

Editorials

Exercise-induced asthma: Is there still a case for histamine?

Key words: Exercise-induced asthma, leukotrienes, osmolarity, water loss

In this issue of The JACI, Barbro Dahlén et al¹ present the first report on the effects of the leukotriene antagonist zafirlukast and the histamine antagonist loratadine, alone and in combination, on exercise-induced asthma (EIA) in asthmatic adults. The drugs were given for 1 week in doses of 80 mg twice a day for zafirlukast and 10 mg twice a day for loratadine. A similar regimen had previously provided a greater protection against responses to inhaled allergen through use of the combination. The study was carried out with a double-blind, double-dummy, randomized crossover design. The results clearly show that zafirlukast, but not loratadine, modified both the reduction in FEV₁ (ie, percent fall in FEV₁) and its recovery to baseline. No extra benefit was demonstrated from the combination of the 2 drugs. A benefit from loratadine, both alone and in combination, might have been expected, given the long-held impression that histamine is a mediator of EIA. This impression has taken hold as a result of the finding by many investigators of a small but significant effect of histamine antagonists on EIA when given orally, intramuscularly, or by inhalation. What conclusions can be drawn from this study about the treatment of EIA and the possible cause of the narrowing of the airways of asthmatic individuals in response to exercise?

In the 16 subjects studied, the asthma was mostly mild; only 4 of the subjects were treated with inhaled steroids. The EIA, although repeatable, was mild in most subjects, only 3 having a fall in FEV₁ greater than 30%. The degree of EIA achieved in this study could relate either to the mild nature of the asthma or to the intensity and duration of the exercise stimulus. Whatever the reason for the mild EIA, we can conclude that leukotrienes contribute to the airway narrowing that follows exercise. These data are all the more convincing because the response to exercise was followed over 60 minutes and showed a more rapid recovery of FEV₁ to baseline in the

Abbreviation used

EIA: Exercise-induced asthma

presence of zafirlukast. This confirms that leukotrienes are the most important mediator for sustaining the asthmatic response to exercise. The results also suggest that leukotrienes might contribute to the maximum percent fall to exercise, a role previously attributed to histamine alone.² The findings presented here, together with those pertaining to montelukast,³ must now surely convince the remaining skeptics that inflammatory mediators—in this case, leukotrienes—play an important role in EIA.

Because leukotriene antagonists provide incomplete (50% to 60%) protection from the effects of exercise, other mediators are also likely to be involved in EIA. Histamine, a preformed mediator in the granules of mast cells, has long been thought an important mediator in EIA. This study clearly does not support such thinking. Other mediators likely to be involved in EIA are prostaglandins. Studies of urinary excretion of mediators after exercise have reported increases in leukotrienes C₄ and prostaglandin D₂ metabolites, but not increases in histamine, after EIA.⁴ Studies of the effects of cyclooxygenase inhibitors² on EIA also support a role for prostaglandins. If we accept that leukotrienes are important mediators of EIA, what is the stimulus for their release and what is the cellular source?

The stimulus for EIA is the loss of water from the airways' surface in the process of humidifying large volumes of air in a relatively short period of time. The thermal (cooling) and osmotic consequences of respiratory water loss are the important determinants of EIA.⁵ In this study, air at ambient room temperature, not at subzero temperatures, was inspired during exercise; accordingly, the osmotic effects of dehydration are likely to be more important than the cooling effects. Provided that the exercise is sufficiently intense to raise the rate of water loss above the normal rate of return, a transient increase in osmolarity will occur in the airways. Initially, the osmotic changes will occur and be greatest in the airway surface liquid as the water evaporates to humidify the air. As the surface fluid is replaced by water from the epithelial cells and nonresident cells in the airways, these cells will suffer volume loss. As the water lost from the epithelial cells is replaced across the basement membrane, a small osmotic gradient is predicted to occur below the basement membrane.⁶ It is the regulatory volume increase following cell shrinkage that is thought to be the stimulus for the release of mediators, because the intracellular events that

From the Department of Respiratory Medicine, Royal Prince Alfred Hospital. Received for publication February 10, 2002; revised February 12, 2002; accepted for publication February 12, 2002.

Reprint requests: S. D. Anderson, PhD, DSc, Department of Respiratory Medicine, E11S, Royal Prince Alfred Hospital, Missenden Road, Camperdown NSW 2050, Australia.

J Allergy Clin Immunol 2002;109:771-3.

© 2002 Mosby, Inc. All right reserved.

0091-6749/2002 \$35.00 + 0 1/39/123644

doi:10.1067/mai.2002.123644

accompany it are similar to those required for release of mediators.⁷ When airway osmolarity is increased by the inhalation of mannitol, the findings are similar to what is seen with exercise, in that leukotrienes and prostaglandin D₂, but not histamine, are increased in urine after challenge.⁸ As with exercise, the airway response to mannitol is sustained by leukotrienes.⁹

Both mast cells and eosinophils are potential sources of bronchoconstricting mediators. Mast cells are known to release histamine, leukotrienes, and prostaglandin D₂, and eosinophils produce leukotrienes. Both of these cell types are commonly found in the airways of asthmatic individuals, but absolute numbers and percentages of eosinophils are usually greater than absolute numbers and percentages of mast cells. Eosinophils are found superficially in the airways and are easily harvested in sputum.¹⁰ Thus they are likely to be among the first cells to lose their water in response to an increase in osmolarity. Mast cells are less common in sputum¹⁰ and more likely to be found between epithelial cells or below the basement membrane.

It has long been appreciated that human lung mast cells release histamine *in vitro* in response to increasing osmolarity, and the released is enhanced in the presence of anti-IgE.¹¹ Recently, it was reported that eosinophils in both asthmatic and control subjects released leukotrienes in response to a 10-minute exposure to hyperosmolar mannitol.¹² The concept that eosinophils might be an important source of leukotrienes in EIA is consistent with the finding that among young asthmatic adults, those with EIA have higher percentages of eosinophils than those without EIA.¹³ Sensitivity of the airways to different mediators might also be important. For example, there is a marked difference in potency between leukotrienes and histamine, such that only one thousandth of the concentration of leukotriene is required to cause the same degree of airway narrowing as histamine.¹⁴ This difference in potency could account for histamine's not being a prerequisite for the airways to narrow in response to exercise.

Given that there are many reports demonstrating a small (30% to 50% protection) but significant effect of histamine antagonists in EIA and that 1 report on loratadine appeared early this year,¹⁵ the failure to find any protective effect of the histamine antagonist in the study by Dahlén et al is surprising. The data on children who received a single daily dose of 10 mg of loratadine for 3 days¹⁵ would lead one to conclude that loratadine gives significant, though incomplete, protection from EIA. It is important to consider what conditions—if any—in the study by Dahlén et al could potentially contribute to the negative finding.

Perhaps the mild nature of the asthma and the short duration of the exercise stimulus could account for their negative finding with loratadine. First, it is likely that both individuals with mild asthma and individuals treated with inhaled steroids will have fewer mast cells in the airway lumen.^{10,16} Because mast cells occur below the surface,¹⁶ they will not be exposed to the large changes in osmolarity that occur on the surface of the airways. In this study, in which an exercise time of 5 minutes was used, it is pos-

sible that the osmotic threshold to cause release of the mast cell histamine was not achieved. Had the increased rate of water loss been sustained for a longer time, the osmotic gradient might have been sufficient to achieve release of histamine, resulting in more severe EIA. Eggleston et al¹⁷ demonstrated histamine release in response to osmolarity that was maximal at 640 mOsm when NaCl was the stimulus. It is possible that this osmolarity was simply not achieved. The studies that have shown benefits of histamine antagonists used 8 minutes of exercise in most cases, so the osmotic threshold for mast cell release of histamine might have been achieved.

It is well known that the maximal airway response to exercise under room air conditions is likely to be achieved when exercise is performed for a period greater than 5 minutes—the time used in this study. An assessment of the dehydrating stimulus cannot be made for this study, inasmuch as heart rate, rather than ventilation, was used as the index of intensity of exercise. In studies of EIA it is preferable to measure ventilation, because it is the best indirect index for rate of respiratory water loss.^{18,19} Breathing dry air at 60 L/min results in a loss of water of approximately 1.8 mL/min, of which 30% would be provided from below the pharynx.⁵

The authors have highlighted the importance of their choice, loratadine, because it is a potent and specific antagonist of histamine. The authors remind us that terfenadine has the potential to prevent the release from cells of a wide variety of substances, including leukotrienes.²⁰ Given that most of the studies showing a positive beneficial effect of a histamine antagonist in EIA used terfenadine, perhaps we need to ask whether the previous findings simply reflect the ability of terfenadine to inhibit release of leukotrienes. Although there is evidence that loratadine can also prevent the release of leukotrienes,²¹ it is unlikely to have done so in this study, because the airway response did not differ from that obtained with the placebo.

EIA is important because the physiologic changes that accompany it make exercise unattractive. The prevention or control of EIA should be part of every management plan, inasmuch as it is the most common cause of attacks of asthma in children and can affect full participation in sports activities. Exercise also plays an important role in maintaining fitness, and many adults participate in competitive sports. EIA appears to be a manifestation of inflammation of the airways, because it responds to treatment with inhaled steroids. This study demonstrates that in subjects with stable asthma and repeatable EIA, exercise is a suitable model for evaluating the effects of drugs that prevent the release of mediators or block their action. Comparison of the effects of such drugs for different durations of exercise of the same intensity might have revealed more information with respect to this study. The attenuation of EIA by the leukotriene antagonist was clear in most of the subjects. It is of interest that of the 5 subjects in whom there was not a clear protective effect of zafirlukast, 4 had a substantial reduction when the zafirlukast was taken in combination with the loratadine.

Although there is still debate about leukotriene antagonists in the treatment of asthma, they should now be accepted as valuable drugs to modify attacks of asthma, such as those provoked by exercise, allergen, and cold air. Furthermore, tolerance to the protective effects does not occur, and the duration of action of leukotriene antagonists is sustained over time. There appears to be no role for the use of a histamine antagonist in individuals with mild asthma performing exercise for 5 minutes. The negative finding here supports many of the studies that have failed to identify histamine directly after exercise. Other studies, however, have shown a beneficial effect of loratadine against EIA¹⁵ when EIA was more severe. Given this information, it might be suggested that before we abandon the concept of histamine being a mediator of EIA, we should be assured that the dehydrating stimulus provided by exercise is sufficient to cause mast cell release of histamine. The important finding in this study is that even people with mild asthma who have good baseline lung function but are not taking inhaled steroids can have EIA caused by a proinflammatory mediator, and steps should be taken to prevent this.

*S. D. Anderson, PhD, DSc
J. D. Brannan, PhD
Camperdown, Australia*

REFERENCES

- Dahlén B, Roquet A, Inman MD, Karlsson Ö, Naya I, Anstrén G, et al. Influence of zafirlukast and loratadine on exercise-induced bronchoconstriction. *J Allergy Clin Immunol* 2002;109:789-93.
- Finnerty JP, Holgate ST. Evidence for the roles of histamine and prostaglandins as mediators in exercise-induced asthma: the inhibitory effect of terfenadine and flurbiprofen alone and in combination. *Eur Respir J* 1990;3:540-7.
- Leff JA, Busse WW, Pearlman D, Bronsky EA, Kemp J, Hendeles L, et al. Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. *N Engl J Med* 1998;339:147-52.
- O'Sullivan S, Roquet A, Dahlén B, Larsen F, Eklund A, Kumlin M, et al. Evidence for mast cell activation during exercise-induced bronchoconstriction. *Eur Respir J* 1998;12:345-50.
- Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is . . . *J Allergy Clin Immunol* 2000;106:453-9.
- Anderson SD, Daviskas E. The airway microvasculature and exercise-induced asthma. *Thorax* 1992;47:748-52.
- Anderson SD, Rodwell LT, Daviskas E, Spring JF, du Toit J. The protective effect of nedocromil sodium and other drugs on airway narrowing provoked by hyperosmolar stimuli: a role for the airway epithelium. *J Allergy Clin Immunol* 1996;98(5 Part 2):S124-S134.
- Brannan JD, Gulliksson M, Kumlin M, Anderson SD, Dahlén S-E. Inhalation of mannitol, used as a model for exercise-induced bronchoconstriction (EIB), causes release of leukotrienes and a mast cell marker in asthmatic subjects. *Eur Respir J* 2001;18(Suppl 13):102S.
- Brannan JD, Anderson SD, Gomes K, King GG, Chan H-K, Seale JP. Fexofenadine decreases sensitivity to and montelukast improves recovery from inhaled mannitol. *Am J Respir Crit Care Med* 2001;163:1420-5.
- Gibson PG, Saltos N, Fakes K. Acute anti-inflammatory effects of inhaled budesonide in asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2001;163:32-6.
- Eggleston PA, Kagey-Sobotka A, Schleimer RP, Lichtenstein LM. Interaction between hyperosmolar and IgE-mediated histamine release from basophils and mast cells. *Am Rev Respir Dis* 1984;130:86-91.
- Moloney ED, Burke CM, Poulter LW, O'Sullivan S. Inflammatory mediator release as a consequence of hyperosmolar stimulation of the eosinophil. *Eur Respir J* 2001;18(Suppl 33):79S.
- Kivity S, Argaman A, Onn A, Schwartz Y, Man A, Greif J, et al. Eosinophil influx into the airways in patients with exercise-induced asthma. *Respir Med* 2000;94:1200-5.
- Barnes NC, Piper PJ, Costello JF. Comparative effects of inhaled leukotriene C₄, leukotriene D₄, and histamine in normal human subjects. *Thorax* 1984;39:500-4.
- Baki A, Orhan F. The effect of loratadine in exercise-induced asthma. *Arch Dis Child* 2002;86:38-9.
- Jeffery PK, Godfrey RW, Adelroth E, Nelson F, Rogers A, Johansson S-A. Effect of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma: a quantitative light and electron study. *Am Rev Respir Dis* 1992;145:890-9.
- Eggleston PA, Kagey-Sobotka A, Lichtenstein LM. A comparison of the osmotic activation of basophils and human lung mast cells. *Am Rev Respir Dis* 1987;135:1043-8.
- Anderson SD, Schoeffel RE, Follet R, Perry CP, Daviskas E, Kendall M. Sensitivity to heat and water loss at rest and during exercise in asthmatic patients. *Eur J Respir Dis* 1982;63:459-71.
- Anderson SD, Lambert S, Brannan JD, Wood RJ, Koskela H, Morton AR, et al. Laboratory protocol for exercise asthma to evaluate salbutamol given by two devices. *Med Sci Sports Exerc* 2001;33:893-900.
- Crampette L, Mainprice B, Bloom M, Bousquet J, Campbell AM. Inhibition of mediator and cytokine release from dispersed nasal polyp cells by terfenadine. *Allergy* 1996;51:346-9.
- Bousquet J, Lebel B, Chanal I, Morel A, Michel F-B. Antiallergic activity of H₁-receptor antagonists assessed by nasal challenge. *J Allergy Clin Immunol* 1988;82:881-7.