

Respiratory pathophysiologic responses

The preventive effect and duration of action of two doses of inhaled furosemide on exercise-induced asthma in children

Elio Novembre, MD, Gianfranco Frongia, MD, Enrico Lombardi, MD, Massimo Resti, MD, Enrico Zammarchi, MD, and Alberto Vierucci, MD
Florence, Italy

Background: Exercise-induced asthma can be prevented by treatment with inhaled furosemide.

Objective: In this study we evaluated the effect and duration of action of two doses (15 and 30 mg) of inhaled furosemide in prevention of exercise-induced asthma in children.

Methods: Ten children with exercise-induced asthma (8 boys and 2 girls, aged 6 to 13 years) were included in the study. Each patient was tested with three treatment regimens (placebo, 15 mg of furosemide, and 30 mg of furosemide) in random order on 3 separate days. Patients performed exercise challenges on a treadmill at 20 minutes and 1, 2, 3, and 6 hours after each treatment. Pulmonary function, urinary output, and fluid intake were monitored.

Results: Both doses of furosemide had a significantly greater protective effect than placebo, but there was no significant difference between the two doses of furosemide. The higher dose of furosemide was associated with increased urinary output and had a longer duration of action.

Conclusion: A 30 mg dose of furosemide is more effective for treatment of exercise-induced asthma in terms of duration but has a significant diuretic effect. (*J ALLERGY CLIN IMMUNOL* 1995;96:906-9.)

Key words: Exercise-induced asthma, furosemide, children

In the first report on prevention of exercise-induced asthma (EIA) by treatment with inhaled furosemide, Bianco et al.¹ demonstrated that the dose of 28 mg was significantly more effective than the dose of 14 mg; in this study, we evaluated the effect and the duration of action of two doses (15 and 30 mg) of inhaled furosemide in prevention of EIA in children.

METHODS

Subjects

Ten asthmatic children (8 boys and 2 girls, aged 6 to 13 years) with asthma and EIA were included in the

Abbreviations used

EIA: Exercise-induced asthma
FEV₁: Forced expiratory volume in 1 second

study. All had perennial or episodic asthma, which could be relieved by antasthmatic therapy. All used inhaled or oral sympathomimetics (salbutamol) for control of symptoms. Additionally, three children used sodium cromoglycate or nedocromil sodium, and one used inhaled steroids. No patients used long-acting β_2 -agonists. Patients who had been treated with sodium cromoglycate or inhaled steroids on a long-term basis until the last month were excluded from the study. None of the subjects had had a respiratory tract infection within 3 weeks of the trial.

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

The patients attended an initial screening day before which they had abstained from use of oral bronchodila-

From the Allergy and Clinical Immunology Unit, Department of Pediatrics, Ospedal A. Meyer, Florence.

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Reprint requests: Elio Novembre, MD, Allergy and Clinical Immunology Unit, Department of Pediatrics—Ospedale A. Meyer, V. L. Giordano 13, Florence, Italy.

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tors and short-acting inhaled bronchodilators for at least 6 hours.

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 pneumotacograph (Cosmed, Rome, Italy) and forced expiratory volume in 1 second (FEV₁), peak expiratory flow rate, and forced expiratory flow, mid-expiratory phase were measured. The presence of EIA was demonstrated by a fall of at least 15% in FEV₁ after the exercise test.

Study design

Ampules of furosemide (Lasix; Hoechst, Frankfurt, Germany), each containing 20 mg of furosemide in 2 ml of saline solution (10 mg/ml) with a pH of 9, were used in this study. The placebo solution was 0.9% NaCl, adjusted daily to a pH of 8.9 to 9.2 by addition of 0.01 mol/L sodium hydroxide. The furosemide 5 mg/ml solution was obtained by mixing 2 ml of furosemide (10 mg/ml) with 2 ml of 0.9% NaCl solution. The pH of this solution was 8.75.

This was a placebo-controlled study. Each patient was tested with three treatment regimens in random order on 3 separate days. Furosemide (5 mg/ml in 0.9% NaCl) was given by means of a jet nebulizer without interruption of the flow (Nebula, Markos) for a period of 15 minutes. Patients were connected to the nebulizer by a plastic cylindrical mouthpiece and asked to breathe normally while wearing a nose clip. The amount of furosemide delivered to the mouth in this time, calculated on six occasions by differential weighing after placing 4 ml of solution in the reservoir, was 15.8 ± 7.5 mg (15 mg dose). Furosemide (10 mg/ml solution) was administered as described above. The amount of furosemide delivered to the mouth in this time, calculated on 6 occasions by differential weighing after placing 4 ml of solution in the reservoir, was 30.3 ± 8.7 mg (30 mg dose). Four milliliters of placebo was administered through a jet nebulizer for 15 minutes.

Patients performed an exercise challenge test 20 minutes (run 1) and 2 (run 2), 4 (run 3) and 6 hours (run 4) after each treatment.

The three treatments were given at the same time of day, on every other day as far as possible (within 2 weeks in 8 cases and within 3 weeks overall). The entire study was completed between December and January, the most allergen-free period in our country.

Lung function measurements (FEV₁; peak expiratory flow rate; forced expiratory flow, mid-expiratory phase) were taken before drug administration, before the exercise test (20 minutes after drug administration), and

then 2, 4, and 6 hours after drug administration. 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, from the pre-exercise baseline values:

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

Urinary output

Urinary output and fluid intake were monitored during the 6-hour period after nebulization. The subjects voided on arrival at the laboratory, and a quantitative urine collection was obtained from the start of nebulization to the completion of the 6-hour challenge. The amount of fluid intake for the first measurement period was recorded and was not exceeded in the following measurement periods.

Statistical analysis

The three 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 patients were either slightly or not at all obstructed, because their baseline values were in the range of predicted normal values.

The first exercise challenge resulted in a mean ($\pm$ SD) maximum fall in FEV₁ of 23.6% $\pm$ 7.6% after administration of placebo, but only of 10.1% $\pm$ 5.9% after administration of 30 mg of furosemide, and 11.5% $\pm$ 8.3% after administration of 15 mg of furosemide.

Both doses of active drug were significantly more protective than placebo, but there was no significant difference between 30 mg and 15 mg of furosemide. The protective effect decreased but was still significant for both doses after 2 hours (mean percent fall: placebo = 20.01 $\pm$ 6.5; furosemide, 15 mg = 11.2 $\pm$ 9.6; furosemide, 30 mg = 10.0 $\pm$ 7.7). During the third exercise of the day, 4 hours after drug administration, only the dose of 30 mg of furosemide induced significant protection against EIA (mean percent fall: placebo = 18.4 $\pm$ 5.9; 15 mg of furosemide = 13.3 $\pm$ 8.3; 30 mg of furosemide = 10.8 $\pm$ 7.5). During the fourth exercise of the day, 6 hours after drug administration, neither drug dose was protective (mean per-

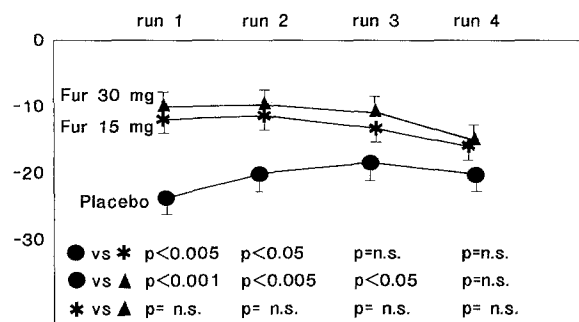


FIG. 1. Mean ($\pm$ SEM) maximum fall in FEV₁ after exercise test performed 20 minutes and 2, 4, and 6 hours after administration of single doses of placebo (circles), 15 mg of furosemide (asterisks), and 30 mg of furosemide (triangles). Fur, Furosemide; n.s., not significant.

cent fall: placebo = 20.2 ± 8.3 ; 15 mg of furosemide = 14.9 ± 11.2 ; 30 mg of furosemide = 15.6 ± 9.1). (Fig. 1).

There were no significant differences between the mean percent falls in FEV₁ after placebo administration, measured after the first exercise challenge when the percent fall was compared with that measured after the second, third, or fourth exercise challenge; thus, repeated challenges at 2-hour intervals did not significantly influence the degree of EIA.

Urinary output was significantly increased after inhalation of 30 mg of furosemide but not after inhalation of 15 mg. In the 6 hours after nebulization, the subjects voided an average of 268.5 ± 111.8 ml after placebo administration, compared with 359.0 ± 95.0 ml after administration of 15 mg of furosemide and 458.5 ± 121.8 ml after administration of 30 mg. No patient complained of orthostatic symptoms or excessive thirst.

DISCUSSION

This study has shown that the 15 and 30 mg doses of furosemide have a comparable protective effect in EIA, but the duration of action is longer with the higher dose. These results do not confirm the previous results of Bianco et al.,¹ who found that both doses were effective in adults when compared with placebo, whereas a 28 mg dose of furosemide was significantly more effective than a 14 mg dose. It is possible that the higher dose with respect to weight used in our study and the difference in the severity of EIA (mean fall in FEV₁ of 34% in patients in the study by Bianco et al.¹ compared with the 23% fall in our patients) can explain these different results.

No studies have evaluated the duration of the effect of furosemide in preventing EIA. In asthma

induced by hyperventilation of cold dry air, it has been demonstrated² that high doses of inhaled furosemide (80 mg) inhibited the airways' responsiveness for not more than 2 hours and that furosemide also caused bronchodilatation (14% rise in the mean FEV₁).

In our study of EIA in children, the preventive effect of furosemide lasted at least 2 hours with the dose of 15 mg and at least 4 hours with the dose of 30 mg; no postnebulization bronchodilatation was observed.

It is possible that the duration of action of furosemide is longer, because there is a slight reduction of the percent fall in FEV₁ after placebo administration in runs 2, 3, and 4 (Fig. 1). It is well known that approximately 50% of patients with EIA will have a "refractory period" of 2 to 4 hours after an initial exercise test, when an identical exercise elicits less than 50% of the initial bronchoconstriction.³ However, none of our patients demonstrated such a phenomenon. The evaluation of the protective effect of different doses of furosemide and their relative effect on diuresis is very important in trying to establish optimum clinical use of this drug. Some investigators have demonstrated a significant increase in urinary output after a nebulized dose of 28 mg of furosemide in children⁴ and 80 mg in adults.²

In this study we demonstrate that the dose of 30 mg of furosemide is more effective in terms of duration but has a significant diuretic effect, whereas the dose of 15 mg has no statistically significant effect on diuresis but has a shorter duration of protection against EIA.

The effectiveness of inhaled furosemide in preventing EIA is similar to that of nedocromil,⁵ but the combination of inhaled nedocromil and furosemide at normally used doses (28 mg) is significantly more protective than nedocromil or furosemide alone. Therefore studies with regular inhaled furosemide should take into account this additive effect, in order to increase efficacy and avoid the side effects of diuresis, which would not be tolerable, especially in long-term trials. A study evaluating the efficacy and duration of action of the combined administration of low doses of furosemide (15 mg) and nedocromil might provide more information in this respect.

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