Acute Effect of Sodium Cromoglycate on Airway Narrowing Induced by 4.5 Percent Saline Aerosol*

Outcome Before and During Treatment With Aerosol Corticosteroids in Patients With Asthma

Sandra D. Anderson, Ph.D., D.Sc.; Jacqueline I. du Toit, B.Sc.; Leanne T. Rodwell, B.Sc.; and Christine R. Jenkins, M.D.

Study objective: To investigate the acute effect of sodium cromoglycate on airway responses to 4.5 percent saline aerosol challenge, before and during treatment with inhaled budesonide—a corticosteroid.

Design: Open study, with a total of five visits, two before budesonide treatment, and three follow-up visits, two between 5 and 6 weeks and one at more than 11 weeks.

Setting: Referral-based Respiratory Investigation Unit at Royal Prince Alfred Hospital, a major Sydney-based teaching hospital.

Patients: Eleven patients with asthma (ten atopic), with a PD20 FEV1 to 4.5 percent saline aerosol challenge and about to commence inhaled budesonide for treatment of their asthma.

Interventions: The 40 mg of sodium cromoglycate was inhaled before a 4.5 percent NaCl challenge, both before and after regular (36 ± 9 d) treatment with budesonide (1,000 µg/d). The final challenge was repeated in ten subjects after 11 weeks or more of treatment with budesonide.

Measurements and results: Sensitivity to 4.5 percent saline aerosol was measured as the dose of saline aerosol required to induce a 20 percent fall in FEV1 (PD20). Reactivity was measured as the dose-response slope by taking the percent fall in FEV1 and dividing it by the dose required to induce the fall. On the control day the geometric mean PD20 (95 percent CI) for 4.5 percent saline aerosol was 2.8 (1.4 to 5.4) and the dose response slope (DRS) 5.6 (2.9 - 11.1). An acute dose of sodium cromoglycate reduced sensitivity (PD20) by 8-fold and reactivity (DRS) 12.3-fold. This effect was similar in magnitude to that measured after regular treatment with budesonide alone. When sodium cromoglycate was given during treatment with budesonide, the PD20 was reduced 16-fold and the DRS 42-fold, and this was greater than the reduction with budesonide taken for 3 months (p < 0.03, p < 0.05 respectively). Conclusions: Sodium cromoglycate inhibits responses to 4.5 percent saline aerosol and has additional benefits to those conferred by aerosol steroids. The mechanism for responsiveness to saline aerosol and efficacy of these drugs may relate to alteration in chloride ion channel regulation by inflammation.

(Bronchial provocation testing is most commonly used for assessing the severity of bronchial responsiveness and its modulation by drugs. Traditionally, the pharmacologic agents histamine and methacholine have been used for bronchial provocation testing. These agents act directly on specific receptors causing bronchial smooth muscle to contract. Bronchial provocation using indirect stimuli such as exercise, cold air, hyperosmolar saline, distilled water, and sulphur dioxide have been less used in the routine lung function laboratory. Provocation testing with indirect stimuli has an advantage over pharmacologic stimuli in that indirect stimuli cause the endogenous release of mediators to which the subject is sensitive. Thus challenge with an indirect stimulus may be preferred to provoke airway narrowing when investigating the effects of drugs that act to reduce the availability of mediators of bronchoconstriction.

We have developed and standardized a bronchial provocation test using a hyperosmolar (4.5 percent) saline aerosol. Hyperosmolar saline aerosol causes the release of histamine and other mediators from human lung mast cells. In asthmatics, the airway response to hyperosmolarity is inhibited by antihistamines. Hyperosmolarity may also stimulate sensory nerves to release neuropeptides causing the airways to narrow.

Aerosol corticosteroids and sodium cromoglycate are widely used in the treatment of asthma. Chronic treatment with inhaled corticosteroids results in,
Table 1 — Anthropometric Details and Atopic Status of the Subjects

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age, yr</th>
<th>Ht, cm</th>
<th>Atopy†</th>
<th>Pred FEV₁, L</th>
<th>Pred FEV₁/Control</th>
<th>PD20FEV₁, ml</th>
<th>Time Receiving Budesonide, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>19</td>
<td>164</td>
<td>Y</td>
<td>3.02</td>
<td>78</td>
<td>1.11</td>
<td>5.0, 5.3, 15</td>
</tr>
<tr>
<td>F</td>
<td>17</td>
<td>155</td>
<td>Y</td>
<td>3.68</td>
<td>83</td>
<td>0.48</td>
<td>3.7, 4.0, 11.9</td>
</tr>
<tr>
<td>M</td>
<td>23</td>
<td>159</td>
<td>...</td>
<td>4.79</td>
<td>100</td>
<td>9.16</td>
<td>5.0, 6.4, 12.0</td>
</tr>
<tr>
<td>F</td>
<td>32</td>
<td>161</td>
<td>Y</td>
<td>2.71</td>
<td>83</td>
<td>0.87</td>
<td>4.9, 5.3, 11.1</td>
</tr>
<tr>
<td>M</td>
<td>41</td>
<td>162</td>
<td>Y</td>
<td>4.01</td>
<td>87</td>
<td>6.05</td>
<td>7.7, 8.0, 22.7</td>
</tr>
<tr>
<td>F</td>
<td>25</td>
<td>162</td>
<td>Y</td>
<td>2.86</td>
<td>84</td>
<td>1.58</td>
<td>4.7, 5.0, 11.1</td>
</tr>
<tr>
<td>M</td>
<td>27</td>
<td>179</td>
<td>Y</td>
<td>4.19</td>
<td>40</td>
<td>1.74</td>
<td>3.4, 3.6, 13.4</td>
</tr>
<tr>
<td>F</td>
<td>19</td>
<td>154</td>
<td>N</td>
<td>2.61</td>
<td>87</td>
<td>5.32</td>
<td>6.6, 6.9, 15.6</td>
</tr>
<tr>
<td>M</td>
<td>23</td>
<td>171</td>
<td>Y</td>
<td>3.88</td>
<td>56</td>
<td>16.3</td>
<td>5.0, 5.3, ...</td>
</tr>
<tr>
<td>F</td>
<td>18</td>
<td>158</td>
<td>Y</td>
<td>2.79</td>
<td>108</td>
<td>7.93</td>
<td>5.1, 6.6, 13.9</td>
</tr>
<tr>
<td>F</td>
<td>24</td>
<td>160</td>
<td>Y</td>
<td>2.79</td>
<td>111</td>
<td>1.47</td>
<td>4.6, 5.3, 13.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values for FEV₁ measured on the control day, expressed as a percentage of the predicted normal value, and the values for the provoking dose of saline aerosol to induce a 20 percent fall in FEV₁ (PD20) on that day and the duration for which 1,000 µg of budesonide was taken before each visit.

†Y = yes; N = no.

among other things, a reduction in mast cell number and thus the availability of histamine and other mast cell mediators. The mechanism for sodium cromoglycate is not precisely known, but it does reduce human mast cell release of histamine in response to hyperosmolarity. It is also thought to have an action on sensory nerves.

We have previously reported the acute inhibitory effect of sodium cromoglycate and nedocromil sodium on challenge with hyperosmolar saline aerosol compared with a placebo. We have also reported that chronic treatment with aerosol beclomethasone dipropionate reduces sensitivity to 4.5 percent saline aerosol. We noted that treatment with beclomethasone, while reducing airway sensitivity to hyperosmolar saline, did not prevent the airways from excessively narrowing when the duration of exposure to the same concentration of hyperosmolar saline aerosol was increased.

The aim of this study was to investigate the acute effect of sodium cromoglycate on airway responses to a hyperosmolar aerosol both before and during treatment with inhaled corticosteroids. The group of patients who had asthma came to the laboratory for assessment of their asthma severity and their response to treatment.

METHODS

Patients

Eleven patients with asthma (ten atopic), whose characteristics, lung function, and response to 4.5 percent saline aerosol are given in Table 1, attended the laboratory on five occasions. Eight of the 11 patients had never taken corticosteroid inhalants and three had not taken steroids within the last 2, 4, and 12 months. These patients were selected for study on the basis that they were about to be given corticosteroid inhalants for treatment of their asthma. Beta-2 adrenoceptor agonists and ipratropium bromide were withheld for 6 h before the study, theophylline and sodium cromoglycate were withheld for 24 h, and aerosol steroids were withheld on the morning of the study. The protocol had been approved by the Central Sydney Health Services Ethics Review Committee and consent was obtained in writing from each patient after explanation of the study was given.

Study Design

On the first visit to the laboratory, bronchial responsiveness to 4.5 percent saline aerosol was documented without premedication. On the second visit the 4.5 percent saline aerosol challenge was repeated 10 min after premedication with sodium cromoglycate. The patients were then immediately given budesonide by inhalation from a Turbuhaler in a dose of 1,000 µg/d. The patients took 600 µg of budesonide in the morning and 400 µg in the evening every day. The patients returned to the laboratory after 24 to 54 days of treatment and repeated the 4.5 percent saline aerosol challenge. They returned to the laboratory on a fourth occasion within 2 to 10 days (average 4 days) and the challenge was repeated 10 min after sodium cromoglycate had been given by inhalation. Ten patients returned for a fifth challenge, after taking budesonide between 11 and 22 weeks.

Delivery of Sodium Cromoglycate

An ultrasonic nebulizer (Fison, Fisons Corp, Rochester, NY) which produces an aerosol with a mass median aerodynamic diameter of 4.7 µm was used to deliver the sodium cromoglycate. Four milliliters containing 40 mg of sodium cromoglycate was placed in the nebulizer. The nebulizer was weighed before and after the patient inhaled the sodium cromoglycate, via a mouthpiece, for 5 min. The difference in the weight was used to estimate the amount of drug nebulized to the patient and this was 20.7 mg ± 2.15. The 4.5 percent saline aerosol challenge commenced 10 min after the sodium cromoglycate had been given and after a measurement of FEV₁ had been made. Sodium cromoglycate did not change the baseline FEV₁.

4.5 Percent Saline Aerosol Challenge

The protocol used for this challenge is that described in detail by Smith and Anderson with some modifications. In brief, it was as follows. The saline aerosol was generated by a large volume ultrasonic nebulizer (Mistogen, Timeter Somerset, Penn) and patients inhaled the aerosol at their resting ventilation rate through a large two-way valve (Hans Rudolph No. 2700, Kansas City, MO). The airway response was measured.
using FEV₁. The FEV₁ was measured in duplicate (Minato Autopsirometer AS 500, Osaka, Japan) before challenge and 60 to 90 s after each exposure to the aerosol. The initial exposure to 4.5 percent saline aerosol was 30 s and this time was doubled to 8 min and then repeated, 1, 2, 4, 8, 8, 8 min until at least a 20 percent reduction in FEV₁ was recorded or the aerosol had been inhaled for a cumulative time of 31.5 min.

The canister and tubing (but not the valve) of the nebulizer was weighed before and after the challenge. The total dose of aerosol delivered to the inspiratory port of the valve was divided by the total time of exposure to obtain the delivered dose per exposure.

The reduction in FEV₁ was expressed as a percentage of the value for FEV₁ measured immediately before the challenge (percent fall in FEV₁). This value was plotted in relation to the dose of 4.5 percent saline aerosol delivered.

The sensitivity of the aerosol was calculated using the dose of 4.5 percent aerosol required to induce a 20 percent fall in FEV₁ (PD20). When the fall in FEV₁ was less than 20 percent but greater than 6.1 percent, the PD20 was taken as the maximum dose of aerosol delivered. When the fall in FEV₁ was equal to or less than the mean value of 6.1 percent observed in normal subjects²⁶ the PD20 was taken as 60 ml. This value of 60 ml was taken as an estimate because the greatest volume delivered during the challenge was 56 ml.

Because a 20 percent fall in FEV₁ was not documented on all occasions after treatment the dose-response slope (DRS), an index of reactivity,²⁰,²¹ was also calculated. This was done by taking the final percent fall in FEV₁ and dividing by the dose of aerosol which caused that fall. On the four occasions out of 54, the percent fall in FEV₁ was zero and a value of 1 percent was assigned to calculate DRS. From our laboratory data, the mean value for DRS for 65 normal subjects with a percent fall in FEV₁ greater than zero (95 percent confidence interval [CI]) is 0.225 (0.18-0.27).

The geometric mean and 95% CI for the PD20 and DRS were calculated and compared on the five occasions using analysis of variance. Where a difference was found, a Student's t test for paired values was used to assess the level of significance which was taken as p < 0.05. Values for the FEV₁ measured on each test day were compared using analysis of variance. Fold change in sensitivity (PD20) and reactivity (DRS) to 4.5 percent saline aerosol was calculated by taking the antilog of the mean of the differences of the log values for PD20 and DRS. The fold changes reported compare each visit with visit 1.

**RESULTS**

The geometric mean values for the PD20 and DRS are given in Table 2, together with the values for FEV₁ immediately measured before challenge on each study day. Individual data are shown in Figures 1 and 2.

The acute administration of a single dose of sodium cromoglycate significantly reduced the sensitivity and reactivity to 4.5 percent saline aerosol in this group of patients with asthma. The magnitude of the reduction in sensitivity (PD20) and reactivity (DRS) after a single dose of sodium cromoglycate, 8-fold and 12.3-fold, respectively, was similar to that observed after 24 to 56 days of treatment with budesonide when there was a reduction in PD20 and DRS from control of 6-fold and 14-fold, respectively. There was a significant relationship (r = 0.88, p < 0.01) between the fold change in PD20 after a single dose of sodium cromoglycate (visit 1) and after 24 to 56 days of treatment with budesonide (visit 3). A further reduction in sensitivity (16-fold) and reactivity (42-fold) to 4.5 percent saline aerosol compared with control was observed when sodium cromoglycate was given during treatment with aerosol corticosteroids. The sensitivity and reactivity in the ten subjects studied after 11 weeks or more of treatment was unchanged compared with their first visit after the commencement of budesonide.

While all patients had a PD20 recorded on the control day (range 0.47 to 16.4 ml), 5 of the 11 patients had less than a 20 percent fall in FEV₁ after a single dose of sodium cromoglycate. After 36 ± 9 days of treatment with budesonide, 4 patients had less than a 6.1 percent fall, but 7 of the 11 patients remained responsive to 4.5 percent saline aerosol, although sensitivity was reduced. When the challenge was repeated after a single acute dose of sodium cromoglycate, five of these seven patients had no PD20 recorded, and in four the fall in FEV₁ was less than 6.1 percent. In the remaining two there was a 20 percent fall in FEV₁ after challenge with saline aerosol but the PD20 values had increased 8-fold in one patient from 1.7 to 13.6 ml and 7-fold in the other from 1.6 to 11.0 ml.

### Table 2 — Mean ± SD for FEV₁ Measured Before Challenge*

<table>
<thead>
<tr>
<th>Challenge Days</th>
<th>Mean/Geometric Mean</th>
<th>Control</th>
<th>SCG</th>
<th>Budesonide, 3-8 wk</th>
<th>SCG + Budesonide, 3-8 wk</th>
<th>Budesonide &gt;11 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁, %pred</td>
<td></td>
<td>83.5</td>
<td>82.7</td>
<td>90.8</td>
<td>91.4</td>
<td>93.7</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>20.6</td>
<td>21.3</td>
<td>13.8</td>
<td>17.2</td>
<td>16</td>
</tr>
<tr>
<td>PD20 FEV₁</td>
<td></td>
<td>2.76</td>
<td>22.2</td>
<td>16.7</td>
<td>44.1</td>
<td>19.4</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>1.41-5.4</td>
<td>13-38</td>
<td>7.1-39.4</td>
<td>30.2-64.3</td>
<td>8.77-42.9</td>
</tr>
<tr>
<td>DRS</td>
<td></td>
<td>5.63</td>
<td>0.45</td>
<td>0.65</td>
<td>0.13</td>
<td>0.5</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>2.86-11.1</td>
<td>0.12-1.21</td>
<td>0.2-2.0</td>
<td>0.06-0.31</td>
<td>0.16-1.53</td>
</tr>
</tbody>
</table>

*Expressed as a percentage of the predicted normal, and geometric mean values ± 95% CI for the PD20 *FEV₁, and the DRS for each study day.
administration of sodium cromoglycate is very effective in preventing airway narrowing induced by a hyperosmolar stimulus. The results show, for the first time, that sodium cromoglycate provides additional protection when given during treatment with aerosol steroids. Further, the reduction in bronchial responsiveness to hyperosmolarity occurred in some patients independently of any improvement in resting lung function and when lung function was within normal limits.

These findings have important clinical implications for patients being treated for asthma with aerosol corticosteroids. We have previously reported that 8 weeks treatment with beclomethasone dipropionate (600 to 1,500 μg/d) reduces airway sensitivity to 4.5 percent saline aerosol in patients with asthma. In that study, 12 of 13 patients studied however; remained responsive to saline aerosol, and the treatment with beclomethasone did not prevent the airways from excessively narrowing in 10 of 13 patients. Thus, with increased time of exposure to the same concentration of saline aerosol, the airways still narrowed after treatment with beclomethasone.

The findings in this study suggest that the majority of patients receiving 1,000 μg of budesonide for 24 to 56 days also remain reactive to this stimulus, although their sensitivity was reduced. We have reported exercise-induced asthma in patients taking beclomethasone regularly over 2 to 3 months. Indeed, daily treatment with this steroid is not an exclusion criteria for studies of exercise-induced asthma. Our findings with 4.5 percent saline aerosol are consistent with these observations as exercise is thought to provoke airway narrowing by airway drying and an increase in osmolarity of the surface fluid.

We have shown that bronchial responsiveness can still remain during treatment with steroids and when lung function is within the normal predicted range. In such patients, the addition of sodium cromoglycate would seem to be warranted, particularly when given immediately before stimuli known to provoke airway narrowing indirectly; eg, cold air, exercise, allergens, sulphur dioxide, and fog. In fact, for all but two patients there was total inhibition of the response to 4.5 percent saline aerosol after sodium cromoglycate in the presence of steroids.

This study also shows the usefulness of bronchial provocation testing using an indirect stimulus for provoking airway narrowing and to assess drug effects. Sensitivity to hyperosmolarity reflects the presence of inflammatory mediators, and a decrease in this sensitivity with long-term treatment with corticosteroids is probably a result of a reduction in airway inflammation. Sensitivity to 4.5 percent sa-

**DISCUSSION**

The results of this study confirm that the acute

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21691/)  

**FIGURE 1.** The FEV\textsubscript{1}, expressed as a % pred, the DRS and dose of 4.5% saline aerosol required to induce a 20% fall in FEV\textsubscript{1}, in the 11 subjects on the five test days (control: SCG = sodium cromoglycate, budes = budesonide 1,000 μg/d).

values observed for PD20 and DRS were significantly different (p < 0.018, p < 0.037, respectively) when the values for these seven patients were compared with visits 3 (budesonide) and 4 (budesonide and sodium cromoglycate). Four of these seven patients remained responsive to 4.5 percent saline aerosol even after 11 or more weeks of treatment with budesonide (Fig 1).

Nine patients in this study had values for FEV\textsubscript{1} greater than 75 percent predicted on the control day. While four individuals had big changes in FEV\textsubscript{1} (up to 33 percent predicted) after treatment with steroids, the values for FEV\textsubscript{1} for the group were not significantly different on the five test days. Changes in PD20 were not related simply to improvement in FEV\textsubscript{1} for the group. There was no significant relationship (r = -0.4) between the ratio of FEV\textsubscript{1} percent predicted after budesonide treatment visit 3 to FEV\textsubscript{1} percent predicted on the control day visit 1 and the ratio of the PD20 visit 3 to PD20 visit 1. For some patients, however, the FEV\textsubscript{1} and PD20 improved at the same time.
line aerosol has been shown to relate to mast cell number\textsuperscript{23} and corticosteroids reduce mast cell numbers,\textsuperscript{15,24,25} so it is not surprising that corticosteroids reduce sensitivity to 4.5 percent saline aerosol. What is more surprising is that only 1 of 11 patients had a PD20 greater after 24 to 56 days of treatment with budesonide than they did after a single treatment with sodium cromoglycate. Furthermore, in the seven patients who remained responsive to 4.5 percent saline aerosol after treatment with budesonide, sodium cromoglycate gave significant additional protection.

The magnitude of the reduction in sensitivity was similar after a single acute dose of sodium cromoglycate as it was after 24 to 54 days of treatment with budesonide, 1,000 μg per day, and the responses were closely related. Measuring the response to 4.5 percent saline aerosol after the acute administration of sodium cromoglycate may provide a useful guide to demonstrate the capacity to which airway hyperresponsiveness may be reduced. The duration of the protective action of sodium cromoglycate from 4.5 percent saline aerosol is not known. On the basis of studies using exercise as the stimulus, it is unlikely to be more than 2 h.\textsuperscript{26} The dose of sodium cromoglycate was probably higher than that normally delivered by jet nebulizer, as 4 ml (40 mg) rather than 2 ml (20 mg) was used in the ultrasonic nebulizer. We have found the Fisonel ultrasonic nebulizer to be very effective for delivering drugs to prevent the airway narrowing provoked by hyperosmolarity.\textsuperscript{6,20,27} The reason we used 40 mg of sodium cromoglycate was to expedite the delivery of 20 mg of the drug over 5 min. For practical purposes, the standard dose of 20 mg could be used and a volume of 2 to 3 ml of saline solution added. In this situation, the nebulization time would need to be longer. The dose would be reduced relative to the dead volume of the nebulizer, which for jet and small ultrasonic nebulizers is usually 1 ml. We would expect that four inhalations of 5 mg cromoglycate from a metered-dose inhaler (Intal Forte) would give the same results as those reported here.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Relationship between the fall in FEV\textsubscript{1}, expressed as a percentage of the prechallenge value (\% Fall), and the cumulative dose of 4.5\% saline aerosol delivered to the inspiratory port of the two-way valve.}
\end{figure}
The major aim in treating asthma with corticosteroids is to achieve normal lung function, reduce symptoms, and decrease bronchial responsiveness. It seems from this and other studies that, to reduce symptoms and achieve normal lung function, the dose of corticosteroid needed is less, and the duration for which it is given shorter compared with the dose required to reduce bronchial responsiveness. Patients may be unwilling to comply with a regimen of high dose and long duration of treatment with steroids once they have achieved good lung function and have few symptoms. The side-effects observed at higher doses may not be warranted if bronchial responsiveness to stimuli such as exercise can be acutely inhibited with the addition of sodium cromoglycate. If the bronchial responsiveness to hyperosmolar saline aerosol does reflect the presence of airway inflammation, then the important question is whether the dose of steroid should be increased until a plateau or complete inhibition is achieved. At present, questions relating to exercise tolerance are often used, by physicians, as a guide to efficacy and dose of corticosteroids. We think that a formal bronchial provocation testing using hyperosmolar saline aerosol would provide objective information. While acknowledging the deficiencies of a trial which is not placebo controlled or blinded to the investigator, we think that the techniques described here are useful in assessing the benefits of both chronic and acute treatment for asthma. The challenge and protocol carried out here could be easily carried out in routine lung function laboratories with the facility to measure bronchial responsiveness.

Although the pharmacologic challenges with methacholine and histamine have been used to assess treatment of asthma with steroids, they cannot be used to assess the effects of sodium cromoglycate. While it is common to use exercise to assess the benefits of sodium cromoglycate, challenge with hyperosmolar saline aerosol is superior to exercise testing in that a dose-response curve can be obtained, and it requires little cooperation from the patient. It is also superior to a bronchial provocation testing with histamine because sensitivity to histamine, although reduced, may be expected to remain during treatment with corticosteroids, as histamine will act directly via H1 receptors causing the bronchial smooth muscle to contract. Some investigators have reported that the responsiveness to histamine and methacholine may take years to return to the normal range. Thus, a pharmacologic challenge while useful to assess the potential for the bronchial smooth muscle to contract is not as useful as hyperosmolar saline aerosol for assessing the effects of anti-inflammatory drugs on reducing the amount or availability of endogenous mediators.

This study was initiated as a result of our findings in a double-blind placebo controlled trial of the inhibitory effect of nebulized nedocromil sodium (Tilade) on responses to 4.5 percent saline aerosol. We noted that six of the eight subjects who had a complete block or who recorded a plateau after saline aerosol in the presence of nedocromil were using beclomethasone on a daily basis. As nedocromil sodium is not marketed in Australia, we wished to investigate if sodium cromoglycate given in the same way, by nebulization, had a similar effect in subjects given budesonide.

This study did not use a placebo controlled double-blind study as it was carried out during the normal course of laboratory assessment and medical treatment of asthma. We were fortunate in being able to study the subjects before they commenced their treatment with steroids. We were careful not to carry out a challenge if there had been a respiratory tract infection in the last 4 weeks. If the subjects had experienced symptoms of asthma in the previous 24 h, they were asked to reschedule their appointment. This resulted in a variation in the time between visits.

The subjects were required to attend the laboratory on five separate occasions with visits 2 and 3 being separated by about 4 weeks. Some normal variation in the PD20 to hyperosmolar saline aerosol would be expected to occur over this time. We have repeated challenges 1 to 37 days apart and found the PD20 to be within 2 ml. This variation occurred both at low and high values of PD20, but there were both increases and decreases between study days. In this study by contrast, the PD20 continued to increase and the improvement from 2.76 ml to 16.7 ml to 44.1 ml, over time and, in response to budesonide and sodium cromoglycate was 3 to 20 times more than the expected by normal variation.

These large increases in PD20 are also unlikely to be accounted for by a placebo effect. We have studied the effects of placebo aerosol on the response to 4.5 percent saline aerosol in 11 subjects on two occasions. The pH of the placebo was 9.0 in one study and 5.5 in the other. We found that for those receiving the placebo with a pH of 9.0 the effect was to make the patient more sensitive to the challenge by saline aerosol (geometric mean ± 95 percent CI, control PD20 1.97 ml 1.07, 3.61 vs placebo PD20 1.32 ml 0.69, 2.53), although the difference was not statistically significant. In the study where the pH of the placebo was 5.5, the expected benefit of increasing airway surface liquid was achieved (placebo PD20 3.19 ml 1.87, 5.44 control PD20 1.55 ml 1.28, 3.2 p < 0.04). The pH of
the sodium cromoglycate we used was 6.1. While the possibility exists that a patient may become negative to hyperosmolar challenge after placebo alone, we have found this only once in a patient who had a PD20 of 15 ml on the control day. Most subjects included in our trials have a PD20 less than 10 ml.

While we cannot be sure of subjective influence, we think that it is unlikely because the subjects were not informed of the possible benefit of the drug and the nature of the protocol we used. This involved a progressive increase in time of exposure to the aerosol, rather than a single exposure to the aerosol. This usually results in a progressive reduction in FEV1 and, where this was not the case, another period of exposure to the aerosol was made. For each exposure, an FEV1 maneuver was performed on at least two occasions and the highest value was the one used.

The mechanism whereby sodium cromoglycate prevents the airways narrowing in response to hyperosmolarity is not known but it may relate to its capacity to act on chloride ion channels. Romainin et al. have shown that sodium cromoglycate blocks Cl−ion channels on mast cells and this may be its action in preventing mediator release in response to hyperosmolarity. It may also block Cl−channels on nerves preventing the release of neuropeptides. Furosemide, a loop diuretic with the capacity to reduce Cl−movement across cells, is also effective in preventing responses to hyperosmolar saline aerosol and mediator release from human lungs. Furosemide is also effective in preventing the airway narrowing caused by metabisulfite that is thought to stimulate sensory nerves. Nedocromil is very effective at inhibiting the asthmatic response to 4.5 percent saline aerosol and recent evidence shows that it blocks Cl−channels on sensory nerves. A unifying concept is that hyperosmolality causes the release of mast cell mediators and neuropeptides by stimulating Cl−secretion, and sodium cromoglycate, nedocromil sodium, and furosemide act to block this effect. An effect on ion channels would explain the wide variety of action these drugs are reported to have in many different organs.

If the airway responsiveness to hyperosmolarity does reflect airway inflammation and if sodium cromoglycate does prevent responses by its action on Cl−channels, then it may be that a reduction in the voltage threshold for opening Cl−channels may be a result of the inflammatory process. This may explain why regular treatment with sodium cromoglycate and nedocromil has beneficial effects that are not the same as corticosteroids. Corticosteroids are required to be given in the long term and probably act by reducing inflammatory cell number and increasing the expression of neutral endopeptidase in airway epithelium.

In conclusion, we have shown that sodium cromoglycate when acutely given before challenge with 4.5 percent saline aerosol markedly inhibits airway narrowing, and this effect is additional to the effect of aerosol steroids. These findings suggest that these two drugs have different modes of action. Challenge with hyperosmolar saline aerosol may cause airway narrowing by stimulating Cl−channels and causing the release of mast cell mediators and sensory neuropeptides. The potency of sodium cromoglycate in this model may relate to its ability to block this ion channel.

ACKNOWLEDGMENTS: The authors thank the subjects who volunteered for this study and their chest physicians who permitted them to continue with the protocol.

REFERENCES
10 Finney MJB, Anderson SD, Black J. Terfenadine modifies airway narrowing induced by the inhalation of nonisotonic aerosols in patients with asthma. Am Rev Respir Dis 1990; 141:1151-57
12 Umeno E, McDonald OM, Nadel JA. Hypertonic saline increases vascular permeability in the rat trachea by producing neurogenic inflammation. J Clin Invest 1990; 851:1905-08
13 Pisarri TE, Jonzon A, Coleridge HM, Coleridge JCG. 
14 Barnes PJ. Asthma as an axon reflex. Lancet 1986; 1:242-44
22 Anderson SD, Rodwell LT, du Toit J, Young IH. Duration of protection by inhaled salmeterol in exercise-induced asthma. Chest 1991; 100:1254-60
26 Woolley M, Anderson SD, Quigley BM. Duration of protective effect of terbutaline sulfate and cromolyn sodium alone and in combination on exercise-induced asthma. Chest 1990; 97:39-45
27 Rodwell LT, Anderson SD, du Toit JI, Seale JP. Inhaled furosemide reduces airway sensitivity to inhaled 4.5% NaCl aerosol in asthmatic patients. Thorax 1993; 48:208-13
35 Edwards AM, Stevens MT. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. Eur Respir J 1993; 6:35-41
36 Petty TL, Rolls DR, Christopher K, Good JT, Oakley R. Cromolyn sodium is effective in adult chronic asthmatics. Am Rev Respir Dis 1989; 139:694-701