

# Effect of nedocromil sodium on exercise-induced bronchoconstriction in children

J. M. HENRIKSEN

Dept. of Pediatrics, Aarhus Kommunehospital, Denmark

A double-blind, placebo-controlled, crossover study investigated the efficacy of nedocromil sodium in reducing bronchoconstriction subsequent to exercise challenge in asthmatic children. Twelve children aged 7-14 years (mean 10.8 years) were pretreated with nedocromil sodium aerosol (2 inhalations; 2 mg/inhalation) or matching placebo, 30 min prior to treadmill running. Lung function was measured at regular intervals post-exercise and the mean maximum percentage decrease in PEF and FEV<sub>1</sub> compared following nedocromil sodium or placebo pretreatment. Nedocromil sodium significantly reduced the fall in PEF ( $P < 0.001$ ) and FEV<sub>1</sub> ( $P < 0.001$ ) and provided significantly greater protection ( $P < 0.001$ ) than placebo. No adverse reactions or unusual symptoms were observed.

*Key words:* asthma; exercise-induced; quinolines; therapeutic use; respiratory function tests; respiratory therapy.

*Accepted for publication 22 April 1988*

## CLINICAL ASPECTS

The majority of asthmatic patients experience some degree of bronchoconstriction after exercise, and this has become an accepted provocation test for the diagnosis and assessment of asthma. Obstruction of the airways during exercise leads to hyperinflation and hypoxemia, an effect which is particularly important in childhood asthma where regular physical activity is likely to be a prominent feature.

An agent such as nedocromil sodium, able to maintain lung function during exercise challenge, could thus exert a significant influence on the quality of life of the asthmatic child.

Nedocromil sodium (Tilade®, Fisons plc) is a new drug developed for the maintenance treatment of reversible obstructive airways disease and designed for broad control of both allergic and inflammatory components of bronchial asthma (3). The drug has been shown effective against exercise-induced bronchoconstriction (EIB) in adults (22, 24). Exertional airways obstruction is one of the most characteristic and frequent features of childhood asthma, and it would be of interest therefore to evaluate the effect of nedocromil sodium on EIB in children.

The present study was designed to compare the efficacy of aerosolised nedocromil sodium and placebo against EIB in children.

## MATERIAL AND METHODS

Twelve asthmatic children (10 boys and 2 girls) aged 7-14 years (mean 10.8) were selected for this double-blind, crossover study on the basis of having EIB. All patients had perennial episodes of airway obstruction which could be relieved by anti-asthmatic therapy. Based on history, skin prick tests with 12 common allergens and RAST analyses, they were all considered atopic. Ten were allergic to house dust mite, 5 to animal dander, 2 to pollen and 1 to microfungi. All used inhaled sympathomimetics (salbutamol or terbutaline) for control of symptoms. Additionally, 4 used sodium cromoglycate, 2 oral theophylline

(slow-release tablets), 2 oral sympathomimetics (plain tablets), 1 steroid spray (budesonide, 200 µg daily).

Prior to lung function measurements, therapy with inhaled bronchodilators was withheld for at least 12 h and with oral drugs and sodium cromoglycate for 24 h. The patient taking steroid continued usage unchanged during the trial.

Informed consent was obtained from the children and their parents, and the study was approved by the hospital ethics committee.

Before the first study day a treadmill exercise schedule was established for each patient to give a fall in FEV<sub>1</sub> of at least 20%. (Baseline values for PEF or FEV<sub>1</sub> were not less than 70% of the predicted normal value (13, 14) in each case).

The exercise schedule involved continuous treadmill running for 5 or 6 min, with a constant work load adjusted to produce a final heart rate of approx. 180 beats/min, measured by radio-telemetry. Work loads range from 2.8–3.4 Watt per kg body weight (mean: 2.9 Watt/kg). The children were provided with a nose clip during exercise (10). Before each exercise test, the absolute water content of the air (g H<sub>2</sub>O/kg dry air) was calculated from room temperature and relative humidity by means of an I-X diagram (Christian Berg, Copenhagen). Relative humidity was measured by a hygrometer.

The exercise schedule for each patient was then kept constant on the 2 treatment study days which were no more than 1 week apart. Treatment consisted of two inhalations, taken as closely together as possible, from identical-looking pressurised aerosol cans delivering 2 mg nedocromil sodium, or placebo, per actua-

tion. The treatments were assigned by random allocation and were given 30 min before exercise challenge on each study day.

Pulmonary function was evaluated by PEF and FEV<sub>1</sub> (best of 3 readings) before and after aerosol premedication, at 10 and 5 min before exercise (mean = baseline value), during exercise (PEF only) and at intervals of 2, 5, 10, 20 and 30 min post-exercise, or until a maximum fall was observed. PEF was measured by Wright's peak flow meter (Airmed Ltd., Harlow, UK), FEV<sub>1</sub> by an electronic spirometer (Spirotron, Dräger). Each test was terminated by use of an aerosol bronchodilator (salbutamol or terbutaline) 30 min after the end of the challenge, or earlier if required. (For such patients only values available for both treatments at equivalent time points after challenge were used in the analyses.)

The bronchial responses to exercise were expressed as maximum percentage fall in PEF and FEV<sub>1</sub> from the pre-exercise baseline values:

$$\text{EIB} = \frac{\text{Baseline value} - \text{lowest post-exercise value}}{\text{Baseline value}} \times 100\%$$

Percentage protection was also calculated to evaluate whether the possible effects on EIB were clinically relevant. The degree of protection provided by treatment with nedocromil sodium or placebo was calculated as the percentage reduction in EIB on the 2 treatment days (EIB<sub>t</sub>) compared with the pre-study control day (EIB<sub>c</sub>):

$$\% \text{ protection} = \frac{\text{EIB}_c - \text{EIB}_t}{\text{EIB}_c} \times 100\%$$

Table 1

Comparative effect of nedocromil sodium (2 × 2 mg) and placebo pre-treatment on exercise-induced bronchoconstriction in asthmatic children (n = 12)

| Treatment         | Maximum % fall post-challenge |             | % Protection     |           |
|-------------------|-------------------------------|-------------|------------------|-----------|
|                   | FEV <sub>1</sub> (l)          | PEF (l/min) | FEV <sub>1</sub> | PEF       |
| Nedocromil sodium | 17.5                          | 17.4        | 67.4             | 62.7      |
| Placebo           | 47.2                          | 45.2        | 1.3              | 4.1       |
| SD (df)           | 13.7 (11)                     | 13.9 (11)   | 12.0 (10)        | 23.8 (11) |
| Significance      | ***                           | ***         | ***              | ***       |

\*\*\*  $P < 0.001$ . n = 11 (FEV<sub>1</sub> not recorded for 1 patient on control day).

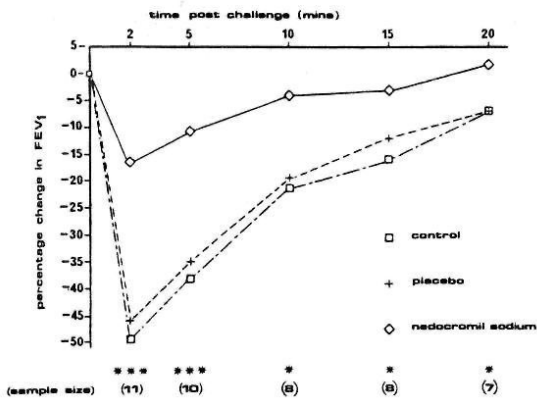


Fig 1. Mean percentage fall in  $FEV_1$  in asthmatic children following exercise challenge when pre-treated with nedocromil sodium 4 mg and placebo. The data from the control challenge are shown for comparison.  $P$ -values = nedocromil sodium vs placebo (\*\*\*)  $P < 0.001$ ; \*  $P < 0.05$ ).

Statistical significance was assessed using analysis of variance, including patient, treatment and treatment order as factors. A 2-tailed 5% level of significance was used. Percentage protection  $> 50\%$  is regarded as clinically significant. In all analyses, the treatment differences were similar in the 2 treatment order groups.

## RESULTS

Exercise challenge on the pre-study control day resulted in a mean maximum fall in  $FEV_1$  of 50% (range 27–79%) and a mean maximum fall in PEF of 49% (range 22–76%). On the 2 treatment study days, significant ( $P < 0.001$ ) differences in favour of nedocromil sodium were seen in the maximum percentage decrease in  $FEV_1$  and PEF, and in protection for  $FEV_1$  and PEF (Table 1). As depicted in Fig. 1, the mean percentage fall in  $FEV_1$  was significantly reduced by nedocromil sodium treatment at all time points measured post-challenge, when compared with placebo (2 and 5 min,  $P < 0.001$ ; 10, 15 and 20 min,  $P < 0.05$ ). The post-exercise fall in PEF followed a similar time course, with the difference in favour of nedocromil sodium, reaching statistical significance at 2 min ( $P < 0.001$ ) and 5 min ( $P < 0.05$ ) after challenge.

Individual values for pre-exercise baseline and lowest post-exercise PEF are given in Table 2 together with maximum percentage fall in PEF, final heart rate, and absolute humidity for all tests. The data show that the majority of the patients had severe EIB on the control day.

Table 2

Individual PEF changes and final heart rates in EIB in 12 patients, with absolute humidity on each test day

| Patient No.                       |   | 1    | 2    | 3    | 4    | 5    | 6    | 7    | 8    | 9    | 10   | 11   | 12   |
|-----------------------------------|---|------|------|------|------|------|------|------|------|------|------|------|------|
| Baseline                          | 0 | 220  | 347  | 270  | 355  | 205  | 267  | 422  | 255  | 310  | 285  | 335  | 307  |
| PEF                               | 1 | 220  | 307  | 265  | 330  | 200  | 272  | 417  | 257  | 230  | 285  | 237  | 300  |
| (l/min)                           | 2 | 220  | 322  | 225  | 340  | 175  | 295  | 382  | 270  | 265  | 272  | 265  | 332  |
| Lowest post-                      | 0 | 95   | 115  | 100  | 260  | 160  | 175  | 250  | 60   | 95   | 115  | 230  | 170  |
| challenge                         | 1 | 75   | 125  | 200  | 255  | 150  | 170  | 325  | 60   | 100  | 105  | 105  | 200  |
| PEF (l/min)                       | 2 | 170  | 240  | 140  | 285  | 170  | 260  | 350  | 180  | 280  | 210  | 170  | 325  |
| Maximum                           | 0 | 56.8 | 66.9 | 63.0 | 26.8 | 22.0 | 34.6 | 40.8 | 76.5 | 69.4 | 59.6 | 31.3 | 44.6 |
| % fall                            | 1 | 65.9 | 59.3 | 24.5 | 22.7 | 25.0 | 37.6 | 22.2 | 76.7 | 56.5 | 63.2 | 55.8 | 33.3 |
| in PEF                            | 2 | 22.7 | 25.5 | 37.8 | 16.2 | 2.9  | 11.9 | 8.4  | 33.3 | -5.7 | 22.8 | 35.9 | 2.1  |
| Final                             | 0 | 160  | 188  | 180  | 186  | 180  | 184  | 170  | 176  | 160  | 161  | 185  | 184  |
| heart rate                        | 1 | 164  | 196  | 174  | 190  | 192  | 179  | 179  | 168  | 173  | 167  | 176  | 188  |
| (beats/min)                       | 2 | 169  | 206  | 170  | 194  | 186  | 178  | 181  | 188  | 170  | 176  | 180  | 188  |
| Absolute                          | 0 | 5.8  | 3.0  | 5.2  | 5.5  | 5.9  | 6.0  | 5.9  | 10.9 | 5.9  | 4.5  | 6.9  | 8.0  |
| humidity                          | 1 | 5.8  | 3.3  | 6.2  | 5.0  | 5.2  | 5.9  | 5.1  | 11.2 | 5.1  | 7.8  | 7.2  | 9.8  |
| (gH <sub>2</sub> O/kg<br>dry air) | 2 | 6.8  | 3.7  | 6.2  | 5.2  | 5.0  | 4.8  | 4.8  | 9.5  | 4.5  | 7.4  | 8.3  | 7.5  |

0: control day; 1: placebo; 2: nedocromil sodium.

After pre-treatment with nedocromil sodium only 3 patients had EIB > 30%; one of these (patient No. 3) showed no benefit at all. Mean values for final heart rate showed a small but significant ( $P < 0.05$ ) increase after nedocromil sodium (182 beats/min) in comparison with the control day (176 beats/min); the mean resting heart rate was also slightly higher in this group. Small fluctuations in absolute humidity between tests did occur, but it seems unlikely that these changes have influenced the results.

Nedocromil sodium had no effect on pre-exercise lung function values; placebo affected neither pre-exercise lung function values nor EIB. No unusual symptoms or adverse reactions were reported during the study.

## DISCUSSION

The present study showed that nedocromil sodium, 4 mg given by inhalation 30 min prior to exercise challenge, provided statistically significant and clinically relevant protection against EIB in asthmatic children. These results are in agreement with those obtained in adult asthmatics (22, 24).

It is not yet fully established whether single dose acute challenge studies are reliable as predictors of clinical efficacy in chronic asthma. However, EIB is a natural phenomenon which is known to occur in the majority of asthmatics (1, 11). It is especially relevant to childhood asthma where it is often a clinical problem (15).

The mechanism of EIB is unclear, although respiratory heat loss (19) and especially water loss (12) are able to induce bronchoconstriction in asthmatics. It is possible that bronchoconstriction occurs as a result of the action of mast cell mediators released by one or other triggering mechanism (2), but other mechanisms cannot be excluded. Evidence for mast cell involvement is supported by studies relating the release of neutrophil chemotactic activity to development of EIB in asthmatic patients (17). Furthermore, sodium cromoglycate, which inhibits mast cell mediator release by stabilising the cell membrane (25), prevents both EIB (7) and the release of NCF (17). Nedocromil sodium shows similar activity to sodium cro-

moglycate in some animal models of immediate type hypersensitivity, but appears to be more potent and has a wider range of activity including stabilisation of mucosal type mast cells (9, 18, 20).

In adult patients, nedocromil sodium has been shown to inhibit both early (21, 26) and late (8) asthmatic responses to allergen challenge. The late asthmatic reaction has been linked with the influx of inflammatory cells in the airways and development of bronchial hyperreactivity (5, 23). Therefore, nedocromil sodium has potential value for the treatment of chronic inflammatory lung disease. The drug has shown significant therapeutic benefit in 4-week (6, 16) and 12-month (4) trials in the control of chronic bronchial asthma in adults.

The results of the present study show that nedocromil sodium is effective against EIB in children, and suggest that it merits further investigation as a therapeutic agent in asthma.

## REFERENCES

1. Anderson, S. D.: Exercise-induced asthma. The state of the art. *Chest* 87 (Suppl. 5), 191-195, 1985.
2. Bar-Yishay, E. & Godfrey, S.: Exercise and hyperventilation-induced asthma. *Clin. Rev. Allergy* 3, 441-461, 1985.
3. Cairns, H., Cox, D., Gould, K. J., Ingall, A. H. & Suschitzky, J. L.: New anti-allergic pyrano [3,2-g]quinoline-2,8-dicarboxylic acids with potential for the topical treatment of asthma. *J. Med. Chem.* 28, 1832-1842, 1985.
4. Carrasco, E. & Sepulveda, R.: The acceptability, tolerability and safety of nedocromil sodium in long-term clinical use. *Eur. J. Respir. Dis.* 69 (Suppl. 147), 311-313, 1986.
5. Cockcroft, D. W.: The bronchial late response in the pathogenesis of asthma and its modulation by therapy. *Ann. Allergy* 55, 857-862, 1985.
6. Cua-Lim, F., Agbayani, B. F. & Lachica, D.: A double-blind comparative trial of nedocromil sodium and placebo in the management of bronchial asthma. *Phil. J. Intern. Med.* 23, 181-190, 1985.
7. Dahl, R. & Henriksen, J. M.: Effect of oral and inhaled sodium cromoglycate in exercise-induced asthma. *Allergy* 35, 363-365, 1980.
8. Dahl, R. & Pedersen, B.: Influence of nedocromil sodium on the dual asthmatic reaction after allergen challenge: a double-blind, placebo controlled study. *Eur. J. Respir. Dis.* 69, 264-265, 1986.
9. Eady, R. P., Greenwood, B., Jackson, D. M., Orr, T. S. S. & Wells, E.: The effect of nedocromil sodium and

- sodium cromoglycate on antigen-induced bronchoconstriction in the *Ascaris*-sensitive monkey. *Br. J. Pharmacol.* 85, 323-325, 1985.
10. Eggleston, P. A., Rosenthal, R. R., Anderson, S. A., et al.: Guidelines for the methodology of exercise challenge testing of asthmatics. *J. Allergy Clin. Immunol.* 64, 642-645, 1979.
  11. Godfrey, S.: Exercise-induced asthma. In: Clark, T. J. H. & Godfrey, S. (eds.): *Asthma*. Chapman and Hall, London, 1977.
  12. Hahn, A., Anderson, S. D., Morton, A. R., et al.: A reinterpretation of the effect of temperature and water content of the inspired air in exercise-induced asthma. *Am. Rev. Respir. Dis.* 130, 575-579, 1984.
  13. Hsu, H. K. H., Jenkins, D. E., Hsi, B. P., et al.: Ventilatory functions of normal children and young adults. I. Spirometry. *J. Pediatr.* 95, 14-23, 1979.
  14. Hsu, H. K. H., Jenkins, D. E., Hsi, B. P., et al.: Ventilatory functions of normal children and young adults. II. Wright peak flow-meter. *J. Pediatr.* 95, 192-196, 1979.
  15. Jones, R. S., Buston, M. H. & Wharton, M. J.: The effect of exercise on ventilatory function in the child with asthma. *Br. J. Dis. Chest* 56, 78-86, 1962.
  16. Lal, S., Malhortra, S., Gribben, D. & Hodder, D.: Nedocromil sodium: a new drug for the management of bronchial asthma. *Thorax* 39, 809-812, 1984.
  17. Lee, T. H., Nagy, L., Nagakura, T., Walport, M. J. & Kay, A. B.: Identification and partial characterisation of an exercise-induced neutrophil chemotactic factor in bronchial asthma. *J. Clin. Invest.* 69, 889-899, 1982.
  18. Leung, K. B. P., Flint, K. C., Brostoff, J., et al. A comparison of cromoglycate and nedocromil sodium on human lung mast cells obtained by bronchoalveolar lavage and by dispersion of lung fragments. *Eur. J. Respir. Dis.* 69 (Suppl. 147), 223-226, 1986.
  19. McFadden, E. R. & Ingram, R. H.: Exercise-induced asthma: observations on the initiating stimulus. *N. Engl. J. Med.* 301, 763-769, 1979.
  20. Orr, T. S. C., Jackson, D. M., Greenwood, B., Wells, E. & Eady, R. P.: Nedocromil sodium: a selective mucosal mast cell stabiliser. In: Kay, A. B. (ed.): *Asthma: Clin. Pharmacol. Ther. Prog.*, pp. 265-273. Blackwell Sci., Oxford, 1983.
  21. Rak, S., Balder, B. & Löwhagen, O.: The effect of nedocromil sodium on bronchial antigen challenge in asthmatic patients. *Eur. J. Respir. Dis.* 69 (Suppl. 147), 280-281, 1986.
  22. Roberts, J. A. & Thomson, N. C.: Attenuation of exercise-induced asthma by pre-treatment with nedocromil sodium and minocromil. *Clin. Allergy* 15, 377-381, 1985.
  23. Robinson, C. & Holgate, S. T.: Mast cell-dependent inflammatory mediators and their putative role in bronchial asthma. *Clin. Sci.* 68, 103-112, 1985.
  24. Shaw, R. J. & Kay, A. B.: Nedocromil, a mucosal and connective tissue mast cell stabiliser, inhibits exercise-induced asthma. *Br. J. Dis. Chest* 79, 385-389, 1985.
  25. Wells, E. & Mann, J.: Phosphorylation of a mast cell protein in response to treatment with anti-allergic compounds. Implications for the mode of action of sodium cromoglycate. *Biochem. Pharmacol.* 32, 837-842, 1983.
  26. Youngchaiyud, P. & Lee, T. B.: Effect of nedocromil sodium on the immediate response to antigen challenge in asthmatic patients. *Clin. Allergy* 16, 129-134, 1986.

## Address

Dr. J. M. Henriksen  
Pediatric Department  
Kolding Sygehus  
6000 Kolding  
Denmark

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.