

Potentialiation of the antireactive, antiasthmatic effect of inhaled furosemide by inhaled lysine acetylsalicylate

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Nonsteroid antiinflammatory drugs interfere with the diuretic activity of furosemide, implying that this effect is at least partially dependent on renal prostaglandin synthesis. To investigate whether prostaglandin production could also modulate the bronchial antireactive activity of this diuretic drug, we investigated the effect of inhaled lysine acetylsalicylate (162 mg) and of furosemide (18 mg), alone and in combination, on the bronchial obstructive response to ultrasonically nebulized water in asthmatic patients. The study was also prompted by the conflicting results obtained in previous studies of oral nonsteroid antiinflammatory drugs. Fifteen asthmatic patients underwent bronchial challenge with a mist of ultrasonically nebulized distilled water at the same time of day on four occasions, 2–4 days apart, 15 min after premedication according to a double-blind, randomized protocol. After placebo, mean PD_{15} to water mist did not differ from a preliminary test (2.1 ± 0.2 and 2.5 ± 0.4 ml, $M \pm SE$, respectively). After lysine acetylsalicylate, mean PD_{15} rose to 5.0 ± 0.7 ml (2.8 ± 0.6 times higher than placebo); after furosemide, to 9.0 ± 1.5 ml (4.4 ± 0.9 times over placebo); and after the two drugs in combination, to 32.2 ± 5.6 ml (16.3 ± 3.0 times higher than placebo). Similar results were obtained with inhaled indomethacin, whereas sodium salicylate had no effect. These data indicate that the bronchial antireactive activity of inhaled furosemide is greatly enhanced by inhaled lysine acetylsalicylate through a mechanism which probably involves inhibition of the local synthesis of prostaglandins, and could have therapeutic implications.

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Nonsteroid antiinflammatory drugs inhibit bronchial hyperreactivity (henceforth defined as antireactive activity) in response to ultrasonically nebulized distilled water in asthmatic patients, this effect being evident at much lower doses when administered by inhalation (8) than by the oral route (5, 31, 32). Unlike aspirin (acetylsalicylic acid), sodium salicylate does not exhibit antireactive activity (8, 33), suggesting that the protective effect afforded by aspirin and other nonsteroid antiinflammatory drugs is in some way related to their anticyclooxygenase activity, and consequently to the inhibition of prostaglandin synthesis. The loop diuretic furosemide has recently been found to be an effective antireactive agent when inhaled (3, 9, 32). This property is probably related to the ability of the drug to influence the transport of ions through the membranes of several

cell structures present in the bronchial wall; for example, epithelial cells, mast cells, neutrophils, eosinophils, and sensory receptors (2, 6, 16).

Several researchers have shown that nonsteroid antiinflammatory drugs affect the diuretic activity of furosemide, suggesting that prostaglandins participate in the activity of the drug at renal level (14, 23). For this reason, it cannot be excluded that prostaglandins may also modulate the antireactive activity of inhaled furosemide. Since conflicting results have been obtained in this field with oral nonsteroid antiinflammatory drugs as inhibitors of prostaglandin synthesis (28, 30, 38), the present study was undertaken to assess the effect of inhaled nonsteroid antiinflammatory drugs on the antireactive, antiasthmatic activity of inhaled furosemide.

Patients and methods

Patients

The subjects were 30 adult nonsmokers, who gave informed consent to participate in the study. All subjects had mild, clinically and functionally stable allergic or nonallergic asthma, and responded positively to a preliminary bronchial challenge with ultrasonically nebulized distilled water performed within 1 week before the study. None of the patients had a history of aspirin asthma, and they had all undergone an aspirin inhalation challenge in the previous 3 months, with negative results. All patients had a base-line FEV₁ > 70% of the predicted value, and had been free of viral or bacterial respiratory infection for at least 6 weeks. All patients were treated with an inhaled β_2 -agonist on demand, usually in association with regularly inhaled beclomethasone. Both drugs were withheld for at least 10 h before the test (12, 22). Patients allergic to pollen were studied outside the pollen season. Clinical and anthropometric data of the study group are reported in Table 1.

Bronchial challenge with ultrasonically nebulized distilled water

Reactivity to a mist of distilled water was measured as previously described (1, 32). Briefly, a mist of distilled water was generated by a DeVilbiss Ultraneb 99 nebulizer to which the patients, wearing noseclips, were connected by plastic, cylindric mouthpieces. Subjects were instructed to breathe normally at tidal volume. By a combination of output rate (2–4 ml/min) and time of exposure (0.25, 0.5, 1, 2, 4, and 8 min), increasing volumes of water in doubling increments were delivered to the mouth at 2-min intervals until a fall of 15% of FEV₁ occurred, or the cumulative dose of 63 ml was reached. FEV₁ was measured before challenge and immediately after each exposure with a dry wedge spirometer (Vitalograph, Buckingham, UK) or a constant-volume body plethysmograph (Fenyves and Gut, Basel, Switzerland), and the higher of the first two satisfactory recordings was taken for analysis. Dose-response curves were constructed by plotting the percentage changes in FEV₁ from their respective base-line values against the cumulative volume (in ml) of nebulized distilled water. The volume of nebulized water needed to decrease the FEV₁ by 15% (PD₁₅) was then calculated by linear interpolation.

Study design

The study was divided into three parts, which were performed in a double-blind, randomized manner.

Table 1. Anthropometric characteristics of patients in study

Patient no.	Sex	Age	FEV ₁ % predicted	Allergy ¹	Therapy ²
1	F	28	106	GR	β_2
2	M	47	81	—	β_2 +CS
3	M	22	94	GR	β_2 +CS
4	M	41	88	—	β_2 +CS
5	M	34	86	DP	β_2 +CS
6	F	39	87	—	β_2 +CS
7	F	47	82	GR	β_2 +CS
8	F	23	95	GR	β_2 +CS
9	M	47	83	—	β_2 +CS
10	F	43	79	—	β_2
11	F	28	83	B	β_2 +CS
12	F	29	88	—	β_2 +CS
13	F	36	102	GR, DP, O	β_2 +CS
14	F	21	88	DP	β_2 +CS
15	F	40	85	DP, GR	β_2 +CS
16	F	21	88	DP	β_2
17	F	35	76	PA	β_2 +CS
18	F	38	74	—	β_2 +CS
19	F	15	68	DP	β_2 +CS
20	F	19	88	DP	β_2
21	F	41	82	DP, GR	β_2 +CS
22	M	24	93	DP	β_2
23	F	22	82	GR, O, DP	β_2
24	F	40	85	DP, GR	β_2 +CS
25	M	27	95	DP	β_2
26	F	23	71	DP, DG, CT	β_2 +CS
27	F	36	92	DP, GR, O	β_2 +CS
28	M	34	90	—	β_2 +CS
29	M	35	93	B	β_2 +CS
30	F	42	85	B	β_2 +CS

¹ DP: *Dermatophagoides pteronyssinus*; GR: grass pollen; PA: weeds; B: birch; O: olive tree; CT: cat dander; DG: dog dander.

² β_2 : inhaled β_2 -agonist; CS: inhaled steroids.

Part I: effect of inhaled lysine acetylsalicylate and furosemide on challenge with distilled water mist. Fifteen patients (nos. 1–15 of Table 1) attended four sessions, 2–5 days apart, to determine the effect of four different aerosol treatments, administered through a jet nebulizer (Mod. Flatus, Markos, Brescia, Italy; output 0.18 ml/min). The patients donned noseclips and were connected to the nebulizer for two periods of 10 min through plastic, cylindric mouthpieces. The aerosols were the following: a) placebo lysine acetylsalicylate (lysine 50 mg/ml, amount delivered 90 mg, pH 5.18, osmolarity 706 mOsm/kg), followed by placebo furosemide (the diluent of furosemide); b) placebo lysine acetylsalicylate followed by 10 mg/ml furosemide (Hoechst AG, Frankfurt am Main, Germany; pH 8.8, osmolarity 277 mOsm/kg), amount delivered 18 mg; c) 90 mg/ml lysine acetylsalicylate (Maggioni Winthrop, Milan, Italy; pH 5.16, osmolarity 931 mOsm/kg), amount delivered 162 mg, corresponding to 90 mg of acetylsalicylic acid; d) lysine acetylsalicylate followed by furo-

semide. Immediately before and 15 min after treatment, FEV_1 was measured and the challenge test with water mist was performed as described.

Part II: effect of inhaled indomethacin and furosemide on challenge with distilled water mist. In eight additional patients with similar clinical characteristics (nos. 16–23 of Table 1), the study was conducted according to the same protocol, except that 7.7 mg/ml indomethacin meglumine (pH 7.73, osmolality 366 mOsm/kg), corresponding to 5 mg/ml of indomethacin (Liometacen, Chiesi Farmaceutici, Parma, Italy) was substituted for lysine acetylsalicylate.

Part III: effect of inhaled sodium salicylate and furosemide on challenge with distilled water mist. In seven patients with clinical characteristics similar to those of the previous group (nos. 24–30 of Table 1), the study was conducted according to the same protocol except that 50 mg/ml sodium salicylate (pH 6.91, osmolality 1309 mOsm/kg) was administered instead of lysine acetylsalicylate.

Statistical analysis

The paired and unpaired *t* tests were used for comparison of different treatments, and two-way ANOVA was used for comparison of multiple groups. The significance of the effect of single drugs, as compared with placebo, and of the interaction of two treatments was investigated by ANOVA according to a treatments-by-treatments-by-subject (or repeated-measures:two factors) design (10). A value of *P* below 0.05 was taken to be significant. Unless stated otherwise, data are reported as mean $\pm$ SE.

Results

Part I

All treatments were well tolerated, and no significant changes in FEV_1 were observed after drug inhalation. After treatment with placebo, the bronchial response to fog was similar to that observed in the preliminary test. Pretreatment with either inhaled lysine acetylsalicylate or furosemide caused a substantial reduction in bronchial reactivity, as indicated by the significant decrease in the PD_{15} to water mist. However, the combined treatment with acetylsalicylate and furosemide caused a striking decrease in the reactivity to water mist, as shown in Fig. 1, where the mean PD_{15} values are reported. Treatment with either inhaled lysine acetylsalicylate or furosemide caused PD_{15} increases of 2.8 ± 0.6 and 4.4 ± 0.9 times that of placebo, respectively. After combined treatment with both drugs, however, fog reactivity was increased 16.4 $\pm$ 3.5-fold, which is

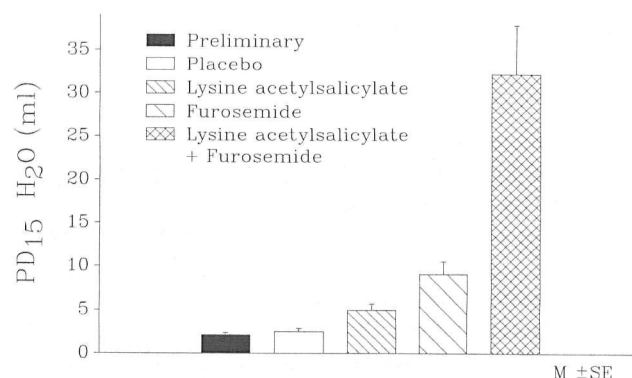


Fig. 1. Mean PD_{15} to H₂O in preliminary test and after treatment with placebo, lysine acetylsalicylate, furosemide, and combination of both drugs ($M \pm SE$).

considerably higher than the sum of the effects of the single drugs. Analysis of variance indicated a significant protective effect by furosemide and lysine acetylsalicylate, as compared with placebo ($P < 0.001$ for each comparison), and a significant interaction between the effects of the two drugs in combination ($P < 0.005$).

Part II

A similar result, although with a less remarkable enhancing effect, was obtained in eight experiments in which indomethacin was used in place of lysine acetylsalicylate, one of which is shown in Fig. 2. The treatment was well tolerated and did not cause changes in base-line FEV_1 values. Mean PD_{15} in this group was 5.0 ± 1.2 ml after placebo, 8.3 ± 1.7 ml after indomethacin ($P < 0.01$, 1.8 ± 0.3 times that of placebo), 10.1 ± 2.0 ml after furosemide ($P < 0.005$, 2.5 ± 0.6 times that of placebo), and 27.6 ± 6.0 ml after indomethacin and furosemide (6.3 ± 1.7 times that of placebo, $P < 0.05$ for the interaction between furosemide and indomethacin).

Part III

In the group of patients who performed the experiment with sodium salicylate instead of lysine acetylsalicylate, neither an antireactive effect nor potentiation on the effect of furosemide was observed. Mean PD_{15} in this group was 4.0 ± 1.3 ml after placebo; 5.6 ± 2.5 ml after salicylate; 19.2 ± 6 ml after furosemide ($P < 0.05$ compared with placebo); and 15.2 ± 8.0 ml after both drugs (not significantly different from furosemide alone).

Discussion

The natriuretic and antivasoconstrictor effect of furosemide is partially inhibited by nonsteroid antiinflammatory drugs through a mechanism which seems

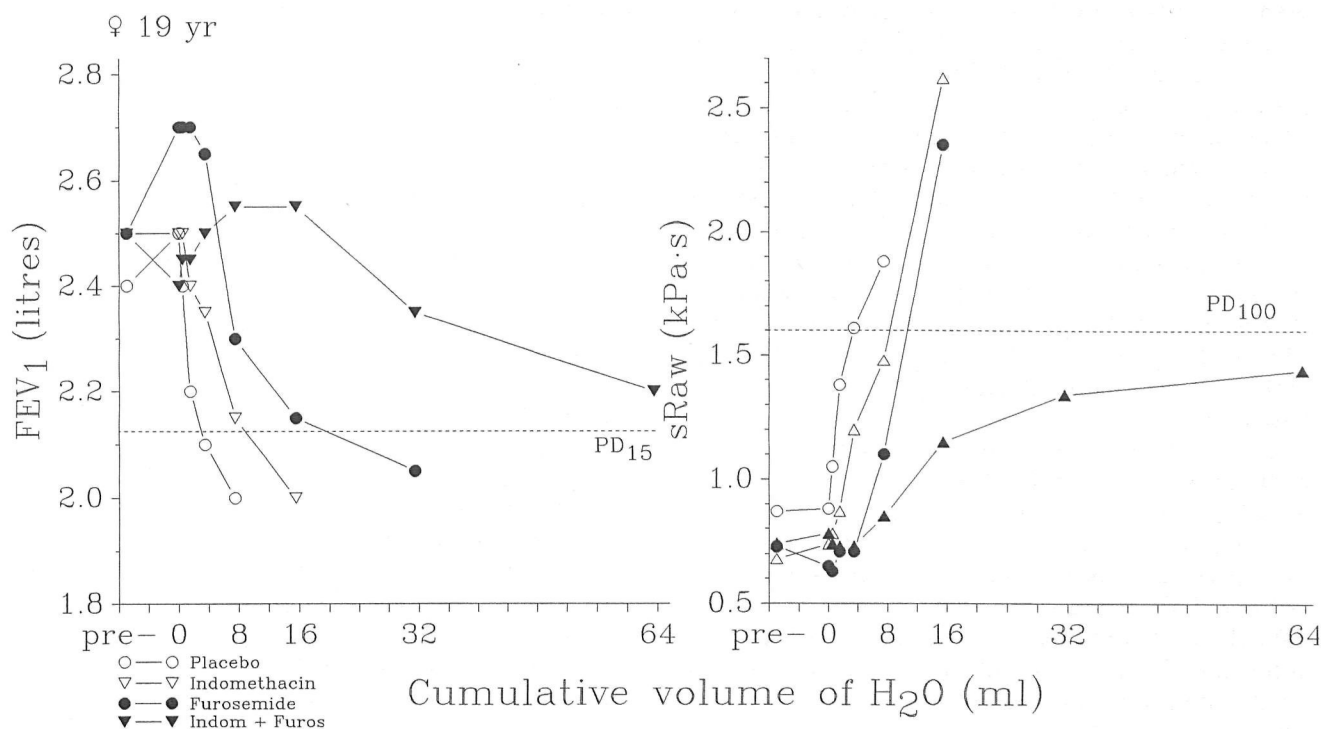


Fig. 2. Mutual potentiation of antireactive effects of indomethacin and furosemide on bronchial response to distilled water mist, measured as changes in FEV₁ (left) and specific airway resistance (right). Case shown is representative of four patients tested with similar results.

primarily to reflect blockade of prostaglandin synthesis (14, 23, 34). The antireactive activity of this diuretic against distilled-water-induced bronchoconstriction was found to be greatly enhanced by inhaled lysine acetylsalicylate and indomethacin, two nonsteroid antiinflammatory drugs which are known to inhibit cyclooxygenase activity through different mechanisms (20). Again, a mechanism involving prostaglandin synthesis, albeit one of potentiation rather than inhibition, seems to be involved, since inhalation of sodium salicylate, a compound which is chemically related to aspirin but without direct anticyclooxygenase effect (20), proved to be ineffective. In the three parts of the study, each using different drugs, the response to ultrasonically nebulized water in the preliminary test was not statistically different from pH- and osmolarity-matched placebo, suggesting that these factors do not participate in the protective or the potentiating effect of these drugs.

After inhalation of distilled water, there is probably a transient decrease in the osmolarity of the periciliary fluid where aerosol particles meet the airway epithelial surface. This change could either activate sensory nerves or induce the release of inflammatory mediators from epithelial and superficial mast cells. There is evidence to suggest that furosemide attenuates the bronchoconstrictor response to some stimuli by a complex mechanism involving the inhibition of both cholinergic and excitatory non-

adrenergic, noncholinergic neurotransmission (16), along with decreased mediator release (2, 18, 27). On the basis of the present data, the hypothesis that the antireactive action of furosemide against distilled-water-induced bronchoconstriction is mediated by increased production of inhibitory prostaglandins, such as PGE₂ (4) and PGF_{2α} (29), must obviously be discarded. However, the cause of the potentiating effect of the two drugs remains unexplained. Inhaled lysine acetylsalicylate and indomethacin may protect against bronchoconstriction by inhibiting the synthesis of bronchoconstrictor prostaglandins, such as PGF_{2α} and TXA₂ (13) released by bronchial epithelium in response to distilled water, or such as PGD₂ released by bronchial mast cells (21). This effect could add to the inhibition of mast cell degranulation and histamine and leukotriene release afforded by furosemide, resulting in a mutually enhancing effect. Alternatively, furosemide might partially counteract the inhibitory activity of nonsteroid antiinflammatory drugs by selectively stimulating the production of antibronchoconstrictor prostaglandins from vascular cells, such as PGI₂ (36), while adding to the repression of bronchoconstrictor eicosanoids by inhibiting their release from epithelial and inflammatory cells (18, 26, 27).

In this connection, it is worth noting that: a) mast cells are more abundant and degranulate more easily in the bronchoalveolar lavage fluid of asthmatic pa-

tients (11, 17); b) PGD_2 and $\text{PGF}_{2\alpha}$ have been found in higher concentrations in asthmatic bronchoalveolar lavage fluid than in that of normal subjects and patients with allergic rhinitis (24); c) plasma levels of 13,14 dihydro-, 15 keto- $\text{PGF}_{2\alpha}$ are very high during asthma attacks (35). Another finding that underscores the role of bronchoconstrictor prostaglandins is the protective effect against water-mist-induced bronchospasm afforded by aspirin but not sodium salicylate, taken either orally or by inhalation (5, 8, 31). However, all the hypotheses relative to the effect of furosemide on different prostaglandins and to their effects on bronchoconstriction remain purely speculative.

The positive results of the present study conflict with those of Vaghi et al. (38) and Pavord et al. (30), who found that a 3-day daily regimen of 100 mg oral indomethacin did not affect, or even decreased, the protective effect of furosemide on exercise-induced asthma. This discrepancy could be ascribed to the different pathophysiologic mechanisms of exercise-induced asthma and bronchospasm induced by distilled water, and to the different involvement of the prostaglandin system in these phenomena. Another explanation might be the different distribution of indomethacin in the respiratory tract for oral administration and inhalation. In fact, it has been shown *in vitro* that indomethacin potentiates the bronchoconstrictor response of the peripheral airways, where one would expect the drug to diffuse after systemic administration, while inhibiting the contractile response of more central bronchi, where one would expect the inhaled drug to become concentrated (19). Finally, as suggested by *in vitro* studies, it is possible that the higher local concentrations obtained after inhalation are more effective in blocking the synthesis of bronchoconstrictor prostaglandins, whereas the lower concentrations attained after oral administration are more effective in blocking broncho-relaxing prostanoids (25) or even stimulating the production of constrictor leukotrienes (37).

Whatever the exact effector mechanism of the potentiation of the antireactive effect of these drugs, treatment with inhaled furosemide and lysine acetylsalicylate is particularly effective in preventing the bronchial obstructive response to a natural stimulus such as water mist in asthma. Whether this protective effect may be clinically useful in the prevention of asthma cannot be addressed in this experimental study; it requires appropriate, long-term clinical studies. From this perspective, it is interesting to speculate that, in addition to this effect, prolonged exposure to powerful antiinflammatory drugs might also help to control bronchial inflammation, which appears to play a fundamental role in the pathogenesis of asthma (15). Indeed, preliminary data suggest that this treatment may be useful for patients with

severe asthma for whom a satisfactory alternative to high doses of steroids is not yet available (7).

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