 2.0 μm particles; in eighty patients given the commercial compound, the mean exercise-induced fall in PEF after placebo was reduced by 56% (P. König & S. Godfrey, personal observations). This formulation must deposit many more particles than in the present experiments and the lack of any greater suppression of exercise-induced asthma suggests that dose is a relatively unimportant determinant of the effect of particles of different sizes.

The alternative conclusion to be drawn from the results of this study, namely that the difference of effect is due to the different penetrations of small and large particles, implies that it should be possible to determine the site of action of the drug. Crucial to this argument is the homogeneity of particle size and the likely distribution of particles in the lung. The method used to generate the particles gave a very uniform size, as assessed by the geometric standard deviation, and because SCG is relatively insoluble, little change due to water effects would be expected when the dry powder was inhaled. A check on this was carried out by humidifying particles under the microscope and no change in size was noted. The fate of the inhaled particles depends upon factors such as tidal volume and flow rate as well as size and our conclusions about the likely site of deposition are based on the analysis of these factors by Hatch & Gross (1964). However, the data upon which they based their calculations were obtained from studies on normal subjects. Although our patients were relatively well at the time of inhalation, they had some airway obstruction and nothing is known for certain about particle distribution in this situation. Changes in flow rate would be unlikely to affect the distribution of 2 μm particles since they are believed to deposit in terminal bronchioli or alveoli, where the flow is already so slow and the cross-sectional area so large. With the patients
breathing deeply and slowly, it is also rather unlikely that the deposition of the larger particles would be much affected by the moderate airways obstruction since this probably affects smaller airways than those in which the particles normally deposit. Evidence to support this concept can be found in the studies of Benatar & König (1974), who showed relatively poor gas-density dependence of flow in a similar group of subjects before exercise and concluded that this represented more peripheral obstruction.

The patient to patient variation of response (Table 2) is difficult to explain on the numerical or area hypotheses, but could be explained by slightly different distribution of particles due to differences in the major sites of airways obstruction.

However, in order to settle this point, further experiments will be needed with particles of intermediate sizes and possibly with different inhaled weights of particles. The results presented in this paper must be regarded as suggestive that SCG acts primarily on receptors in or around the terminal airways and alveoli, but final proof has yet to be established.

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REFERENCES


