CASE REPORTS

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Intraoperative Bronchospasm Caused by Adenosine

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ADENOSINE is an endogenous nucleoside, which exhibits a variety of pharmacologic effects, including potent systemic and coronary vasodilation,[1,2] attenuation of norepinephrine release,[3] inhibition of neutrophil-mediated injury to endothelial cells,[4] and depressant effects on cardiac impulse generation, conduction, and contractility.[5] Clinically, adenosine has been used successfully as a primary or adjuvant therapy for deliberate hypotension[1,6,7] and is presently available as an alternative therapy to verapamil for the treatment of paroxysmal supraventricular tachycardia and tachycardia associated with Wolf-Parkinson-White syndrome.[9–11]

The incidence of adverse reactions following the administration of adenosine is rare but includes new arrhythmias, such as premature atrial or ventricular contractions, sinus bradycardia or tachycardia, varying degrees of atrioventricular block, and asystole.[5,8] In addition to arrhythmias, other adverse reactions to adenosine that have been described are facial flushing, headache, chest pressure, nausea, and shortness of breath. Inhaled adenosine has been reported to cause bronchoconstriction in asthmatics, although the mechanism of this complication is unknown and is probably multifactorial.[12–14] The following case study describes the first report of an intraoperative episode of bronchospasm caused by intravenous adenosine.

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Case Report

A 57-yr-old male was scheduled for radio-frequency ablation for treatment of Wolf-Parkinson-White syndrome. He had experienced an increasing frequency of palpitations and tachycardia with occasional chest pain over the 2 yr before admission. Cardiac catheterization demonstrated a normal coronary anatomy and a left ventricular ejection fraction of 0.75. Electrophysiological studies revealed a left-sided accessory pathway (Type-B Wolf-Parkinson-White syndrome) with non-life threatening atrial flutter and noninducible atrial fibrillation. The patient was admitted for elective radio-frequency ablation of his accessory atrioventricular pathway after drug therapy with encainide, quinidine, and ethmozine proved unsuccessful. Past medical history included non–Q-wave myocardial infarction (20 yr before admission), well-controlled hypertension, and chronic obstructive pulmonary disease. The patient had undergone an appendectomy in the remote past without anesthetic complications. Admission medications were acetaminophen with codeine as needed for headaches secondary to ethmozine, nifedipine for hypertension, and albuterol, ipratroprium bromide, and triamcinolone inhalers for chronic obstructive pulmonary disease.

Physical examination was noteworthy for the presence of a barrel-shaped chest and bilateral, diffuse, mild expiratory wheezes. Preoperative laboratory parameters were normal except for mild hypoxemia. Chest x-ray demonstrated hyperinflated lungs consistent with chronic obstructive pulmonary disease. The electrocardiogram revealed nonspecific intraventricular conduction delay, short PR interval (160 ms), and delta waves consistent with Wolf-Parkinson-White syndrome. Both the patient and a pulmonary medicine physician felt that the respiratory status was as optimal as possible.

In addition to standard monitors, blood pressure was monitored *via* a radial artery catheter. Anesthesia was induced with propofol and alfentanil. Succinylcholine was used to facilitate tracheal intubation. Anesthesia and muscle relaxation were maintained with propofol, alfentanil, and doxocurium. A 2:1 mixture of air and oxygen was used to ventilate the lungs.

The electrophysiologic study proceeded uneventfully. The patient received isoproterenol intravenously (1–3 $\mu g \cdot min^{-1}$) intermittently to produce atrial tachycardia. During one such episode, adenosine (6 mg) was administered intravenously to terminate a supraventricular dysrhythmia. After injection of adenosine, the peak airway pressure increased from 22 to 50 cm of water, and on auscultation, diffuse bilateral inspiratory and expiratory wheezes were heard. Ventilation was continued with 100% O_2, and six puffs (450 μg) of albuterol were introduced into the endotracheal tube. After 15 min, despite an additional dose of albuterol, there was no resolution of the

wheezing and peak airway pressures remained unchanged. Arterial blood gas tensions during the episode of bronchospasm revealed a *p*H of 7.22, an arterial carbon dioxide tension of 54 mmHg, and an arterial oxygen tension of 207 mmHg (fractional inspired oxygen tension of 1.0). The patient was given aminophylline (5 $mg \cdot kg^{-1}$) as an intravenous bolus over 10 min, and an intravenous infusion of aminophylline was started at 0.9 $mg \cdot kg^{-1} \cdot hr^{-1}$. The wheezing resolved, and the peak airway pressure decreased to 25 cm of water within several minutes after the bolus of aminophylline was administered. The remainder of the anesthetic course was unremarkable, and the left free-wall accessory pathway was successfully ablated *via* the aortic valve approach. The trachea was extubated in the electrophysiology laboratory without complications, and the aminophylline infusion was discontinued gradually in the recovery room. A repeat arterial blood gas analysis on 30% O_2 was done in the recovery room and indicated a *p*H of 7.32, an arterial carbon dioxide tension of 42 mmHg, and an arterial oxygen tension of 102 mmHg. An electrophysiologic study performed 3 days postoperatively confirmed the satisfactory elimination of the accessory pathway. The patient was discharged after an uneventful postoperative course, during which there were no further exacerbations of respiratory difficulties.

Discussion

Causes of wheezing and increased airway pressures that occur intraoperatively include obstruction to airflow from either material within the lumen of bronchi, and decreases in the diameters of respiratory passages, including that of the endotracheal tube. In the case presented above, the endotracheal tube was found to be patent and wheezing was generalized; therefore, the cause of this episode was considered to be bronchospasm. Bronchospasm may occur because of anaphylactic drug reactions, light levels of anesthesia, pulmonary edema, aspiration of gastric contents, and side effects of various drugs. The only medications this patient received were propofol, alfentanil, and doxacurium. Of these agents, only propofol has been reported to cause bronchospasm in patients, but these cases were associated with life-threatening anaphylactoid reactions and occurred in the first few minutes following intravenous injection of propofol.[15] In the present case, there was no additional evidence of anaphylaxis, and the episode of bronchospasm occurred late in the maintenance of anesthesia. Although the light levels of anesthesia used in this case cannot be ruled out as the cause of this episode, this probably was not the likely cause: there was minimal surgical stimulation, no change was made in the infusion rates of anesthetic agents, and the patient's condition was stable while he received these medications for several hours. Adenosine was considered to be the provocative agent, because the onset of bronchospasm was related temporally to the administration of this drug. There have been no previous reports of intraoperative episodes of bronchoconstriction after intravenous administration of adenosine, but inhaled adenosine has been demonstrated to cause bronchoconstriction in asthmatic patients.[11–14,16] Eagle and Boucher[17] reported that during a thallium-dipyridamole stress test, sever asthma can be precipitated by the infusion of dipyridamole, an agent that inhibits the facilitated uptake of adenosine thereby increasing its extracellular concentration. In addition, 1 of 341 patients undergoing adenosine-thallium scintigraphy for evaluation of coronary artery disease was reported to have experienced acute bronchospasm.[8] Although the mechanism for adenosine-induced bronchoconstriction is unknown, possible causes include: direct effects on bronchial smooth muscle,[18] indirect effects on modulation of mast cell mediator release,[19] stimulation of peptidergic and/or cholinergic neuronal pathways,[14,20] or activation of adenosine receptors leading to alterations in cyclic adenosine monophosphate.[16]

Bronchial smooth muscle tone and reactivity reflects the balance of various contractile and relaxant inputs. The parasympathetic nervous system is the dominant autonomic influence, and because of the basal activity of this system, some degree of resting tonic contraction is always present. Human bronchial smooth muscle receives only minimal innervation from the sympathetic nervous system, and the majority of bronchodilatation is mediated by circulating catecholamines. The third limb of the autonomic nervous system, the nonadrenergic, noncholinergic system, has efferent fibers that synapse at the airway smooth muscle *via* the vagus nerve; the probable neurotransmitter in this system is vasoactive intestinal peptide. Activation of this system results in prolonged bronchodilatation.

Ng and colleagues[14] proposed that the primary action of adenosine may be to excite sensory neurons or downregulate inhibitory neurons that could induce bronchoconstriction by a local axon reflex causing histamine release from mast cells, a local release of bronchoconstrictive mediators (*e.g.*, substance P or neurokinin A), or a polysynaptic reflex leading to cholinergic stimulation of bronchial smooth muscle. The contractile response is antagonized partially by atropine and therefore, at least in part, is mediated by cholinergic nerves.[14,20]

Mast cells, present in the walls of airways and alveoli, are activated specifically by the binding of appropriate antigens to immunoglobulin-E antibodies and nonspe-

cifically by complement fractions, various medications, and organic molecules. Once activated, mast cells release various mediators, including histamine, serotonin and chemotactic factors, and products of arachidonic acid metabolism, such as platelet activating factor and leukotrienes; all of these agents may cause bronchoconstriction by activating various receptors on bronchial smooth muscle. The release of these mediators also is influenced by the autonomic nervous system *via* adrenergic and muscarinic receptors located on the cell membranes of mast cells. Adenosine A_2 and A_3 receptors have been reported to be present in the membrane of mast cells, and stimulation of adenosine A_2 receptors may result in mediator release from mast cells.[14] Adenosine interaction with newly described A_3 purinergic receptors also may mediate the release of bronchoactive substances from mast cells by enhancing calcium influx,[21] which is essential for immunologically released histamine. Several studies have shown that pretreatment with mast cell stabilizers, such as cromolyn sodium, blunt the response to adenosine[19] and that histamine levels rise in conjunction with the onset of bronchoconstriction following adenosine monophosphate inhalation.[32] The contractile response to adenosine *in vitro* has been found to be inhibited by a specific adenosine A_1 antagonist, a combined adenosine A_1 and A_2 antagonist, histamine antagonism, and both a leukotriene receptor blocker and synthesis inhibitor. This finding suggests that adenosine-induced bronchoconstriction is mediated indirectly *via* leukotriene and histamine release.[23]

Numerous receptors closely associated with contraction or relaxation are present in the cell membrane of bronchial smooth muscle. β_2-Adrenergic receptors are the primary receptors mediating bronchodilatory responses, because they cause an increase in cyclic adenosine monophosphate that ultimately results in a decrease in cytosolic calcium and smooth muscle relaxation. Alternatively, bronchoconstrictive agents such as α_2-adrenergic agents, muscarinic agonists, adenosine, adenosine triphosphate, and leukotrienes, acting through receptors coupled to specific guanine nucleotide binding proteins, increase cytosolic calcium concentration by either inhibition of cyclic adenosine monophosphate or an increase in the concentration of inositol 1,4,5-triphosphate and 1,2-diacylglycerol.[24–27] Intracellular calcium, after binding with calmodulin, activates myosin light-chain kinase which, in turn, stimulates myosin magnesium adenosine triphosphatase. This chain reaction leads to an increase in actin-myosin cross-bridging and bronchoconstriction. In this way, activation of adenosine A_1 receptors results in a decrease in cyclic adenosine monophosphate and subsequent bronchoconstriction.

Adenosine released locally or administered exogenously stimulates receptors associating with several different subunits of guanine nucleotide binding proteins to mediate secondary responses.[28] Endogenous adenosine is derived from enzymatic breakdown of adenosine triphosphate or S-adenosylhomocysteine and, in humans, is released locally secondary to the activation of mast cells caused by a wide variety of stimuli, including hypoxia[29] and bronchial provocation.[30] Plasma adenosine levels increase dramatically following allergen or methacholine challenge sufficient to cause a 25% decrease in the forced expiratory volume asthmatic patients are able to generate in 1 s.[30] Previous results have demonstrated a biphasic plasma adenosine response with an early rise in adenosine possibly caused by mediator secreting cells, and a later increase secondary to regional hypoxia caused by bronchoconstriction.[30] Although endogenous adenosine interacts with purinergic receptors to mediate bronchoconstriction, it has been suggested that this agent plays only a minor role in causing bronchospasm in patients with preexisting reactive airway disease.[31] Evidence for a role of adenosine as a possible mediator of bronchospasm is the finding that aerosolized adenosine produces bronchoconstriction in patients with asthma, but it has no effect in normal subjects.[12] Bronchospasm following inhalation of adenosine in asthmatic patients peaks at 2–5 min; patients gradually recover over the next 45–60 min.[12] Recently, Bjorck and coworkers[23] demonstrated that isolated bronchi from asthmatic patients are more sensitive to adenosine than bronchi from nonasthmatics.

The bronchospasm described in this report was resistant to inhaled β-adrenergic agonists and occurred in the presence of intravenous isoproterenol. Therefore, at least in this patient, it appears that adenosine was a more potent bronchoconstrictor than isoproterenol was a bronchodilator. Although β-adrenergic agonists may fail to relieve adenosine-induced bronchospasm, as was observed in the present case, methylxanthines such as aminophylline are antagonists at adenosine A_2 receptors and should be considered the treatment of choice. Theophylline has been demonstrated to antagonize bronchoconstriction occurring after inhaled adenosine specifically.[16,32] Aminophylline also was found to relieving bronchospasm promptly in

the present case. Finally, induction and maintenance of anesthesia in this case was accomplished without the use of volatile anesthetics. The ability of these agents to antagonize the actions of adenosine is unknown.

In summary, although the importance of endogenous adenosine as a mediator of asthma remains unclear, this agent should be used with caution in patients with asthma or chronic obstructive pulmonary disease with a component of reversible bronchoconstriction.[9] In addition, xanthines, such as theophylline, are direct antagonists of adenosine-mediated pharmacologic effects and may be useful as a first-line treatment for bronchoconstriction secondary to adenosine.

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