BRIEF SUMMARY ADENOSCAN® adenosine injection

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 reflux 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 PCO_2 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%	Lightheadedness/dizziness	12%	Hypotension	2%
Chest discomfort	40%	Upper extremity discomfort	4%	Nervousness	2%
Dyspnea or urge to breathe deeply	28%	ST segment depression	3%	Arrhythmias	1%
Headache	18%	First-degree AV block	3%		
Throat, neck or jaw discomfort	15%	Second-degree AV block	3%		
Gastrointestinal discomfort	13%	Paresthesia	2%		

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.

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.

DOSAGE 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

47101/Revised: April 2005

Drug-Eluting Stent Uses Rapidly Proliferating

BY MITCHEL L. ZOLER
Philadelphia Bureau

Despite their higher cost, and despite recent concerns about late thrombosis, drug-eluting stents now own coronary stenting.

In the last quarter of last year, drug-eluting stents were estimated to have been used for 87% of all interventional coronary procedures in the United States, Martin B. Leon, M.D., said last November at the American Heart Association's scientific sessions in New Orleans. Less than 2 years earlier, during the first quarter of 2003, not a single drug-eluting stent had been used in the United States outside of a clinical trial. The Food and Drug Administration first approved a drug-eluting stent in April 2003.

'There has never been a technology in the world with this kind of rapid penetration over a short period of time.'

DR. LEON

"There has never been a technology in the world with this kind of rapid penetration over a short period of time," said Dr. Leon, associate director of the Center for Interventional Vascular Therapy at Columbia University in New York.

"We have not yet identified any subsets of patients who don't benefit from receiving drug-eluting stents [by having less restenosis] compared with bare metal stents," said David J. Cohen, M.D., associate director of interventional cardiology at Beth Israel Deaconess Medical Center in Boston. "De facto practice in the United States today is to use drug-eluting stents whenever the available stent lengths and diameters fit. At Beth Israel Deaconess, most of the time when patients [who are undergoing coronary stenting] don't receive drug-eluting stents it's because the vessel is too small or too large to accommodate available stent sizes," he told this newspaper.

In fact, use of drug-eluting stents has become so widespread that medicolegal concerns may now drive their use even more than purely clinical factors. "When the risk of restenosis is low, operators must balance the need for drug-eluting stents with the medicolegal risk of avoiding what has become the de facto standard of care for all patients," said Herbert D. Aronow, M.D., director of the cardiac catheterization laboratories at the Veterans Affairs Medical Center in Philadelphia.

According to the results of one recently reported study, during 2003, about a third of all sirolimus-eluting (Cypher) stents used in the United States were for off-label, coronary-artery indications.

As of presstime, no expert group had issued formal recommendations on the appropriate uses of drug-eluting stents, although these are expected soon. In the meantime, some experts have given their personal opinions.

One set of standards was laid out by Gregg W. Stone, M.D., in a talk at the AHA scientific session. "In workhorse lesions, in patients undergoing elective coronary interventions with de novo lesions up to 46 mm in length and in vessels with reference diameters of 2.5-3.75 mm without acute coronary syndrome or acute myocardial infarction, in general the safety and efficacy of two drug-eluting stents, Cypher and Taxus, has been proved," said Dr. Stone, an interventional cardiologist at Columbia University in New York. "Using drug-eluting stents over bare metal stents in these lesions is the appropriate thing to do."

But, he added, "we desperately need more data regarding the safety and efficacy of drug-eluting stents in unapproved and high-risk indications before their use should be considered routine. We must be very circumspect about extending drug-eluting stents to more complex patients and lesions. We are in the midst of stent frenzy, where everyone is putting in drug-eluting stents in every single lesion. You need to be aware of the evidence so you know what you are doing."

According to Dr. Stone's assessment, there are "pretty good grounds" for using a single drug-eluting stent to treat in-stent restenosis within a bare metal stent.

Use of a drug-eluting stent can "probably be recommended" for the following: treating in-stent restenosis in place of brachytherapy when the existing stent was bare metal; bifurcations when the drug-eluting stent is placed in the main branch with angioplasty only for the side branch; aorto-ostial lesions; chronic, total occlusions; patients with multivessel disease instead of bypass surgery if they have only simple, focal lesions; and saphenous vein grafts.

But because of an "absence of sufficient data to warrant routine use," Dr. Stone cautioned physicians to "think twice" about using drug-eluting stents outside of an investigational setting for these indications: bifurcations when two stents are used; ultralong lesions; unprotected left main disease; in-stent restenosis following failed brachytherapy, and in patients with acute myocardial infarction. It is completely unclear how cardiologists should manage restenosis within a drug-eluting stent. ■

VERBATIM

'We have oceans of lotions, potions, and notions out there for vulvodynia. There is not going to be one simple cure.'

Dr. Hope K. Haefner, p. 52