

Steroid-sparing effect of inhaled lysine acetylsalicylate and furosemide in high-dose beclomethasone-dependent asthma

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Background: Inhaled lysine acetylsalicylate and furosemide exert a mutually potentiating protective activity on experimentally induced bronchoconstriction in asthma.

Objective: Our purpose was to investigate the clinical effectiveness of combined treatment of asthma with inhaled lysine acetylsalicylate and furosemide.

Methods: We performed a randomized, double-blind, crossover study in nine patients with chronic asthma requiring a high dose (2 mg/day) of inhaled beclomethasone for clinical control. Patients were treated with a combination of 720 mg inhaled lysine acetylsalicylate and 40 mg furosemide twice daily, or with matched placebo in addition to inhaled steroids. The dose of inhaled steroids was reduced by half every 15 days and eventually suspended unless a patient's respiratory condition worsened.

Results: During treatment with placebo, all patients had worsening of asthma at dosages of 1 or 0.5 mg/day beclomethasone (mean $\pm$ SE, 833 ± 83 μ g/day). During combined treatment complete suspension of inhaled steroids in two patients and reduction to 0.5 to 0.25 mg in the remaining seven patients (mean, 250 ± 72 μ g/day) was achieved, with a mean reduction of $71\% \pm 7\%$. Forced expiratory volume in 1 second, weekly peak expiratory flow rate, symptom score, and bronchodilator intake remained significantly better with combined treatment than with placebo.

Conclusions: Treatment with inhaled lysine acetylsalicylate and furosemide allows a considerable sparing of inhaled steroids without significant side effects in patients with severe asthma. (*J ALLERGY CLIN IMMUNOL* 1995;95:937-43.)

Key words: Lysine acetylsalicylate, aspirin, furosemide, nonsteroidal antiinflammatory drug, beclomethasone, steroid-dependent asthma

Inhaled corticosteroids are the primary treatment for many patients with asthma who would otherwise require excessive use of bronchodilators for relief of symptoms.¹⁻³ When given in low doses (up to 400 to 600 μ g/day), inhaled corticosteroids are relatively safe, but doses greater than 1 mg/day may often be needed to stabilize asthma and to avoid oral corticosteroids.⁴ At such large doses systemic side effects have been reported.⁴⁻⁶ Young

Abbreviations used

FEV₁: Forced expiratory volume in 1 second
LASA: Lysine acetylsalicylate
PEFR: Peak expiratory flow rate

patients are subject to growth retardation,^{7,8} and osteoporosis can be a problem in elderly and postmenopausal women.⁹

We previously showed that inhalation of either furosemide¹⁰⁻¹² or lysine acetylsalicylate (LASA), a soluble form of aspirin, significantly reduces the bronchial response to a variety of constrictor stimuli in patients with asthma.¹³ We subsequently observed that the protective effect of inhaled furosemide against physiologic bronchoconstrictor stimuli such as ultrasonic fog and exercise can be greatly enhanced by low doses of LASA given by

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TABLE I. Patient data

Patient No.	Sex/ age (yr)	Atopy	FEV ₁ (% predicted)	Duration of asthma (yr)	Duration of steroid treatment (mo)	Therapy
1	F/70		68	20	18	IS, β_2
2	F/63		68	19	24	IS, β_2 , IP
3	F/16	DP	68	14	20	IS, β_2 , IP
4	M/57		79	3	24	IS, β_2 , IP
5	F/52		71	>10	>24	T, IS, β_2 , IP
6	M/50		54	>10	>24	T, IS, β_2 , IP
7	F/45	DP	69	>10	>24	T, IS, β_2 , IP
8	F/67		100	>10	>24	T, IS, β_2 , IP
9	M/50	DP	83	>10	>24	IS, β_2 , IP
Mean $\pm$ SE	52 $\pm$ 5		73 $\pm$ 4			

β_2 , Inhaled β_2 -agonist; DP, *Dermatophagoides pteronyssinus*; IP, inhaled ipratropium bromide; IS, inhaled steroids; T, oral sustained-release theophylline.

the same route, resulting in a protective effect greater than the sum of the two separate effects.^{14, 15} In an open study on a small group of severely steroid-dependent patients with asthma, we found that treatment with this combination of drugs for 10 to 28 weeks was well tolerated and resulted in an impressive steroid-sparing effect.¹⁶ These encouraging results prompted us to perform a controlled study in a group of high-dose beclomethasone-dependent patients with asthma.

METHODS

Patients

We studied nine patients with moderately severe asthma, requiring 2 mg/day beclomethasone to maintain clinical stability. Some of their clinical characteristics are reported in Table I. All patients had been followed up in our outpatient clinic for more than 12 months, and at least one attempt to taper inhaled steroids in this period had failed, with relapse of asthma symptoms. At the time of entering the study all patients were in stable clinical condition and had been free of infections for at least 4 weeks. None of the patients had a history of aspirin asthma. Patients who had not taken aspirin in the previous 12 months underwent an inhalation challenge¹⁷ no more than 3 months before entering the study, with negative results.

Methods

Asthma symptoms and use of bronchodilators were monitored by patients on a diary card. Separate scores on a 5-point scale were recorded for cough and respiratory symptoms at night, on awakening, and during the day. The use of inhaled bronchodilators was recorded as the number of puffs of bronchodilator taken each day. Allowed bronchodilators were either salbutamol (100 μ g/puff) or the combination of fenoterol and ipratropium bromide (100 and 40 μ g/puff, respectively); the same drug was used by each patient throughout the

study. Lung function was monitored at home by recording morning and evening peak expiratory flow rate (PEFR) with a MiniWright Peak Flow meter (Markos, Monza, Italy). The highest value of three consecutive PEFR measurements performed before taking any bronchodilator was used for further analysis. Forced expiratory volume in 1 second (FEV₁) and forced vital capacity were measured with a dry-wedge spirometer (Vitalograph, Buckingham, U.K.). Methacholine challenge was performed with a Mefar dosimeter (Mefar, Bovezza, Italy) and the dose causing a 20% decrease in FEV₁ was computed by interpolation on the cumulative dose-response curve plotted on a semilogarithmic scale.¹²

Study design

Each patient was followed up for two study periods, during which inhaled steroids were tapered to the lowest tolerated dose while the patient was treated with combined inhaled LASA and furosemide, or with placebo. Before each study period patients underwent medical examination, FEV₁ was recorded before and 20 minutes after treatment with 400 μ g inhaled fenoterol, and a methacholine inhalation challenge was performed. The patients were then given a diary card for recording symptoms and medication, and a peak flow meter. The patients recorded these data for 2 weeks while continuing their usual therapy with 2 mg/day inhaled beclomethasone, then treatment with inhaled LASA and furosemide, or placebo, twice daily, was added to the previous therapy according to a randomized protocol. Treatment consisted of 720 mg LASA powder (corresponding to 400 mg acetylsalicylic acid and 320 mg lysine; Maggioni Winthrop, Milan, Italy) dissolved in 4 ml saline solution immediately before inhalation, followed by 40 mg furosemide in 4 ml saline solution (Lasix, Hoechst, Frankfurt am Main, Germany). Placebo consisted of 400 mg lysine alone in 4 ml saline solution, followed by 4 ml saline solution. At the same time the patients began to taper the dosage of inhaled steroids by half every 15 days, to 1000, 500, and 250 mg/day. Beyond

this lowest dosage, inhaled steroids were withheld for an additional 2 weeks. Before each decrement the patient underwent medical examination and spirometry. The trial was suspended before complete steroid withholding was achieved if the patient reported worsening of symptoms and was unwilling to reduce dosage further, or if a decrease in mean weekly PEF_R or morning FEV₁ by more than 25% from baseline was observed. Although it is possible that a more gradual schedule of steroid tapering might provide a more accurate estimate of the minimum dose of steroids required by our patients to maintain clinical stability, we judged that it would add little to our conclusions about the relative power of treatment with LASA and furosemide versus placebo and that it would introduce sources of variability because of the increased length of the study.

After the trial with one treatment was completed, the original dose of inhaled steroids was restored and the procedure was repeated with the other treatment. A prerequisite for beginning the second treatment was a stable clinical condition for a period of at least 2 weeks. The time required to achieve stable condition between the two treatments ranged from 4 to 8 weeks and sometimes necessitated a short course of oral steroids.

No changes in drug intake were allowed during the study period except for inhaled steroids and bronchodilators on demand, both of which were recorded on the diary card.

Statistical analysis

The risk of withdrawal from the trial because of relapse of asthma was compared with the Wilcoxon signed-rank test.¹⁸ We estimated that an even chance of obtaining a significant result could be achieved if the chance of the patient's withdrawal while receiving the better treatment, at the dose when half the patients on the worse treatment had withdrawn, was less than about 20%.¹⁹ This result was compatible with our previous observation in an open study.¹⁶

Symptom scores were expressed as a weekly mean by averaging the daily sum of scores for all symptoms. Morning and evening PEF_R results were averaged at weekly intervals. Mean weekly PEF_R was obtained by averaging morning and evening scores. Daily variability was computed as the difference between the evening and morning values, expressed as a percentage of their mean. The use of inhaled bronchodilators was expressed as the weekly mean number of puffs of bronchodilator per day. Because the data after averaging appeared to be normally distributed, they were treated as parametric data. The paired Student *t* test was used for comparison of the two groups, and analysis of variance with the method of the least significant difference was used to correct for multiple comparisons.²⁰ A *p* value less than or equal to 0.05 was considered statistically significant. Unless stated otherwise the data are expressed as mean $\pm$ SE.

The study design was such that patients withdrew at different time points, and it was impossible to compare

each parameter at all the time points. Only baseline measurements and those after the first reduction of inhaled steroids were obtained in all patients for both treatment periods. Because all patients receiving placebo suspended the trial while taking a dose of inhaled steroids greater or equal to that taken during combined treatment with furosemide and LASA, we were also able to compare the results obtained at withdrawal during placebo with those recorded at the same dose of steroids together with furosemide and LASA. We refer to this time point as to the equivalent dose point. We also compared the data obtained before the last steroid reduction that led to relapse (i.e., at the lowest dose of steroids affording control of symptoms).

RESULTS

Respiratory condition of the patients was similar at the start of the two study periods. FEV₁ was 1.93 ± 0.23 L before and 2.31 ± 0.29 L after fenoterol (increase of $16\% \pm 4\%$) at the start of placebo treatment. At the start of combined treatment FEV₁ was 2.02 ± 0.25 L before and 2.31 ± 0.31 L after administration of fenoterol (increase of $12\% \pm 4\%$). The geometric mean of methacholine dose causing a 20% decrease in FEV₁ was 273 μ g (geometric SE = 1.8 μ g) before placebo and 398 (1.6 μ g) before combined treatment, with a nonsignificant change of 0.5 ± 0.3 when doses between the two measurements were doubled. Morning and evening PEF_R were 338 ± 25 L/min and 379 ± 30 L/min, respectively, with a daily variation of $16\% \pm 4\%$ in the week preceding the start of placebo, and 343 ± 23 L/min and 388 ± 26 L/min, respectively, (variation, $13\% \pm 2\%$) at the start of combined treatment.

None of the patients reported any side effects caused by treatment with LASA and furosemide, or with placebo aerosol. During treatment with placebo all patients had worsening of asthma when beclomethasone was decreased to 1 or 0.5 mg/day (mean, 833 ± 83 μ g/day) and none achieved complete withdrawal of inhaled steroids (Fig. 1). During treatment with LASA and furosemide complete removal of inhaled steroids was achieved by two patients (Nos. 3 and 5; Table I). Of the other patients, one (patient 1) reported worsening of symptoms 1 week after withholding steroids, three while taking 0.25 mg/day (patients 6, 7, and 9), and three at 0.5 mg/day (mean, 250 ± 72 μ g/day). The duration of the study before relapse of symptoms was 30 ± 3 days during placebo versus 57 ± 4 days during combined treatment (*p* < 0.01 by Wilcoxon signed-rank test). The minimum steroid requirement during treatment with furosemide and LASA (i.e., the minimum

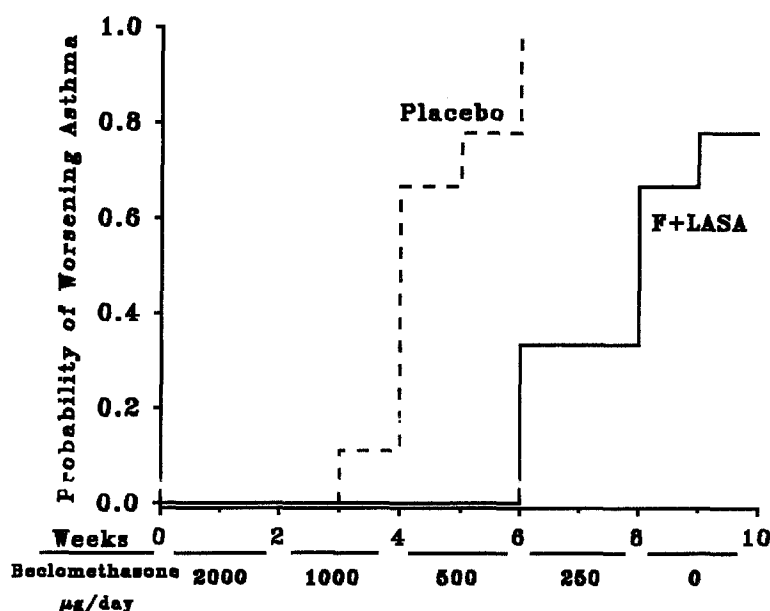


FIG. 1. Kaplan-Meier analysis of probability of worsening asthma during tapering of inhaled steroids in patients receiving inhaled furosemide and LASA or placebo. During treatment with placebo patients had higher risk of worsening asthma ($p < 0.005$ by Wilcoxon signed-rank test).

TABLE II. Clinical and functional changes during tapering of inhaled steroid dosage

	Beclomethasone (μg/day)	Symptom score	β ₂ -agonist (puffs/day)	PEFR (% of baseline)	
				Morning	Evening
Placebo					
Baseline	2000 ± 0	1.4 ± 0.5	2.3 ± 0.3	100 ± 0	100 ± 0
2nd baseline	2000 ± 0	1.3 ± 0.5*	2.2 ± 0.4†	102 ± 2‡	100 ± 1*
1st halving	1000 ± 0	1.9 ± 0.5	2.3 ± 0.7	96 ± 2	96 ± 3
Minimum effective dosage	1667 ± 167	1.6 ± 0.5	2.2 ± 0.4	99 ± 3	98 ± 2
Withdrawal	833 ± 83	4.1 ± 0.8	4.3 ± 0.5	88 ± 3	90 ± 4
LASA and furosemide					
Baseline	2000 ± 0	1.4 ± 0.5	2.5 ± 0.4	100 ± 0	100 ± 0
2nd baseline	2000 ± 0	1.2 ± 0.5†	2.3 ± 0.5†	103 ± 1*	101 ± 2†
1st halving	1000 ± 0	1.1 ± 0.5	1.8 ± 0.6	106 ± 2§	104 ± 3
Minimum effective dosage	472 ± 121	1.6 ± 0.5	2.1 ± 0.7	100 ± 3	97 ± 3
Withdrawal	250 ± 72	2.8 ± 0.9	3.3 ± 0.9	90 ± 4	92 ± 3
Equivalent dose point	833 ± 83	1.5 ± 0.6*	2.1 ± 0.6*	102 ± 3‡	100 ± 3*

* $p < 0.01$ versus withdrawal.

$^\dagger p < 0.05$ versus withdrawal.

$^\ddagger p < 0.001$ versus withdrawal.

$^\S p < 0.01$ versus placebo at same time point.

dose affording control and allowing further reduction) was $472 \pm 121 \mu\text{g/day}$ compared with $1667 \pm 167 \mu\text{g/day}$ during placebo, corresponding to a steroid sparing effect of $71\% \pm 7\%$.

Bronchodilator intake, symptom score, and PEFR did not change appreciably in the 2 weeks preceding the start of therapy with LASA and furosemide, or placebo (Table II). FEV₁ also remained stable during the run-in period before

both treatments (Fig. 2). After the first halving of inhaled steroids, FEV₁ decreased by $16\% \pm 4\%$ in relation to baseline during placebo but did not differ from baseline during combined treatment (change, $0\% \pm 3\%$, $p < 0.001$ vs placebo at the same time point). At the same time point weekly mean PEFR also decreased slightly during placebo but increased slightly during furosemide and LASA treatment (Fig. 3). A significant difference

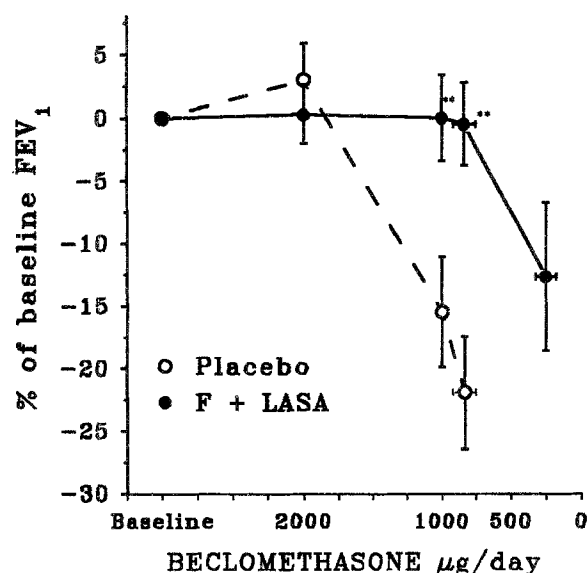


FIG. 2. Changes in FEV₁ (before bronchodilators) expressed as percentage of baseline in patients tapering inhaled steroids during treatment with inhaled furosemide and LASA, or placebo. FEV₁ changes are plotted against corresponding dosage of inhaled beclomethasone. Points at baseline and at 2000 µg/day correspond to start of run-in period and to start of treatment, respectively, and reflect patient stability at fixed dosage of 2 mg/day beclomethasone. Point at 1 mg/day corresponds to end of first halving of beclomethasone, and last point of each curve corresponds to withdrawal. Additional point plotted on line of combined treatment curve corresponds to FEV₁ measurement recorded for dosage of beclomethasone corresponding to withdrawal on placebo. Double asterisk, $p < 0.001$ versus corresponding dosage of beclomethasone during placebo treatment.

between the two treatments was observed at this time point for morning PEFR ($p < 0.01$), evening PEFR ($p < 0.01$), and mean weekly PEFR ($p < 0.001$). No significant changes were observed at any time point for percentage variations between morning and evening PEFR values (not shown). All the parameters studied deteriorated significantly at the time of withdrawal in both treatments, without significant differences between the two treatments. Furthermore, no differences were observed at the lowest dose affording control, before the last steroid reduction (Table II).

When the data obtained at withdrawal during placebo were compared with those obtained at the same dosage of steroids together with furosemide and LASA, all the parameters investigated were significantly better with combined treatment than with placebo. Furthermore, mean values observed during combined treatment at this steroid dosage were in all cases comparable to or better than

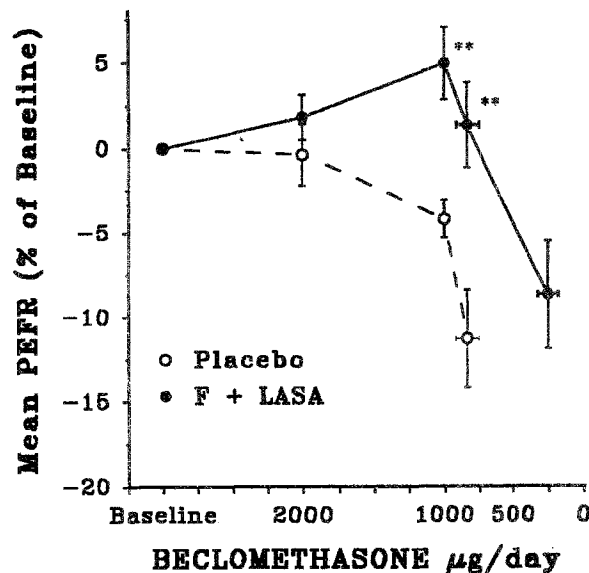


FIG. 3. Changes in weekly mean PEFR expressed as percentage of baseline in patients tapering inhaled steroids during treatment with inhaled furosemide and LASA, or placebo. Points at baseline and at 2000 µg/day correspond to 1 and 2 weeks before start of treatment and reflect patient stability at fixed dosage of 2 mg/day beclomethasone. The points at 1 mg/day correspond to first week after first halving of beclomethasone. Other points are as for Fig. 2, relative to PEFR. Double asterisk, $p < 0.001$ versus corresponding dosage of beclomethasone during placebo treatment.

baseline values, as opposed to the significant worsening observed with placebo.

DISCUSSION

Our data indicate that aerosol treatment with furosemide and LASA provided a significant steroid-sparing effect in a group of patients with severe asthma requiring very high doses of inhaled steroids to control asthma symptoms. Although complete withholding of inhaled beclomethasone was achieved by two patients only, most were able to reduce the required dose of inhaled steroids to less than 1 mg/day, a dosage that is not associated with significant long-term side effects.⁴

It is noteworthy that during treatment with furosemide and LASA, values of FEV₁, weekly PEFR, symptom score, and β_2 -agonist consumption were all significantly better than with the same dose of steroids that was insufficient to maintain clinical stability during treatment with placebo. Furthermore, as opposed to placebo treatment, these parameters were not modified with respect to baseline at this time point, indicating that patients receiving inhaled LASA and furosemide

maintained clinical stability despite a marked reduction in inhaled steroids.

The present study was not designed to evaluate the relative contribution of LASA and furosemide to the therapeutic effect or to identify their specific mechanisms of action. Because the question of the effectiveness of these drugs is important for future research in this field, we decided to perform this study with the combination that had given the best results in experimental challenges and that had shown synergistic action against some bronchoconstrictor stimuli^{14, 15}; we deferred the study of their individual relative efficacy. Our starting hypothesis was that both drugs could be useful to reduce episodes of bronchoconstriction, as observed experimentally with a variety of stimuli.^{13, 21} In addition to this protective effect, LASA also has well-documented antiinflammatory activity,²² which may contribute to its clinical efficacy in our patients. Although we observed a synergistic or additive protective effect of these drugs against several bronchoconstrictor stimuli,^{14, 15, 23} observations on possible interactions between furosemide and cyclooxygenase inhibitors in asthma are conflicting,²⁴⁻²⁶ and specific studies are needed to investigate whether the drugs interact during long-term treatment.

A most impressive aspect of our results was the complete lack of side effects of the treatment. Inhaled furosemide at the doses used in the present study has been shown to have few systemic effects,²⁷ and the dosage of aspirin absorbed by our patients was probably less than 100 mg/day,²⁸ a well-tolerated dose in the range used for long-term prevention of thrombotic and ischemic heart disease.²⁹ Other proposed alternatives to steroid treatment in asthma, such as methotrexate, gold salts, and cyclosporine are all associated with a high incidence of side effects and a steroid-sparing effect ranging from 30% to 40%.³⁰⁻³² Although in our study we tested the sparing effect on inhaled steroids rather than on oral steroids as in the cited studies, the results are probably comparable because the therapeutic efficacy of 2 mg inhaled beclomethasone corresponds to 10 to 16 mg of oral prednisone,⁴ which is the dose taken by most patients in those studies. Although further studies are needed to evaluate possible long-term effects of LASA inhalation, the present treatment is by far the most effective and the least toxic alternative to steroid treatment ever tested in steroid-dependent asthma.

Other issues that need to be addressed include the assessment of risk in aspirin-sensitive patients,

the development of more practical methods of administration with respect to conventional nebulizers, and the assessment of optimum doses and timing. Nevertheless, it is an attractive prospect that familiar drugs such as aspirin and furosemide may find application in the treatment of asthma.

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