Adenosine Airways Responsiveness
What Does It Mean?

The role of adenosine in mediating airway hyperreactivity is an interesting and emerging area of study. Subjects with asthma were noted to have airway hyperresponsiveness to inhaled adenosine in 1983.1 This observation led to a series of clinical and basic investigations that have resulted in our current paradigm for the role of adenosine and adenosine receptors in airways allergic inflammation. This topic has been recently reviewed in detail by Meade et al2 and Polosa et al.3

Bronchial hyperreactivity to adenosine may be found in atopic and nonatopic asthmatic patients,1 patients with COPD,4 and patients with allergic rhinitis without asthma.5 In general, patients with COPD tend to be less responsive than asthmatic patients (but they are still responsive compared to healthy individuals).4 Adenosine hyperreactivity does not correlate with methacholine reactivity in these various populations,4 suggesting different mechanisms and clinical significance.

It has been shown that adenosine hyperreactivity in asthmatic patients is more closely associated with sputum eosinophilia compared to methacholine hyperreactivity and is less closely associated with baseline FEV1.6 Bronchial constriction in response to adenosine in patients with COPD is also closely linked to airway eosinophilia.7 There are differences, however, in the response to adenosine between patients with asthma and those with COPD in that adenosine airways hyperreactivity improves after effective treatment of asthma, whereas there seems to be no significant change in the responsiveness of COPD patients to adenosine following effective treatment (ie, the overall sensitivity follows that of methacholine).5 This has led to the assumption that adenosine hyperreactivity indicates an allergic inflammatory state.

In contrast to methacholine and other agents that act directly on airway smooth muscle (eg, cold air, hyperventilation, exercise, and kinins), adenosine is believed to act predominantly in an indirect manner by way of the activation of mast cells with the subsequent release of mediators or by stimulating the release of neurotransmitters. These mediators act on airways smooth muscle and other cells to cause bronchospasm. As with most things, this probably represents an oversimplification.

The identification of the adenosine receptor subtypes and a better understanding of their activity with different cell populations have helped us to understand the action of adenosine in the lung.2,3 There appear to be four separate adenosine receptors in lung tissue.2,3 The classic adenosine receptor, A1, is found primarily in smooth muscle and nerve tissue, and it causes a reduction in cyclic adenosine monophosphate (cAMP), leading to direct or neurogenic mediated bronchospasm. The A2a receptor, which is found in the mast cell and in the bronchial epithelium, causes an increase in cAMP, thereby inhibiting the release of the mediators of inflammation from mast cells. The A2b receptor, which is closely related to the A2a receptor, is also found in the bronchial epithelium and mast cells. This receptor utilizes different signal-transducing systems than does the A2a receptor. As a result, the A2b receptor stimulates the release of mediators from the mast cell, thereby increasing bronchial reactivity. Among the mast cell mediators that have been shown to be released by the A2b adenosine receptor are tryptase, histamine, interleukins, lipooxygenase products, and other cytokines. The A2a receptor activity predominates at low adenosine concentrations, while the A2b effect predominates at high adenosine concentrations. Finally, the A3 receptor, which is less well-characterized but is known to be present in lung tissue, acts very much like the A1 receptor, reducing cAMP levels. The net result is that the stimulation of the A1 receptor, the A2b receptor, or the A3 receptor leads to bronchoconstriction by both direct and indirect methods. The stimulation of the A2a receptor, on the other hand, would lead to a bronchodilation by inhibiting the mast cell release of mediators of the immune response.

Adenosine is released in the lung in response to both specific and nonspecific mechanisms. Adenosine is released from mast cells as a result of IgE
activation. Adenosine that is released in this way has an amplifier effect on the mast cell via the A2b receptor and has a direct effect on target organs in allergic inflammation. Nonspecific tissue damage also results in the hydrolysis of adenosine nucleotides and the release of free adenosine. No matter how it is released, adenosine is rapidly metabolized in the lung. It can, however, accumulate to very high levels in the lung tissue of asthma patients. Therefore, adenosine can be increased in the airways by allergic and nonallergic airway injury and, acting through adenosine receptors, has the potential to be an important modulator of both nonspecific and IgE-mediated inflammation and bronchospasm in the airways.

How do we reconcile the clinical observations with the biology of adenosine release and its subsequent effects on airway reactivity in different disease states? The relationship with asthma and allergic airway inflammation is straightforward. The relationship with COPD and other airway diseases is less clear. The release of adenosine in response to the nonspecific trauma of cigarette smoking may explain the hyperresponsiveness to adenosine in patients with COPD. On the other hand, mast cells have also been demonstrated in smokers and in patients with chronic bronchitis. The exact role of adenosine bronchial responsiveness in human disease, therefore, remains an area of speculation and investigation.

The article by Prieto et al in this issue of CHEST (see page 993) illustrates this issue. They found an incremental increase in adenosine bronchial reactivity when the nonspecific stimulus of airways inflammation/damage (ie, smoking) was superimposed on allergic airways inflammation that was associated with allergic rhinitis in the absence of overt airways disease. The fact that these subjects did not have asthma must be accepted at face value. That patients with allergic rhinitis would demonstrate bronchial hyperreactivity to adenosine (or to methacholine for that matter) is not surprising. Likewise, it is expected that smoking might increase bronchial reactivity to either adenosine or methacholine. The fact that the provocative concentration of a substance causing a 20% fall in FEV1 (PC20) for both adenosine and methacholine was lower in patients with allergic rhinitis who also smoked suggests that nonmast cell-mediated adenosine mechanisms may be important for this incremental hyperresponsiveness in smokers.

Finally, what is the clinical significance of tests of adenosine responsiveness? Bronchial hyperactivity in general is not specific for asthma and neither is adenosine hyperreactivity. Like methacholine hypersensitivity, adenosine hyperreactivity may be found in smokers with COPD and in patients with other diseases of the airways. The current model for the action of adenosine and airways hyperresponsiveness suggests that it may correlate better than direct stimuli (ie, histamine and methacholine) with airway inflammation, and it has been suggested that adenosine hyperresponsiveness may be a way to discriminate between asthma and COPD. However, the observations of Oosterhoff et al make this problematic. The distribution and varied effects of adenosine receptors and the specific and nonspecific sources of adenosine in the airways provide a rationale for adenosine responsiveness being a marker for airway mucosal injury but make it difficult to know how much of the effect is specific for allergic inflammation vs other mechanisms. It is clear that patients with atopic asthma respond to much lower doses of adenosine than do patients with COPD, smokers, or healthy individuals. The problem is that clear dose-response criteria with standardized, population-based cutoff points for the PC20 of adenosine are not available. This suggests that, while the adenosine challenge may have an important role in research that is aimed at understanding disease mechanisms and treatment response, its role in the clinical arena is very limited.

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Not the Perfect Study, but Helpful Wisdom for Treating Asthma Patients With Gastroesophageal Reflux Disease

Several years ago for this same journal, I wrote an editorial entitled “Asthma and Gastroesophageal Reflux Disease: The Truth Is Difficult To Define.” In that editorial and another review article, I outlined the major limitations in current studies on this subject and lamented our progress over the last 20 years in resolving this complex interaction. Over the last 3 years in the adult literature, it is disappointing that only one study has addressed this subject using a placebo-controlled crossover design and omeprazole, 40 mg for 4 weeks. The sample size was only five patients, and they found no improvement in pulmonary function tests results. On the other hand, this issue of CHEST (see page 1008) has an excellent study by Khoshoo and colleagues, which overcomes many of the methodological limitations of other studies and defines better the role of gastroesophageal reflux disease (GERD) treatment with proton pump inhibitors (PPIs) in children with difficult-to-control asthma. Impressively, this study was not performed in an academic medical center but rather by dedicated physicians in private practice who are interested in asthma and GERD, and who worked together to define an effective clinical algorithm for approaching all of their difficult-to-manage asthma patients. Let us look at the relevance of this important study to the methodological limitations of many previous studies relating asthma and GERD.

Lack of Attempt To Optimize Conventional Asthma Therapy

These authors do a commendable job in defining their asthma population and the failure of those patients to respond to optimal asthma therapy. Children with the following criteria were included in the study: (1) no family history of asthma; (2) no personal or family history of atopic disease; (3) parents who did not smoke; and (4) no history of respiratory syncytial virus bronchitis. All children had been treated for their asthma for > 2 years, and their conditions were difficult to manage, with at least three emergency department visits or hospital admissions in the last year, despite aggressive management of their asthma with a combination of short-acting and long-acting bronchodilators, leukotriene antagonists, and inhaled/oral corticosteroids. Despite this difficult group of patients, all of those individuals with abnormal 24-h pH studies (27 subjects) had at least a 50% reduction in their need for medications after 1 year of follow-up, while receiving lansoprazole, 30 mg, in the morning and a prokinetic drug. In the vast majority of patients, therapy with long-acting bronchodilators, leukotriene antagonists, and inhaled/oral steroids could be discontinued because the patient’s asthma could be easily controlled with as-needed puffs of short-acting bronchodilators.

Small Number of Patients

Over a 2.5-year period, 482 patients with asthma of > 2 years’ duration were screened. A total of 46 consecutive patients (10%) with difficult-to-control asthma were referred to a pediatric gastroenterologist to rule out GERD and fulfilled all the entrance criteria for study enrollment. None of the patients were lost to follow-up, and all were treated by a team of experienced pediatric gastroenterologists and asthma specialists. Symptoms were assessed by personal diaries and the use of asthma drugs, the doses of which were adjusted based on National Institutes of Health guidelines and symptom responses that were observed for > 1 year. The number of patients studied was very respectable, exceeding the number in all but two previous studies reported in the medical/surgical literature on this subject. Furthermore, these authors give us a realistic idea of the percentage of children who clinically require this approach, which is much more relevant than the reported GERD prevalence rates of 33 to 90% of asthmatic patients from various study populations.