Effect of inhaled furosemide on bronchial responsiveness to methacholine (I)

distilled water could be reduced by pretreatment in spite of the action on release of mediators.

We examined the effect of inhaled furosemide on bronchial responsiveness to methacholine, a nonspecific bronchoconstrictor, in healthy volunteers. Nineteen subjects underwent a methacholine provocation test. Methacholine was inhaled for two minutes by tidal breathing from a nebulizer (DeVilbiss 646), and spirometry was performed immediately afterward. The agent was given in increasing concentrations until a fall of 20 percent or more in the forced expiratory volume in one second (FEV_1) was noted (i.e., the PC_{20}—the provocative concentration inducing this fall). The measured values were plotted on a semilogarithmic scale, and the concentration of methacholine ($PC_{20} - FEV_1$) producing a 20 percent fall in FEV_1 was calculated. In 11 of the volunteers, the $PC_{20} - FEV_1$ value was less than 20 mg per milliliter. All of these 11 subjects were women; their mean age was 21 years (range, 20 to 22). Within four days they underwent a second methacholine provocation test 10 minutes after inhaling 40 mg of furosemide. Their $PC_{20} - FEV_1$ values before and after the inhalation of furosemide are shown in Figure 1. There was a significant increase in the geometric mean value of $PC_{20} - FEV_1$ ($P<0.002$) after furosemide administration, from 7.76 mg per milliliter (geometric SEM, 1.35) to 17.8 mg per milliliter (geometric SEM, 1.32).

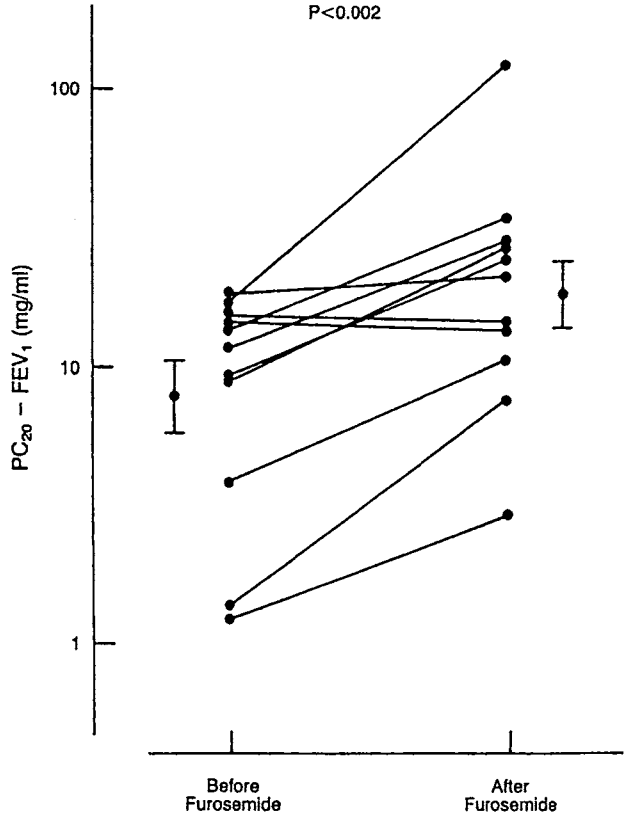

Figure 1. $PC_{20} - FEV_1$ Values for Methacholine in 11 Women, before and after the Inhalation of Furosemide.
I bars denote means ±SEM.

In view of these results, we think that the protective effect of inhaled furosemide against bronchoconstriction that was observed by Bianco et al. may be partially due to the attenuation of bronchial responsiveness by this agent.

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EFFECT OF INHALED FUROSEMIDE ON BRONCHIAL RESPONSIVENESS TO METHACHOLINE

To the Editor: The paper by Bianco et al. (Oct. 19 issue)[1] demonstrated a protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. The authors had previously reported that inhaled furosemide had a protective effect against bronchoconstriction induced by exercise[2] and ultrasonically nebulized distilled water.[3] They supposed that the mechanism of action of furosemide involves the control of the osmotic or ionic environment of epithelial cells, which in turn may affect the activation of mast cells and other inflammatory cells or may influence the responsiveness of sensory epithelial nerves. It was, however, not discussed whether or not inhaled furosemide could influence bronchial responsiveness to bronchoconstrictive agents. If nonspecific bronchial responsiveness is attenuated by inhaled furosemide, the bronchoconstriction induced by allergens, exercise, and

1. Bianco S, Pieroni MG, Refini RM, Rottoli L, Sestini P. Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. N Engl J Med 1989; 321:1069-73.
2. Bianco S, Vaghi A, Robuschi M, Pasargiklian M. Prevention of exercise-induced bronchoconstriction by inhaled frusemide. Lancet 1988; 2:252-5.
3. Robuschi M, Vaghi A, Gambaro G, Spagnotto S, Bianco S. Inhaled furosemide (F) is highly effective in preventing ultrasonically nebulized water (UNH_2O) bronchoconstriction. Am Rev Respir Dis 1988; 137:412. abstract.

The above letter was referred to the authors of the article in question, who offer the following reply:

To the Editor: Ion-transport mechanisms may be involved in many cellular processes, and furosemide-sensitive pathways have been described in a large variety of tissues and cell types.[1] Indeed, the Souhradas have provided experimental evidence that ion-transport mechanisms have a pivotal role in the contractile response of the bronchial smooth muscle to allergens[2] and chemical mediators.[3] The data reported by Fujimura and colleagues on the attenuation of the bronchial response to methacholine after furosemide inhalation are of great potential interest, since they indicate that a furosemide-sensitive mechanism does participate in the control of bronchial tone in humans. Our experience, however, does not support the results of Fujimura et al.

In a randomized, double-blind, placebo-controlled study performed in 10 adults with asthma, we found no effect of inhaled furosemide on methacholine-induced bronchoconstriction.[4] The geometric mean of the PC_{20} for methacholine was 186 mg per milliliter (95 percent confidence interval, 133 to 260) after the inhalation of furosemide (40 mg in 4 ml), and 173 (108 to 176) after placebo. It is not clear whether the difference from the results reported by Fujimura and colleagues is due to the slight difference in the technique used to measure bronchial reactivity or to the selection of healthy subjects rather than patients with asthma. In a similarly conducted study of the effect of furosemide on histamine-induced bronchoconstriction in 20 subjects with asthma,[5] we found only a modest although statistically significant increase in the PC_{20} for histamine, from 113 mg per milliliter (95 percent confidence interval, 83 to 154) after placebo to 166 mg per milliliter (117 to 234) after furosemide. In subsequent studies, we have observed that the protective effect of inhaled furosemide on bronchoconstriction induced by ultrasonically nebulized distilled water is almost completely lost three hours after treatment. Since we observed a protective effect against the late asthmatic reaction, which typically begins about four hours after allergen challenge, it seems unlikely that this effect is due to a direct inhibition of the response to mediators released during the reaction.

Taken together, these results suggest that a direct inhibition of the bronchial response to chemical mediators has only a minor role in the protective effect of furosemide in asthma.

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4. Vaghi A, Robuschi M, Chilaris N, Bianco S. Inhaled furosemide (F) does not attenuate the bronchial response to methacoline (M) in asthmatics. Presented at the 23rd annual SEPCR meeting, Athens, 1988. abstract.
5. Vaghi A, Robuschi M, Berni F, Bianco S. Effect of inhaled furosemide (F) on bronchial response to histamine (H) in asthmatics. Presented at the 23rd annual SEPCR meeting, Athens, 1988. abstract.