

REFERENCES

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;108:S147-334.
2. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol* 2003;111:1171-83.
3. Stephens L, Proud D, Togias A. Nasal cold, dry air (CDA) challenge results in stronger nasal and pulmonary responses in asthmatics compared to patients with rhinitis. *J Allergy Clin Immunol* 1996;97:A315.
4. Braunstahl GJ, Kleinjan A, Overbeek SE, Prins JB, Hoogsteden HC, Fokkens WJ. Segmental bronchial provocation induces nasal inflammation in allergic rhinitis patients. *Am J Respir Crit Care Med* 2000;161:2051-7.

Available online November 12, 2004.
doi:10.1016/j.jaci.2004.09.035

Dipyridamole (Persantin)-induced asthma during thallium stress testing

To the Editor:

Coronary artery disease and bronchial asthma commonly coexist in adults. The status of coronary myocardial perfusion is commonly evaluated with the thallium stress test (TST). A TST is performed during exercise or after injection of a coronary vasodilator when patients are unable to perform exercise. The need for a nonexercise or resting TST may be particularly common in patients with asthma whose exercise capacity is limited; however, it may present additional hazards to patients with asthma. The resting TST commonly includes a preceding intravenous infusion of dipyridamole (Persantin, Sicor Pharmaceuticals, Irvine, Calif), a purine nucleoside that blocks the reuptake of extracellular adenosine. The resultant transient increase of serum levels of adenosine causes coronary vasodilation, increasing the sensitivity of the TST. Adenosine can cause significant bronchoconstriction in patients with bronchial hyperresponsiveness. We report a case of a stable patient with asthma who developed sudden bronchospasm immediately after receiving intravenous dipyridamole during an elective TST. Our objective is to alert physicians to the possible risks involved when their patients with asthma undergo a resting dipyridamole TST.

S.K. is a 69-year-old nonsmoking woman with a 30-year history of cat allergy and mild persistent asthma. Her asthma has been well controlled with medications and cat avoidance. Because of atypical chest discomfort, she was referred to a cardiologist, who scheduled her for a TST. Three hours before the TST, she took her only medications: inhaled salmeterol and 88 μ g fluticasone. Within minutes of the intravenous dipyridamole injection, the patient had coughing, audible wheezing, and dyspnea typical of previous asthma. Oxygen saturation on room air was 89%. The cardiologist immediately infused 150 mg aminophylline intravenously. The pulmonary symptoms and hypoxemia resolved within 5 minutes before albuterol nebulization was needed. The stress test was completed and was normal.

The bronchospasm seen in patients undergoing the TST, although not commonly known, has been described in occasional reports. Ranhoskey and Rawson¹ reported 6 (0.15%) cases of acute asthma after intravenous dipyridamole in a retrospective multicenter review of 3911

unselected adults undergoing TST. Four of the 6 reactors were known to be patients with asthma. All 6 bronchospastic reactions were reversed with intravenous aminophylline. In addition, 19% of the patients in the same study population complained of dyspnea. It is unclear how many of them were actually experiencing bronchospasm. Shaffer et al² reported an acute increase in observed wheezing in 39% of 72 adults with asthma and/or COPD after intravenous dipyridamole despite pretreatment with albuterol. Thurnheer et al³ documented reductions in FEV₁ greater than 15% with spirometry in 9 of 20 patients with advanced COPD after a dipyridamole TST. We are not aware of pulmonary function studies to investigate whether there is reduction in expiratory airflow after intravenous dipyridamole infusion in patients with asthma.

Because dipyridamole injection results in increased extracellular levels of endogenous adenosine,⁴ we postulate that the bronchospasm in our patient after intravenous dipyridamole injection was induced by increased *in vivo* levels of extracellular adenosine. Most studies of adenosine effects in asthma use an inhalational model. Adenosine appears to induce bronchoconstriction in patients with asthma indirectly by the synthesis and release of autacoids from airway mast cells.^{5,6} Pretreatment with 10 mg montelukast for 2 days or 1000 μ g fluticasone propionate inhaled 2 hours before adenosine inhalational challenge provided significant protection against adenosine-induced bronchoconstriction.^{6,7}

The role of an increased concentration of serum adenosine as an *in vivo* cause of clinical bronchospasm is not well defined. The rapid intravenous infusion of adenosine to convert supraventricular tachyarrhythmias has been reported to cause bronchospasm when administered to patients with asthma. The package insert for a commercial adenosine product warns against using intravenous adenosine in patients with asthma.⁸ Intravenous adenosine infusion has been substituted for the intravenous dipyridamole injection on occasion in resting TST procedures. Mild airway obstruction, documented by pulmonary function tests, was reported in a selected group of 94 patients with COPD receiving a drip of intravenous adenosine before the TST.⁹ The airway obstruction occurred in these patients despite pretreatment with inhaled albuterol and persisted at least 15 minutes after adenosine was stopped. The bronchospasm occurring after intravenous dipyridamole can be reversed rapidly by treatment with intravenous aminophylline. Because methylxanthines competitively antagonize the physiological effects of extracellular adenosine through their interaction with specific cell surface purinoreceptors,⁴ this beneficial effect of aminophylline provides indirect evidence that dipyridamole-induced bronchospasm is adenosine-mediated.

Intravenous dipyridamole injection in the TST is considered relatively safe in the evaluation of coronary artery disease.¹ Awareness of the risk of bronchospasm in those with obstructive airways disease has resulted in most cardiologists having parenteral aminophylline available when performing a TST. Clinicians who do not perform TSTs may not be as knowledgeable about the risk of broncho-

spasm after dipyridamole or adenosine. Many adult patients with asthma will need cardiac stress testing in the future. Asthma care specialists as well as patients with obstructive airways disorders should be aware of the risk of acute bronchospasm associated when dipyridamole or even adenosine is to be infused in a resting TST. In such cases, consideration of an alternative coronary vasodilator dobutamine³ or preprocedure prophylactic treatment with leukotriene inhibitors or inhaled steroids should be considered. Pretreatment with β -agonist inhalers has apparently been insufficient in preventing dipyridamole-induced or adenosine-induced bronchospasm.^{2,3,9} Thus, the efficacy of β -agonist therapy to reverse such bronchospasm is unclear. Aminophylline should therefore be a first-line therapy in reversing resting TST-related bronchospasm.

Frederick Cogen, MD^a

Burton Zweiman, MD^b

^aRobert Wood Johnson School of Medicine
Camden, NJ

1650 Huntingdon Pike, #101
Meadowbrook, PA 19046

^bUniversity of Pennsylvania
Philadelphia, Pa

Disclosure of potential conflict of interest: Burton Zweiman has no conflict of interest to declare. Frederick Cogen has no conflict of interest to declare.

REFERENCES

1. Ranhosky A, Rawson J. The safety of intravenous dipyridamole thallium myocardial perfusion imaging. *Circulation* 1990;81:1205-9.
2. Shaffer J, Simbartl L, Render ML, Snow E, Chaney C, Nishiyama H, et al. Patients with stable chronic obstructive pulmonary disease can safely undergo dipyridamole thallium-201 imaging. *Am Heart J* 1998;136:307-13.
3. Thumheer R, Laube I, Kaufmann PA, Stumpe KD, Stammberger U, Bloch KE, et al. Practicability and safety of dipyridamole cardiac imaging in patients with severe chronic obstructive pulmonary disease. *Eur J Nucl Med* 1999;26:812-7.
4. Sollevi A, Ostergren J, Fagrell B, Hjemdahl P. Theophylline antagonizes cardiovascular responses to dipyridamole in man without affecting increases in plasma adenosine. *Acta Physiol Scand* 1984;121:165-71.
5. Rorke S, Holgate ST. Targeting adenosine receptors: novel therapeutic targets in asthma and COPD. *Am J Respir Med* 2002;1:99-105.
6. Rorke S, Jennison S, Jeffs JA, Sampson AP, Arshad H, Holgate ST. Role of cysteinyl leukotriene in adenosine 5'-monophosphate induced bronchoconstriction in asthma. *Thorax* 2002;57:323-7.
7. Ketchell RI, Jensen MW, Lumley P, Wright AM, Allenby MI, O'Connor BJ. Rapid effect of inhaled fluticasone propionate on airway responsiveness to adenosine 5-monophosphate in mild asthma. *J Allergy Clin Immunol* 2002;110:603-6.
8. Adenocard (adenosine injection). Package insert. Deerfield (FL): Fujisawa Corp. 2001.
9. Johnston DL, Scanlon PD, Hodge DO, Glynn RB, Hung JCY, Gibbons RJ. Pulmonary function monitoring during adenosine myocardial perfusion scintigraphy in patients with chronic obstructive pulmonary disease. *Mayo Clin Proc* 1999;74:339-46.

doi:10.1016/j.jaci.2004.09.041