

Respiratory pathophysiologic responses

Comparative efficacy of inhaled furosemide and disodium cromoglycate in the treatment of exercise-induced asthma in children

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Background: Inhaled furosemide has been shown, in patients with asthma, to have prophylactic properties similar to those of disodium cromoglycate.

Objective: The aim of this study was to evaluate the protective effect of these drugs in the treatment of exercise-induced asthma.

Methods: Fifteen children with exercise-induced asthma (mean age, 10.8 years) underwent exercise challenge after a single dose of nebulized placebo, furosemide (20 mg/m² body area), or disodium cromoglycate (20 mg), 2 days apart, in a single-blind crossover trial.

Results: Both furosemide and disodium cromoglycate exerted significant protection against the bronchial response to exercise challenge, with a mean maximum percentage falls in FEV₁ of 4.66% and 7.22%, respectively ($p < 0.05$). On the placebo day, the mean maximum percentage fall in FEV₁ was 34.50% ($p < 0.05$).

Conclusion: The results of this study suggest that furosemide and disodium cromoglycate provide comparable efficacy in preventing exercise-induced asthma in children, with no side effects. (*J Allergy Clin Immunol* 1997;99:204-9.)

Key words: Exercise-induced asthma, inhaled furosemide, disodium cromoglycate, children

Recently, it has been reported that inhaled furosemide, an inhibitor of Na-K-Cl cotransport, significantly inhibits the bronchoconstriction provoked by exercise¹; cold and dry air challenge^{2,3}; and inhalation of allergens,⁴ distilled water,⁵⁻⁷ metabisulfite,⁸ adenosine 5'-monophosphate,⁹ 4.5% sodium chloride,¹⁰ and lysine-aspirin.¹¹

It seems that furosemide does not exert a direct effect on bronchial muscle. In fact, inhaled furosemide failed to protect against deterioration in lung function after inhalation of histamine¹² and methacholine.⁸ Nevertheless, O'Donnell et al.³ observed bronchodilation with inhaled furosemide when they used the elevated dose of 80 mg, and two clinical trials in acute asthma reported controversial results.^{13,14}

The precise mechanism is still unknown, but the action of furosemide resembles that of disodium cromoglycate, a prophylactic drug that may act on the postgan-

Abbreviation used

EIA: Exercise-induced asthma

glionic cholinergic fibers, in addition to its stabilizing effect on the membranes of mast cells.¹⁵

Some observations confirm this hypothesis: (1) in vitro release of histamine and other mediators by mast cells and basophils was inhibited in the presence of furosemide^{16,17}; (2) the increase in neutrophil chemotactic activity observed during distilled water challenge was prevented by inhaled furosemide⁵; (3) furosemide had no action on airway epithelial ion transport, measured by nasal potential difference¹⁸; and (4) nedocromil and furosemide provided comparable effects in the prevention of exercise-induced asthma (EIA) in children.¹⁹

The purposes of this study were to determine whether inhaled furosemide provides protection against EIA in children, by using a dose of 20 mg/m² body area, and to compare the effects of inhaled furosemide and inhaled disodium cromoglycate.

METHODS

Subjects

Fifteen children with moderate to severe asthma, according to American Thoracic Society criteria,²⁰ (9 boys and 6 girls; mean age, 10.8 years) attended the Division of Allergy and Immunology—Escola Paulista de Medicina on 3 different days, 2

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TABLE I. Subject characteristics and baseline data

Patient No.	Sex	Age (yr)	Weight (kg)	Height (cm)	FEV ₁ (% pred)	Severity of asthma	Therapy
1	M	14	46.3	159	74.2	Moderate	IS, β_2
2	M	9	37	133.5	79.4	Moderate	β_2
3	M	10	35.7	151	67.9	Moderate	β_2
4	M	9	30.5	147	73.2	Severe	IS, β_2
5	M	12	34.2	146	81.3	Moderate	β_2
6	F	14	52	152	100.0	Severe	β_2
7	M	10	27.2	135.5	123.7	Severe	IS, β_2
8	F	8	23	123.5	90.0	Severe	T, β_2
9	F	11	49	164.5	70.8	Severe	β_2
10	M	14	45	168	75.6	Moderate	T
11	F	13	41	152	77.8	Severe	β_2
12	F	9	38.9	142.5	82.2	Severe	T, β_2
13	M	10	28.7	131.5	83.8	Severe	T, β_2
14	M	11	41.2	14.5	85.1	Severe	T
15	F	8	28.2	130	94.8	Moderate	β_2

IS, Inhaled steroids; β_2 , inhaled β_2 -agonist; T, oral theophylline.

days apart, at the same time of day. Anthropometric details of subjects are given in Table I.

All patients were nonsmokers, had been free of respiratory tract infections for 1 month before the study, and had a positive skin prick test response to *Dermatophagoides pteronyssinus* (Ifidesa Aristegui, Spain). All patients had previous positive exercise challenge results, confirming the diagnosis of EIA. All drugs, except for inhaled steroids, were withheld for at least 12 hours before the beginning of each challenge.

The acceptable baseline FEV₁ before drug administration was 65% or more of the predicted value or 80% of the best previously recorded value. The protocol was approved by the Escola Paulista Ethical Committee, and parents gave informed consent.

Exercise challenge

The exercise challenge consisted of a 6-minute bicycle ergometry test (workload equivalent to 80% of predicted maximum working capacity; heart rate, 170 to 180 beats/min) while breathing cold air. The laboratory temperature was between 20 and 23° C.

Spirometry was performed through a Vitatrace pneumotachograph under BTPS conditions (i.e., at body temperature and ambient pressure, saturated with water vapor), and the best of three reproducible measurements was recorded to determine FEV₁.

Study design

The effects of furosemide and disodium cromoglycate were determined by a placebo-controlled crossover study. Each patient was tested with three treatment regimens on 3 separate days. On the placebo day, baseline lung functions were measured twice: before and 30 minutes after a placebo inhalation (saline solution, 4 ml/m² body area; maximum, 6 ml) delivered from a jet nebulizer (De Vilbiss model 645, 0.02 to 6 L/min). The exercise challenge was performed; and lung function values were determined at 1, 5, 10, 15, 30, and 60 minutes after exercise. On day 2, the patients inhaled nebulized furosemide (Lasix in saline solution, 5 mg/ml) in a total amount of 20 mg (4 ml)/m² body area (maximum, 30 mg) 30 minutes before exercise challenge. On day 3, they inhaled nebulized disodium cromoglycate (Intal) in a standard dose of 20 mg.

Statistical analysis

Differences in baseline FEV₁ and the efficacy of the three treatments were determined by means of analysis of variance. Baseline FEV₁ and FEV₁ after drug administration, within each study day, were compared by using Student's paired *t* test. The level of statistical significance was set at *p* < 0.05. The decrease in lung function, expressed as a percentage of the prechallenge baseline value, was used to represent the bronchial response to the exercise challenge after each drug treatment as shown in Fig. 1.

RESULTS

The results of lung function tests of most of the patients, regarding baseline values, were within normal range. Data are reported as individual and mean absolute values of FEV₁ and standard deviation in Table II (day 1, placebo), Table III (day 2, furosemide), and Table IV (day 3, disodium cromoglycate). There were no significant differences in FEV₁ baseline values between the study days; the inhalation of placebo, furosemide, or disodium cromoglycate had no effect on resting lung function.

On the placebo day, exercise challenge induced bronchospasm in all patients within the first 5 minutes. Deterioration of lung function after administration of furosemide and disodium cromoglycate, compared with placebo, was significantly diminished (Fig. 1). Postexercise changes in FEV₁ values were similar after furosemide and cromoglycate inhalation, with no statistical differences; whereas the difference between placebo and the two other drugs was highly significant at 1, 5, 10, 15, and 30 minutes after challenge. There were no adverse effects.

DISCUSSION

Parenteral and oral furosemide have been advocated for treatment of infants with bronchopulmonary dysplasia.²¹ The underlying mechanism, unrelated to its diuretic properties, is still unknown. Other diuretics did not improve either lung mechanics or oxygenation.²²

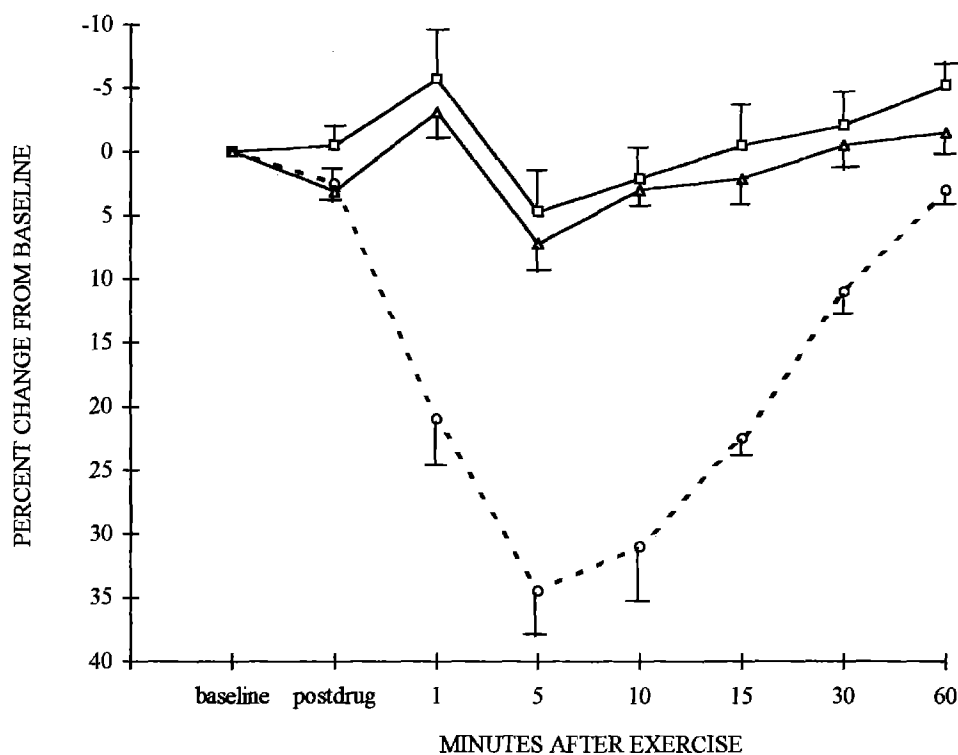


FIG. 1. Graph representing effects of pretreatment with inhaled placebo (circles), furosemide (squares), and disodium cromoglycate (triangles) on exercise-induced changes in FEV₁ (mean postexercise value measurement minus percent baseline, mean $\pm$ SEM). There was a significant difference between placebo and the two drugs ($p < 0.05$) at 1, 5, 10, 15, and 30 minutes after exercise.

TABLE II. Individual and mean absolute values of FEV₁ (in liters) on day 1 (placebo), standard deviation, and percentage fall from baseline

Patient No.	Saline inhalation		Minutes after exercise					
	Before	After	1	5	10	15	30	60
1	2.30	2.35	2.60	1.70	1.70	1.70	1.95	2.45
2	1.50	1.40	1.30	1.10	1.20	1.30	1.45	1.40
3	1.80	1.70	1.80	1.40	1.60	1.70	1.70	1.80
4	1.80	1.75	1.80	1.40	1.60	1.70	1.75	1.80
5	2.00	2.00	1.80	1.60	1.60	1.70	2.00	1.90
6	2.70	2.60	1.80	1.70	1.60	1.70	2.00	2.50
7	2.40	2.10	1.00	0.70	0.85	1.20	1.80	2.00
8	1.35	1.20	0.50	0.50	0.40	0.55	0.70	1.20
9	2.40	2.50	1.65	1.55	1.80	2.05	2.30	2.60
10	2.70	2.70	2.70	2.30	2.50	2.65	2.60	2.70
11	2.10	2.00	1.20	1.10	1.10	1.45	1.90	2.10
12	1.85	1.80	1.50	1.15	1.30	1.45	1.60	1.60
13	1.50	1.60	1.00	0.80	0.90	1.10	1.20	1.40
14	2.00	1.95	1.70	1.30	1.00	1.35	2.10	2.00
15	1.65	1.60	1.35	1.30	1.60	1.60	1.60	1.60
Mean	2.00	1.95	1.58	1.31	1.38	1.55	1.78	1.94
SD	0.427	0.440	0.575	0.451	0.501	0.465	0.453	0.465
% Fall	0.00	2.50	21.00	34.50	31.00	22.50	11.00	3.00

However, long-term therapy may have undesirable side effects.²³

In response to a simple question (i.e., What is the possible role of Na-K-Cl cotransporter in the develop-

ment of hyperosmolarity of airway lining fluid in EIA?), Bianco et al.¹ started a new field study, the inhaled diuretics. After serial trials, furosemide, the first studied drug, continues to demonstrate the best pharmacokinetic

TABLE III. Individual and mean absolute values of FEV₁ (litres) on day 2 (furosemide), standard deviation, and percentage fall from baseline

Patient No.	Furosemide inhalation		Minutes after exercise					
	Before	After	1	5	10	15	30	60
1	2.70	2.90	3.10	2.60	2.40	2.35	2.60	2.95
2	1.50	1.50	1.55	1.50	1.60	1.60	1.50	1.60
3	1.70	1.80	1.85	1.90	1.90	2.00	2.10	2.00
4	1.60	1.50	2.00	1.50	1.60	1.60	1.70	1.70
5	2.10	2.00	2.10	2.00	2.00	1.95	2.05	2.00
6	2.30	2.25	2.10	1.80	1.80	2.30	2.10	2.20
7	1.80	2.00	2.20	2.00	2.00	2.10	2.10	2.10
8	1.45	1.30	1.30	1.10	1.40	1.30	1.40	1.40
9	2.20	2.30	2.35	1.90	2.20	2.40	2.30	2.45
10	2.60	2.70	2.90	2.70	2.70	2.70	2.80	2.80
11	2.10	2.00	2.10	2.10	2.20	2.10	2.10	2.20
12	1.50	1.65	1.70	1.50	1.60	1.75	1.70	1.70
13	1.40	1.30	1.30	1.20	1.20	1.30	1.30	1.30
14	2.40	2.20	2.50	1.60	2.20	2.05	2.30	2.40
15	1.50	1.70	1.50	1.40	1.55	1.55	1.55	1.60
Mean	1.93	1.94	2.04	1.84	1.89	1.94	1.97	2.03
SD	0.444	0.476	0.527	0.460	0.407	0.413	0.439	0.488
% Fall	0.00	-0.50	-5.70	4.70	2.10	-0.50	-2.10	-5.20

TABLE IV. Individual and mean absolute values of FEV₁ (in liters) on day 3 (disodium cromoglycate), standard deviation, and percentage fall from baseline

Patient No.	Cromolyn inhalation		Minutes after exercise					
	Before	After	1	5	10	15	30	60
1	2.60	2.60	3.20	2.80	2.70	2.60	2.40	2.55
2	1.40	1.40	1.40	1.20	1.45	1.40	1.40	1.40
3	1.70	1.50	1.90	1.70	1.70	1.90	1.80	1.75
4	1.70	1.65	1.80	1.60	1.50	1.75	1.70	1.85
5	2.00	2.00	2.10	1.70	1.75	1.80	2.20	1.85
6	2.40	2.40	2.00	2.00	2.50	2.35	2.50	2.70
7	1.90	1.80	2.10	1.90	1.95	2.05	2.20	2.15
8	1.10	1.00	1.00	1.10	1.15	1.10	1.10	1.10
9	2.35	2.40	2.50	2.20	2.35	2.35	2.55	2.65
10	2.80	2.70	2.85	2.60	2.60	2.70	2.70	2.80
11	2.10	2.00	1.90	1.70	1.90	1.80	2.00	2.00
12	1.70	1.70	1.70	1.40	1.60	1.80	1.50	1.65
13	1.45	1.10	1.00	1.30	1.30	1.25	1.30	1.30
14	2.20	2.40	2.70	2.10	2.20	2.20	2.30	2.40
15	1.60	1.50	1.85	1.50	1.50	1.50	1.60	1.40
Mean	1.94	1.88	2.00	1.80	1.88	1.90	1.95	1.97
SD	0.475	0.536	0.624	0.490	0.491	0.476	0.503	0.553
% Fall	0.00	3.10	-3.10	7.20	3.00	2.10	-0.50	-1.50

ics in the airways,^{6, 24} surprisingly independent of Na-Cl inhibition.²⁵

We decided to compare the efficacy of inhaled furosemide and disodium cromoglycate because they have revealed, until now, a similar pattern of results in preventing bronchospasm induced by various stimuli.^{1, 4, 10}

Although views on the way effects of different drugs on EIA should be reported vary, we have chosen to express the changes in pulmonary function as mean percentage fall in FEV₁, with regard to values of the

treatment before drug administration (i.e., each postexercise value measurement minus percent baseline). Before exercise, FEV₁ should be at least 65% of predicted value, as indicated by the American Academy of Allergy.²⁶ All patients were atopic, as in other studies with inhaled furosemide.^{4, 24, 27}

To date, most studies in adults have been carried out with 28 to 40 mg of this loop diuretic, an equivalent of 16 to 22 mg/m² body area (based on a hypothetical adult with a body area of 1.8 m², weight of 70 kg, and height of 175 cm).²⁸ Some authors used the same adult dose for

children and observed increased diuresis.^{2,19} In two studies, after administration of nebulized water and cough-inducing acid, children with asthma received furosemide, 10 mg/m² body area; and the protection was not accompanied by any direct bronchodilator effect.^{7,29} Chin et al.,¹³ in the only study of crescent doses of inhaled furosemide according to weight in children with mild stable asthma, observed a significant increase of forced expiratory flow, mid-expiratory phase, with the dose of 1.0 mg/kg.

When we administered inhaled furosemide, 20 mg/m² body area, we did not notice a bronchodilator effect, any significant urinary output, or any changes in pulse rate or blood pressure. The controversial results, as far as the bronchodilator effect is concerned,^{3,8,12,14} may be explained by indirect action through bronchial smooth muscle relaxation factor release. Prostaglandin E₂, an inhibitory prostanoid that attenuates EIA and has considerable bronchoprotective effects in patients with asthma,³⁰ could be such factor,^{31,32} in spite of negative findings in nasal mucosa studies.^{33,34}

Furosemide increases the production of Prostaglandin E₂ in the kidneys,³⁵ possibly inducing the same stimulation within the airways, because indomethacin, a nonsteroidal antiinflammatory drug, blocked the preventive effect of furosemide.³⁶ Nevertheless, O'Connor et al.³⁷ observed opposing effects with flurbiprofen. Those studies failed to establish whether the antiinflammatory drugs interfered mainly with inhibitory or bronchoconstrictor cyclooxygenase products.

Our results showed significant but incomplete prevention of EIA in some patients with furosemide (3 of 15) and disodium cromoglycate (5 of 15). The mean maximum percentage decreases in FEV₁ were 7.64% and 11.52%, respectively. Indeed, disodium cromoglycate offers 80% protection in EIA, compared with almost 100% efficacy provided by salbutamol.³⁸ Novembre et al.,¹⁹ in 1994, reported mean maximum fall in FEV₁ of 11.37% after administration of furosemide (30 mg) and 15.42% after administration of nedocromil (4 mg) and, interestingly, increased protective effect after combined administration of the two drugs, casting doubts on the theory of an identical mechanism of action.

We conclude that inhaled furosemide prevents EIA in children, with no increase in diuresis, with a dose of 20 mg/m² body area and efficacy comparable to that of disodium cromoglycate. Further studies are needed to elucidate the mechanism of action of this diuretic.

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