

Respiratory pathophysiologic responses

The preventive effect of nedocromil or furosemide alone or in combination on exercise-induced asthma in children

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Background: Recent evidence suggests that inhaled nedocromil and furosemide are effective in preventing asthma by ultrasonically nebulized distilled water, allergen, and exercise. There are, however, no studies that compare the effects of these two drugs. The aim of this study was to investigate the effect of inhaled furosemide (30 mg), nedocromil (4 mg), the combination of these two drugs, and placebo aerosol in preventing exercise-induced asthma.

Methods: Twenty-four children with exercise-induced asthma, aged 6 to 16 years, performed a treadmill test before and 20 minutes after a single dose of drug(s) in a double-blind trial. Lung function measurements were taken before drug administration, before the exercise test (20 minutes after drug administration), and then 2, 4, 6, 8, 10, 15, 20, and 30 minutes after the exercise test.

Results: Both active drugs performed significantly better than placebo. In fact, the exercise challenge resulted in a mean maximum fall in forced expiratory volume in 1 second of $28.46\% \pm 13.84\%$ after administration of placebo, but of only $15.42\% \pm 8.35\%$ after administration of nedocromil ($p < 0.001$) and of $11.37\% \pm 9.14\%$ after administration of furosemide ($p < 0.001$). When the two drugs were given together, there was a statistically significant additive effect because the mean maximum fall in forced expiratory volume in 1 second was $5.75\% \pm 3.57\%$ (nedocromil vs nedocromil + furosemide: $p < 0.001$; furosemide vs nedocromil + furosemide: $p < 0.01$).

Conclusion: This study suggests that nedocromil and furosemide provide a comparable effect in preventing exercise-induced asthma in children. The combined administration of the two drugs significantly increases the protective effects, suggesting a potential therapeutic use. (*J ALLERGY CLIN IMMUNOL* 1994;94:201-6.)

Key words: Exercise-induced asthma, furosemide, nedocromil, children

Exercise-induced asthma (EIA) is a common phenomenon in children with asthma,¹ and it is well known that nedocromil, a nonbronchodilating, nonsteroidal antiasthmatic agent, is effective in preventing EIA,^{2, 3} probably through a stabilization of mast cells⁴ and an inhibitory effect on the activation of other inflammatory cells or an effect on sensory nerves.^{5, 6}

Recently, it has been suggested that water loss and hyperosmolality of the fluid bathing the air-

Abbreviations used

EIA:	Exercise-induced asthma
FEF ₂₅₋₇₅ :	Forced expiratory flow rate during the middle half of the forced vital capacity
FEV ₁ :	Forced expiratory volume in 1 second
PEFR:	Peak expiratory flow rate

way mucosa are important initiating factors in EIA,⁷ and drugs such as furosemide, a diuretic able to interfere with ion and water movement across airway epithelium,⁸ have been shown to prevent EIA.⁹

In this study we compared the protective effect of the administration of nedocromil or furosemide alone and in combination in the prevention of EIA in children.

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TABLE I. Baseline lung function values (mean + SD and percent predicted) after treatment with various drugs

	FEV ₁	PEFR	FEF ₂₅₋₇₅
Placebo			
Mean ± SD	2.05 ± 0.57	4.38 ± 1.20	2.44 ± 0.81
% Predicted	93.96 ± 10.05	97.25 ± 9.04	82.58 ± 15.10
Ned			
Mean ± SD	2.01 ± 0.61	4.13 ± 1.12	2.26 ± 0.75
% Predicted	90.42 ± 8.30	95.83 ± 13.43	77.67 ± 15.06
Fur			
Mean ± SD	2.07 ± 0.67	4.29 ± 1.40	2.40 ± 0.80
% Predicted	91.75 ± 10.25	95.79 ± 17.43	80.92 ± 17.92
Ned + Fur			
Mean ± SD	2.05 ± 0.66	4.13 ± 1.25	2.25 ± 0.82
% Predicted	90.67 ± 12.10	93.62 ± 18.47	77.79 ± 22.36

Ned, Nedocromil; *Fur*, furosemide.

METHODS

Subjects

Twenty-four children (16 boys and 8 girls, aged 6 to 16 years) with EIA were included in the study. All patients had perennial or episodic asthma, which could be relieved by antiasthmatic therapy. On the basis of history and skin prick test responses to 16 common allergens, they were all considered atopic. All children were allergic to house dust mite, and 12 were allergic to pollen, 10 to animal dander, and 4 to microfungi. All used inhaled or oral sympathomimetics (salbutamol or terbutaline) for control of symptoms. In addition, six used sodium cromoglycate or nedocromil sodium, four used orally administered theophylline (slow-release tablets), and two used steroid sprays (beclomethasone 400 µg/daily).

The patients attended an initial screening, the day before which they abstained from orally administered bronchodilators and long-acting inhaled β₂-agonist for at least 12 hours and from short-acting inhaled bronchodilators for at least 6 hours. Patients who had been treated with sodium cromoglycate or inhaled steroids in the previous month were excluded from the study. None of the subjects had had respiratory infections within 3 weeks of the trial.

Informed consent was obtained from both children and parents. The protocol was in accordance with the Helsinki Declaration of 1975 and had the approval of the hospital ethical committee.

Exercise challenge

Each child ran on a treadmill for 6 minutes with a slope and speed adjusted to produce an increase in pulse rate to 170 to 180 beats/min. The temperature in the laboratory throughout the study was between 20° and 22° C, and the relative humidity ranged between 45% and 50%.

Pulmonary function was monitored with a pneumotachograph (Cosmed, Rome, Italy) and forced expiratory

volume in 1 second (FEV₁), peak expiratory flow rate (PEFR), and forced expiratory flow during the middle half of forced vital capacity (FEF₂₅₋₇₅) were measured.

Predicted normal values were obtained from Zapletal et al.¹⁹ The presence of EIA was demonstrated by a fall of at least 15% in FEV₁ after the exercise test.

Study design

This was a placebo-controlled study. Each patient was tested with four treatment regimens in random order on 4 separate days. The four regimens were:

1. Nedocromil (2 mg/puff): 2 puffs given in successive breaths with use of a spacer (Volumatic; Glaxo SPA, Verona, Italy) to optimize compliance plus inhalation of saline solution for 15 minutes by means of a jet nebulizer (Nebula; Markos SRC, Monza, Italy) without interruption of the flow.
2. Two puffs of propellant only plus furosemide 10 mg/ml solution given by means of a jet nebulizer (Nebula) without interruption of the flow for a period of 15 minutes (Patients were connected to the nebulizer through a plastic cylindric mouth-piece and asked to breathe normally while wearing a nose clip. The amount of furosemide delivered to the mouth in this time, which was calculated on six occasions by differential weighing after placing 4 ml of solution in the reservoir, was 30.5 ± 9.2 mg.)
3. Nedocromil furosemide (administered as described above)
4. Placebo (2 puffs of propellant plus saline solution administered by jet nebulizer for 15 minutes)

The four treatments were given at the same time of day, on every other day as much as possible (within 2 weeks in 16 cases and within 3 weeks overall). The entire study was completed between January and February, because the most common symptomatic seasons of our subjects were autumn and spring.

TABLE II. Postexercise maximum percentage decrease (mean $\pm$ SD) in FEV₁, PEFR, and FEF₂₅₋₇₅ after administration of placebo, nedocromil, furosemide, and nedocromil + furosemide

	FEV ₁	PEFR	FEF ₂₅₋₇₅
Baseline	29.79 $\pm$ 13.92	22.33 $\pm$ 15.92	71.46 $\pm$ 28.28
Placebo	28.46 $\pm$ 13.84	22.46 $\pm$ 15.13	60.21 $\pm$ 33.09
Ned	15.42 $\pm$ 8.35	15.04 $\pm$ 7.90	36.29 $\pm$ 27.33
Fur	11.37 $\pm$ 9.14	13.29 $\pm$ 10.15	26.25 $\pm$ 19.12
Ned + Fur	5.75 $\pm$ 3.57	7.13 $\pm$ 5.19	13.92 $\pm$ 11.59
Baseline vs placebo	$p = \text{NS}$	$p = \text{NS}$	$p = \text{NS}$
Placebo vs Fur	$p < 0.001$	$p < 0.05$	$p < 0.001$
Placebo vs Ned	$p < 0.001$	$p < 0.05$	$p < 0.01$
Ned vs Fur	$p = \text{NS}$	$p = \text{NS}$	$p = \text{NS}$
Fur vs Ned + Fur	$p < 0.01$	$p < 0.05$	$p < 0.05$
Ned vs Ned + Fur	$p < 0.001$	$p < 0.001$	$p < 0.001$
Placebo vs Ned + Fur	$p < 0.001$	$p < 0.001$	$p < 0.001$

Ned, Nedocromil; Fur, furosemide; NS, not significant.

Lung function measurements (FEV₁, PEFR, FEF₂₅₋₇₅) were taken before drug administration, before the exercise test (20 minutes after drug administration), and then 2, 4, 6, 8, 10, 15, 20, and 30 minutes after the exercise test. The mean of two readings taken before the challenge was used as the baseline for comparison.

The bronchial responses to exercise were expressed as maximum percentage fall in FEV₁, PEFR, and FEF₂₅₋₇₅ from the preexercise values:

$$\frac{\text{Pre-exercise baseline values} - \text{Lowest postexercise value}}{\text{Pre-exercise baseline values}} \times 100$$

The percentage fall in FEV₁ at different time points after treatments was also calculated.

Clinical protection was considered to be obtained if the percent of fall in FEV₁ after treatment was within the normal range (<15%).

Statistical analysis

The four treatments were compared by means of analysis of variance. Treatment order was found to have little influence on the results. Statistical significance was assessed at the 5% level with two-tailed tests. The effects of the treatments on the response to exercise challenge were compared with the maximum decrease in lung function expressed as a percentage of the prechallenge baseline value.

RESULTS

The mean preexercise baseline lung function after administration of placebo, nedocromil, furosemide, and nedocromil + furosemide is reported in Table I. There were no statistically significant differences among these values. The patients were either slightly or not at all obstructed, since these baseline values were in the range of the predicted normal values.

Both active drugs were significantly more protective than placebo; in fact, the exercise challenge resulted in a mean maximum fall in FEV₁ of 28.46% $\pm$ 13.84% after administration of placebo, but of only 15.42% $\pm$ 8.35% after administration of nedocromil ($p < 0.001$), and of 11.37% $\pm$ 9.14% after administration of furosemide ($p < 0.001$). When the two drugs were given together, there was a statistically significant additive effect because the mean maximum fall in FEV₁ was 5.75% $\pm$ 3.75% (nedocromil vs nedocromil + furosemide: $p < 0.001$; furosemide vs nedocromil + furosemide: $p < 0.01$). Measurements of PEFR and FEF₂₅₋₇₅ provided similar results (Table II).

The percentage change in FEV₁ at different time points is shown in Fig. 1. The percent fall in FEV₁ was significantly lower than that of placebo for nedocromil, furosemide, and the combination of the two drugs at all time points. A comparison between nedocromil and furosemide showed a statistically significant difference at 2 minutes ($p < 0.05$) and at 30 minutes ($p < 0.05$) (Fig. 1).

In individual patients clinical protection (percent of fall in FEV₁ <15%) was provided in 3 of 24 (12.5%) children receiving placebo, in 14 of 24 (58.3%) receiving nedocromil, in 19 of 24 (79.1%) receiving furosemide and in 24 of 24 (100%) receiving nedocromil + furosemide (Table III). All 14 patients who received clinical protection with nedocromil were also protected with furosemide, whereas five patients received clinical protection with furosemide but not with nedocromil. All children were completely protected with the combined treatment.

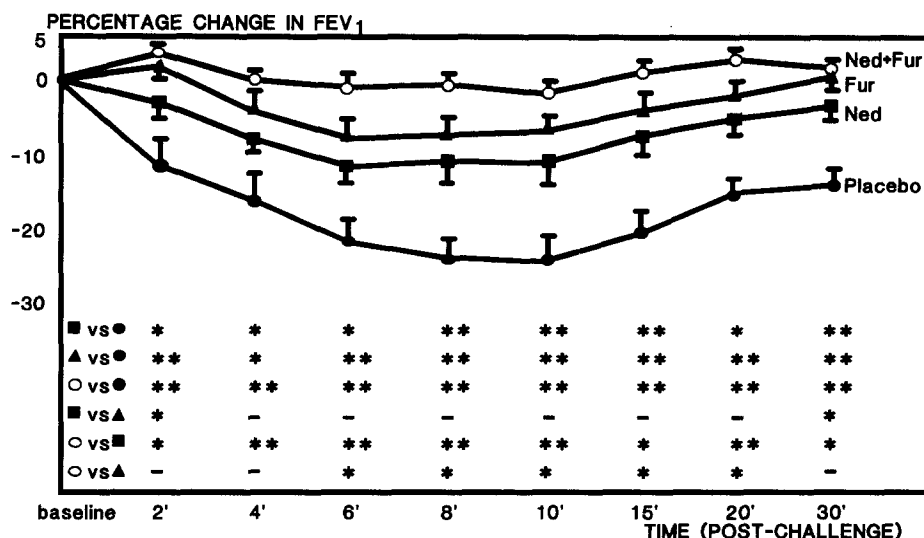


FIG. 1. Effect of pretreatment with aerosolized furosemide (30 mg), nedocromil (4 mg), furosemide + nedocromil, and placebo on exercise-induced changes in FEV₁ (mean $\pm$ SEM) from baseline. Asterisk denotes significant differences with $p \leq 0.05$. Double asterisks denote significant differences with $p \leq 0.001$. Minus sign denotes differences not significant. Ned, Nedocromil; Fur, furosemide.

TABLE III. Individual patient protection (number of patients) in 24 children performing treadmill exercise challenge after a single dose of medication

	Clinical protection	No protection
Placebo	3 (12.5%)	21 (87.5%)
Ned	14 (58.3%)	10 (41.6%)
Fur	19 (79.1%)	5 (20.8%)
Ned + Fur	24 (100%)	0 (0%)

Values in parentheses represent percent of patients.

Clinical protection equals percent of fall in FEV₁ within normal range.

Ned, Nedocromil; Fur, furosemide.

Side effects

Six subjects complained of an unpleasant taste after inhalation of nedocromil. Three of these subjects also complained of mild throat irritation after inhalation of nedocromil. No side effects were reported after inhalation of furosemide. One patient complained of headache after inhalation of placebo. None of the treatments induced changes in pulse rate or blood pressure. Effects on diuresis were not investigated.

DISCUSSION

This study has shown that furosemide is at least as effective as nedocromil in preventing EIA in children and that the combined administration of the two drugs completely inhibits the broncho-obstructive response to exercise.

EIA is a very common phenomenon in children

with asthma, and therefore an effective and safe therapy is very important in clinical practice. The precise mechanisms responsible for EIA are not yet known; on the basis of increased levels of circulating histamine and neutrophil chemotactic factor after exercise challenge in subjects with asthma, it has been suggested¹¹ that physical stimulus leads to mast cell degranulation and mediator release, which in turn cause bronchoconstriction.¹²

Other investigators, however, have not observed these findings,^{13, 14} and bronchoalveolar lavages performed immediately after exercise have demonstrated the lack of mast cell mediators.^{15, 16}

Nedocromil is a new drug of proven efficacy in the prevention of asthma, with a demonstrated capacity to stabilize both submucosal and mucosal mast cells and other cells, such as eosinophils and

macrophages.⁴ Nedocromil also has an inhibitory effect on sensory nerves.^{5, 6} The protective effect of nedocromil on EIA has been demonstrated in clinical studies performed in children³ and adults.^{2, 17}

Water loss and subsequent increase in osmolarity of fluid interface of the respiratory epithelium and airway mast cells has been proposed as the major stimulus for EIA.⁷ Inhaled furosemide, a diuretic able to interfere with ion and water movement across epithelium,⁸ has recently been shown to prevent bronchoconstriction induced by various triggers such as ultrasonically nebulized distilled water,¹² cold air,¹⁸ metabisulphite,¹⁹ allergen,²⁰ and lysine-aspirine^{21, 22} but not metacholine¹⁹ or histamine.²²

These effects of furosemide, resembling the action of nedocromil, may provide new insights into the basic mechanisms of asthma.²³

How inhaled furosemide exerts its protective effect on EIA must be established. *In vitro*, furosemide inhibits Cl⁻ secretion into bronchial lumen by blocking an electrically neutral Na-Cl-cotransport process in the basolateral membrane of epithelial cells.⁸

These changes in osmotic and ionic epithelial environment probably dampen the responsiveness of sensory epithelial receptor and thus inhibit the reflex vagally mediated component of the reaction or reduce the local release of mediators.²⁴ The possibility that furosemide might alter the reactivity of bronchial vessels, thus influencing the normal events (cooling and rewarming) that take place within the airways during exercise, must also be considered.⁹

In asthma induced by ultrasonically nebulized distilled water, furosemide prevents bronchoconstriction and the increase of neutrophil chemotactic activity, supporting the theory that furosemide acts on mast cells.¹²

Furosemide might also act by releasing bronchodilator prostaglandins from airway epithelium, as has been shown with vascular endothelium in the presence of furosemide.²⁵ In fact, indomethacin, a prostaglandin synthetase inhibitor, inhibits the protective effect of furosemide against EIA.²⁶

In this study we demonstrated that furosemide and nedocromil have a comparable protective effect on EIA because there is no statistically significant difference in the mean maximum fall in FEV₁ (15.42% ± 8.35% after administration of nedocromil and 11.37% ± 9.14% after administration of furosemide). Among individual patients a clinical protective effect was observed in 19

receiving furosemide and in 14 receiving nedocromil, indicating that at the dosage used, there are only slight differences between these two drugs in the prevention of EIA. However, the combined administration of nedocromil and furosemide is significantly more effective than the use of nedocromil and furosemide alone.

Doses of the two drugs used in this study were those that provided the best protection in other studies. In fact, comparative studies have demonstrated that 2, 4, and 8 mg of nedocromil administered by metered dose inhaler were equally effective in preventing EIA.²⁷⁻²⁹

In one dose-response study,³⁰ nebulized nedocromil administered in concentrations from 0.5 to 20 mg/ml was effective in attenuating the fall in FEV₁, with no significant differences in the inhibitory effect among the four concentrations. Degree of protection was about 50%, which was similar to that induced by 4 mg nedocromil from a metered dose inhaler. This dose also provided plasma concentrations similar to the 5 mg/ml nebulizer concentration, suggesting that the dose adsorbed was similar. These results suggest that the response to nedocromil was not dose-dependent over the range of doses studied and that the 4 mg given by a metered dose inhaler lies near the top of the dose-response curve.

In the first report on prevention of EIA by inhaled furosemide, Bianco et al.⁹ demonstrated that the dose of 28 mg was significantly more effective than the dose of 14 mg, but no other real dose-response studies that evaluate increasing dosages are available.

Recently, it has been reported that urinary output is significantly increased after administration of 28 mg of nebulized furosemide in children³¹ and after administration of 80 mg in adults.³² There are, however, no dose-response studies that compare the effect of inhaled doses of furosemide on diuresis with the protective effect on EIA. In this respect, the combined use of nedocromil and furosemide could permit reducing the dose of furosemide in order to avoid side effects that might be significant, especially in long-term trials.

In conclusion, our study has demonstrated that 30 mg of furosemide given by means of a jet nebulizer and 4 mg of nedocromil given by a metered dose inhaler have a comparable effect on EIA in children and that the combination of these treatments induces an additive effect, with a complete inhibition of EIA in all the patients studied. These results are very exciting, and may have

therapeutic implications. However, other studies investigating the dose-response effects of furosemide are required before a role of this drug in the therapy of asthma can be suggested.

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