

BRIEF SUMMARY

For Intravenous Infusion Only
DESCRIPTION

Adenosine is an endogenous nucleoside occurring in all cells of the body. It is chemically 6-amino-9-beta-D-ribofuranosyl-9-H-purine. Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in alcohol. Solubility increases by warming and lowering the pH of the solution. Each Adenoscan vial contains a sterile, non-pyrogenic solution of adenosine 3 mg/mL and sodium chloride 9 mg/mL in Water for Injection, q.s. The pH of the solution is between 4.5 and 7.5.

INDICATIONS AND USAGE:

Intravenous Adenoscan is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately. (See **WARNINGS**).

CONTRAINDICATIONS:

Intravenous Adenoscan should not be administered to individuals with:

1. Second- or third-degree AV block (except in patients with a functioning artificial pacemaker).
2. Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except in patients with a functioning artificial pacemaker).
3. Known or suspected bronchoconstrictive or bronchospastic lung disease (e.g., asthma).
4. Known hypersensitivity to adenosine.

WARNINGS:**Fatal Cardiac Arrest, Life Threatening Ventricular Arrhythmias, and Myocardial Infarction.**

Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and nonfatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk. Appropriate resuscitative measures should be available.

Sinoatrial and Atrioventricular Nodal Block

Adenoscan exerts a direct depressant effect on the SA and AV nodes and has the potential to cause first-, second- or third-degree AV block, or sinus bradycardia. Approximately 6.3% of patients develop AV block with Adenoscan, including first-degree (2.9%), second-degree (2.6%) and third-degree (0.8%) heart block. All episodes of AV block have been asymptomatic, transient, and did not require intervention. Adenoscan can cause sinus bradycardia. Adenoscan should be used with caution in patients with pre-existing first-degree AV block or bundle branch block and should be avoided in patients with high-grade AV block or sinus node dysfunction (except in patients with a functioning artificial pacemaker). Adenoscan should be discontinued in any patient who develops persistent or symptomatic high-grade AV block. Sinus pause has been rarely observed with adenosine infusions.

Hypotension

Adenoscan is a potent peripheral vasodilator and can cause significant hypotension. Patients with an intact baroreceptor reflex mechanism are able to maintain blood pressure and tissue perfusion in response to Adenoscan by increasing heart rate and cardiac output. However, Adenoscan should be used with caution in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, or uncorrected hypovolemia, due to the risk of hypotensive complications in these patients. Adenoscan should be discontinued in any patient who develops persistent or symptomatic hypotension.

Hypertension

Increases in systolic and diastolic pressure have been observed (as great as 140 mm Hg systolic in one case) concomitant with Adenoscan infusion; most increases resolved spontaneously within several minutes, but in some cases, hypertension lasted for several hours.

Bronchoconstriction

Adenoscan is a respiratory stimulant (probably through activation of carotid body chemoreceptors) and intravenous administration in man has been shown to increase minute ventilation (Ve) and reduce arterial PCO₂, causing respiratory alkalosis. Approximately 28% of patients experience breathlessness (dyspnea) or an urge to breathe deeply with Adenoscan. These respiratory complaints are transient and only rarely require intervention.

Adenosine administered by inhalation has been reported to cause bronchoconstriction in asthmatic patients, presumably due to mast cell degranulation and histamine release. These effects have not been observed in normal subjects. Adenoscan has been administered to a limited number of patients with asthma and mild to moderate exacerbation of their symptoms has been reported. Respiratory compromise has occurred during adenosine infusion in patients with obstructive pulmonary disease. Adenoscan should be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (e.g., emphysema, bronchitis, etc.) and should be avoided in patients with bronchoconstriction or bronchospasm (e.g., asthma). Adenoscan should be discontinued in any patient who develops severe respiratory difficulties.

PRECAUTIONS:**Drug Interactions**

Intravenous Adenoscan has been given with other cardioactive drugs (such as beta adrenergic blocking agents, cardiac glycosides, and calcium channel blockers) without apparent adverse interactions, but its effectiveness with these agents has not been systematically evaluated. Because of the potential for additive or synergistic depressant effects on the SA and AV nodes, however, Adenoscan should be used with caution in the presence of these agents. The vasoactive effects of Adenoscan are inhibited by adenosine receptor antagonists, such as methylxanthines (e.g., caffeine and theophylline). The safety and efficacy of Adenoscan in the presence of these agents has not been systematically evaluated. The vasoactive effects of Adenoscan are potentiated by nucleoside transport inhibitors, such as dipyridamole. The safety and efficacy of Adenoscan in the presence of dipyridamole has not been systematically evaluated. Whenever possible, drugs that might inhibit or augment the effects of adenosine should be withheld for at least five half-lives prior to the use of Adenoscan.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals have not been performed to evaluate the carcinogenic potential of Adenoscan. Adenosine was negative for genotoxic potential in the Salmonella (Ames Test) and Mammalian Microsome Assay.

Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. Fertility studies in animals have not been conducted with adenosine.

Pregnancy Category C

Animal reproduction studies have not been conducted with adenosine; nor have studies been performed in pregnant women. Because it is not known whether Adenoscan can cause fetal harm when administered to pregnant women, Adenoscan should be used during pregnancy only if clearly needed.

Pediatric Use

The safety and effectiveness of Adenoscan in patients less than 18 years of age have not been established.

Geriatric Use

Clinical studies of Adenoscan did not include sufficient numbers of subjects aged younger than 65 years to determine whether they respond differently. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

ADVERSE REACTIONS:

The following reactions with an incidence of at least 1% were reported with intravenous Adenoscan among 1421 patients enrolled in controlled and uncontrolled U.S. clinical trials. Despite the short half-life of adenosine, 10.6% of the side effects occurred not with the infusion of Adenoscan but several hours after the infusion terminated. Also, 8.4% of the side effects that began coincident with the infusion persisted for up to 24 hours after the infusion was complete. In many cases, it is not possible to know whether these late adverse events are the result of Adenoscan infusion.

Flushing	44%	Gastrointestinal discomfort	13%	Second-degree AV block	3%
Chest discomfort	40%	Lightheadedness/dizziness	12%	Paresthesia	2%
Dyspnea or urge to breathe deeply	28%	Upper extremity discomfort	4%	Hypotension	2%
Headache	18%	ST segment depression	3%	Nervousness	2%
Throat, neck or jaw discomfort	15%	First-degree AV block	3%	Arrhythmias	1%

Adverse experiences of any severity reported in less than 1% of patients include:

Body as a Whole: back discomfort; lower extremity discomfort; weakness.

Cardiovascular System: nonfatal myocardial infarction; life-threatening ventricular arrhythmia; third-degree AV block; bradycardia; palpitation; sinus exit block; sinus pause; sweating; T-wave changes; hypertension (systolic blood pressure > 200 mm Hg).

Central Nervous System: drowsiness; emotional instability; tremors.

Genital/Urinary System: vaginal pressure; urgency.

Respiratory System: cough.

Special Senses: blurred vision; dry mouth; ear discomfort; metallic taste; nasal congestion; scotomas; tongue discomfort.

Post Marketing Experience (see **WARNINGS):** The following adverse events have been reported from marketing experience with Adenoscan. Because these events are reported voluntarily from a population of uncertain size, are associated with concomitant diseases and multiple drug therapies and surgical procedures, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, (3) strength of causal connection to the drug, or a combination of these factors.

Body as a Whole: Injection site reaction

Central Nervous System: Seizure activity, including tonic clonic (grand mal) seizures, and loss of consciousness

Digestive: Nausea and vomiting

Respiratory: Respiratory arrest

OVERDOSAGE:

The half-life of adenosine is less than 10 seconds and side effects of Adenoscan (when they occur) usually resolve quickly when the infusion is discontinued, although delayed or persistent effects have been observed. Methylxanthines, such as caffeine and theophylline, are competitive adenosine receptor antagonists and theophylline has been used to effectively terminate persistent side effects. In controlled U.S. clinical trials, theophylline (50-125 mg slow intravenous injection) was needed to abort Adenoscan side effects in less than 2% of patients.

DOSE AND ADMINISTRATION:

For intravenous infusion only.

Adenoscan should be given as a continuous peripheral intravenous infusion.

The recommended intravenous dose for adults is 140 mcg/kg/min infused for six minutes (total dose of 0.84 mg/kg).

The required dose of thallium-201 should be injected at the midpoint of the Adenoscan infusion (i.e., after the first three minutes of Adenoscan).

Thallium-201 is physically compatible with Adenoscan and may be injected directly into the Adenoscan infusion set.

The injection should be as close to the venous access as possible to prevent an inadvertent increase in the dose of Adenoscan (the contents of the IV tubing) being administered. There are no data on the safety or efficacy of alternative Adenoscan infusion protocols.

The safety and efficacy of Adenoscan administered by the intracoronary route have not been established.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Rx only

Marketed by Astellas Pharma US, Inc.

Deerfield, IL 60015

Manufactured by Hospira Inc.

Lake Forest, IL 60045 USA

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Cardiac Catheterization A Must in PAH Diagnosis

BY NANCY WALSH
New York Bureau

NEW YORK — Any patient with suspected pulmonary hypertension must have a thorough work-up, including right heart catheterization, before initiating treatment, Dr. Roxana Sulica said at a meeting sponsored by the Pulmonary Hypertension Association and the University of Michigan.

Because the typical presenting symptoms of pulmonary arterial hypertension (PAH) are subtle and nonspecific, with dyspnea, fatigue, and syncope or near syncope being the most common, a high index of suspicion is needed or the diagnosis may not be made until the disease is advanced and the prognosis is poor, she said.

Risk factors for PAH include underlying connective tissue disease, especially limited scleroderma and mixed connective tissue disease, a family history of PAH, the presence of congenital heart disease, and environmental factors such as exposure to anorexigens.

Clinical assessment of the patient with possible PAH includes an electrocardiogram, which may show changes in the right ventricle, including right axis deviation, right atrial enlargement, and right ventricular hypertrophy, said Dr. Sulica.

A chest x-ray may reveal prominent proximal pulmonary arteries, peripheral hypovascularity, and reduced retrosternal air space.

An echocardiogram should then be done, and typical—but not diagnostic—findings on the echocardiogram include right atrial and ventricular enlargement, right ventricular dysfunction, and intra-ventricular septal flattening.

The definitive diagnosis of PAH can only be made by cardiac catheterization, which can exclude congenital heart disease, measure wedge pressure, and establish the degree of hemodynamic impairment, according to Dr. Sulica, who is director, Beth Israel Pulmonary Hypertension Program, Beth Israel Medical Center, New York.

The hemodynamic definition of PAH is a mean pulmonary artery pressure greater than 25 mm Hg, with a pulmonary capillary wedge pressure less than 15 mm Hg and a calculated pulmonary vascular resistance greater than 3 Wood units.

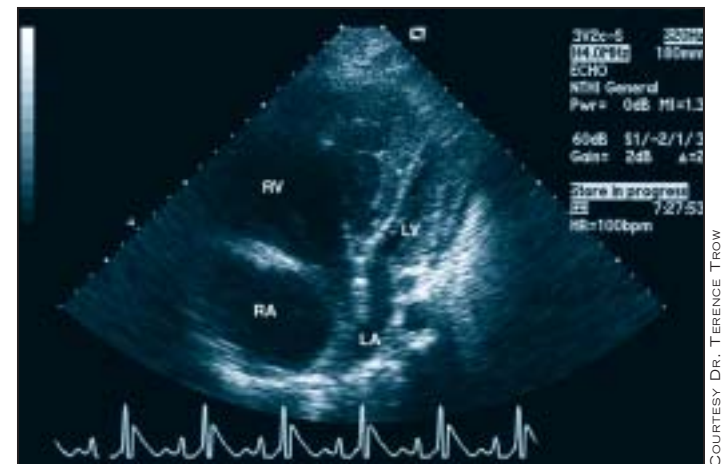
Right heart catheterization also permits a determination of the pulmonary vasodilator reserve through vasodilator testing using inhaled nitric oxide, intravenous epoprostenol, or intravenous adenosine. A positive response is defined as a reduction in mean pulmonary artery pressure of 10 mm Hg or more to a mean of 40 mm Hg

or less, with an unchanged or increased cardiac output. Only positive responders should be given treatment with calcium channel blockers, Dr. Sulica cautioned.

Newly released guidelines from the American College of Chest Physicians emphasize the limited role of calcium channel blockers, which have been studied for PAH for 2 decades.

The guidelines point to a study of 557 patients with idiopathic PAH who underwent acute pulmonary vasodilator testing, with the 70 positive responders receiving long-term oral calcium channel blocker monotherapy. By 1 year, only 38 (6.8% of the total group) showed a favorable clinical response (Circulation 2005;111:3105-11).

Another recent study found that inappropriate—and potentially harmful—calcium channel blocker use remains common. In a registry that enrolled 1,360 PAH patients, 31% were on calcium channel



An echocardiogram shows right atrial and right ventricular enlargement that is impinging on the left side.

blockers at the time of referral to a tertiary care center (Eur. Respir. J. 2007 Sept. 5 [Epub doi:10.1183/09031936.00042107]).

In patients who are not responders to vasodilation, the use of calcium channel blockers can decrease cardiac output and systemic vascular resistance, without improving pulmonary artery pressure or pulmonary vascular resistance. Routine vasodilator testing before treatment initiation could eliminate this inappropriate use of calcium channel blockers, Dr. Sulica said.

The prognosis for PAH is still fairly poor. Two-year survival among patients with scleroderma complicated by PAH is only 40%, compared with 80% among those without pulmonary complications (Respiratory Care 2006;51:368-81).

The prognosis also is grim for patients in advanced functional classes and those with poor exercise endurance, as well as for those whose hemodynamic findings include elevated right atrial pressure and reduced cardiac index. But improved understanding of pathophysiology and recent advances in medical therapy may change this.

“What we have learned so far is that screening patients with scleroderma can lead to an earlier diagnosis of PAH. Soon we may see if early treatment can improve the long-term prognosis,” Dr. Sulica said. ■