Nedocromil sodium and exercise induced asthma

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SUMMARY Serial exercise tests were carried out by 12 children with asthma on two study days. After a control exercise test either nedocromil sodium 4 mg or placebo were given double blind by metered dose inhaler. Highly significant inhibition of exercise induced asthma occurred after nedocromil, lasting for over two hours.

Nedocromil sodium (Tilade) is a new anti-asthma drug that has selective mucosal mast cell stabilising properties. In single dose human studies nedocromil has been shown to protect against exercise induced asthma, while in clinical studies, in which it has been administered four times a day for one month, improvements have been shown in the control of adult asthma. There are no published data in children.

Exercise induced asthma has been used as a provocation test for a number of years to assess the relative efficacy and duration of action of different drugs. In this study the protective effect of inhaled nedocromil sodium on exercise induced asthma was studied in a double blind, placebo controlled manner in a group of children with asthma.

Patients and methods

Twelve children with asthma were studied. There were nine boys and three girls, all well known to our asthma clinic, whose ages ranged from 8 to 15 years (mean 13·9 years). All were skilled in the use of metered dose inhalers and each had a history of exercise induced asthma. Sodium cromoglycate, theophylline, and beta agonists were stopped 12 hours before each test, but they were allowed to have treatment with steroids.

The forced expiratory volume in one second (FEV₁) and forced vital capacity were measured using a rolling seal spirometer (Ohio) before exercise. Exercise testing consisted of steady state running on an inclined treadmill at an inclination of 12% (10% if the baseline FEV₁ was less than 60% predicted) for six minutes. The speed of the treadmill was such that the patient’s pulse rate at the end of the exercise period was at least 170 beats a minute. The same setting and duration was used for each test in any one patient. FEV₁ was measured before and after exercise and the severity of exercise induced asthma was defined as the ratio of maximum fall in FEV₁ to the pre-exercise value expressed as a percentage.

There were two study days within one week. On each day a baseline exercise test was carried out. Ninety minutes after the start of the first test two puffs of either placebo or nedocromil (2 mg/puff) were administered double blind, using a metered dose inhaler. Lung function recordings were made before and after treatment. Three further exercise tests were then carried out on each of the two days 30, 150, and 270 minutes after treatment—that is, two, four, and six hours after the baseline exercise test. Paired t tests were used for comparisons between the mean level of exercise induced asthma at various times after challenge in the two study days. The degree of protection against exercise induced asthma was calculated after administration of nedocromil for each post-dose test as the difference between the baseline test and the post-dose test, expressed as a proportion (%) of the baseline value.

Results

The initial spirometric values were similar on the two study days. Nedocromil had no significant effect on these values over the 30 minute interval between administration and the succeeding exercise test. Towards the end of the control day, however, the FEV₁ was minimally, though statistically, lower than on the active study day. Before the fourth exercise test the mean difference in FEV₁ between the active and control studies was 0·21 l (9·5%) (Figure).

The exercise tests revealed two important effects. Firstly, analysis of variance was used to show that there was a significant decline in the severity of exercise induced asthma during the course of the study days, independent of treatment (p<0·001). Secondly, treatment with nedocromil had an additional significant overall effect on the level of exercise induced asthma (p<0·001). The difference was significant at 30 and 150 minutes and insignificant at 270 minutes (Figure).

Individual responses to nedocromil were determined using the protection index. Protection of at
Nedocromil sodium and exercise induced asthma

The exercise tests were performed under ambient laboratory conditions. The exercise load was constant for each child for all eight exercise tests. Although it may be possible to increase the response to exercise by providing subfreezing or dry air during exercise, the overall response to the first (control) test on each study day suggests that the exercise stimulus was quite adequate. Only one child had a fall in FEV<sub>1</sub> of less than 25% on either control test.

In spite of the randomisation, the mean difference in exercise induced asthma before the control tests on the nedocromil and placebo test days was surprisingly large but not significant. We have no explanation for this difference other than random variation in a small population.

The mechanism by which nedocromil protects against induced bronchoconstriction has still to be understood in man. In the monkey, however, it can prevent release of histamine from anti-IgE stimulated bronchoalveolar lavage cells, which contain a high proportion of mucosal mast cells. The evidence for two subpopulations of mast cells in man (the so called ‘mucosal’ and ‘connective tissue’ populations) is controversial. If nedocromil is selectively more active against mucosal mast cells it may represent an important advance in treatment of asthma over other agents whose presumed action is also on sensitised cells. As previously noted, however, the search for mast cell stabilising drugs has not led in general to major advances in the management of asthma.

The use of exercise tests for screening in new preparations for asthma has had a long history. The little clinical data that exist suggest that protection against exercise induced asthma in childhood may correlate with the outcome of long term treatment.

If there is a dose-effect relation for nedocromil then a glance at the Figure suggests that the 4 mg dose should be increased. By increasing the dose, both the degree and duration of protection may be improved. Nedocromil could provide an important therapeutic advance in the management of childhood asthma.

Discussion

Although no direct comparison was made, in the 4 mg dose used, the effect of nedocromil on exercise induced asthma in children seems to be similar to that of sodium cromoglycate, both in the overall degree of protection and its duration. As with cromoglycate given in the normal dosage there was no obvious change in pre-exercise spirometry after administration of the drug. After repeated exercise challenges on the two study days, however, there was a steady decline in FEV<sub>1</sub> on the placebo compared with the active treatment. Thus there was both short term protection against exercise induced asthma and longer term protection against the additive effects on lung function of repeated exercise.

References

4. Silverman M, Konig P, Godfrey S. Use of serial exercise tests to


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### Management of asthma in schools

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**SUMMARY** A questionnaire on asthma in schools was circulated to 291 Nottingham schools. The response rate was 91%. Three areas of concern were identified: are schools aware of all their asthmatic pupils; should children have more access to their medications in school; and do teachers need more guidance in supervising illnesses.

Asthma is the most common chronic disease of childhood. It is associated with school absenteeism and reduced participation in school activities and games. Modern treatment of asthma is based on inhaled drugs administered from pressurised aerosols and dry powder inhalers. These can be safely self-administered by virtually all children of school age, and when used appropriately symptoms of asthma and absences from school are reduced.

The management of asthma in schools and the role that teachers assume in this has not been described previously, despite the fact that children spend much of their time in school. We have looked into the awareness of asthma in schools and the policies adopted towards medications used to treat asthma to see whether there are specific problems for either teachers or children.

**Methods and results**

A questionnaire was posted to headteachers of 245 primary and 46 secondary state schools in the Nottingham area. The questionnaire asked how many pupils had asthma and how the schools were notified of this. Headteachers were questioned on their policy towards the administration and supervision of asthma medications and whether teachers had received instruction in the supervision of asthma or other childhood illnesses. Teachers were asked if they had experienced any particular problems when teaching children with asthma. Permission for the survey was granted by the local director of education and the city hospital ethical committee.

The questionnaire was returned by 92% of primary and 87% of secondary schools. The number of pupils known to have asthma ranged from 0 to 12% (mean 3-6%) in primary schools and from 1 to 6% (mean 2-9%) in secondary schools. The reported prevalence of asthma did not vary according to the size of the schools.

The majority of both primary and secondary schools were alerted to the fact that pupils had asthma by their parents (Table), usually verbally—

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
<th>School (response as a %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>How would you be informed if a child had asthma when he first joins the school?</td>
<td>Verbal report from parent</td>
<td>73</td>
</tr>
<tr>
<td>How would you be informed if a child developed asthma later?</td>
<td>Questionnaire to parent</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Previous school records</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>School health service</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Parents</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>School health service</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Pupil</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>General practitioner/hospital</td>
<td>3</td>
</tr>
<tr>
<td>Who is responsible for supervising the needs of children with asthma?</td>
<td>Class teacher</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Head teacher</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Senior teacher</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Pastoral staff</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>School nurse</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Nursery nurse</td>
<td>14</td>
</tr>
<tr>
<td>Management of inhalers</td>
<td>Children keep</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Children hand in hand</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>Children keep or hand in according to child</td>
<td>25</td>
</tr>
</tbody>
</table>

NA=Not applicable.
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