

ADENOSCAN[®]
adenosine injection

BRIEF SUMMARY OF PRESCRIBING INFORMATION**For Intravenous Infusion Only****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

Rx only

Marketed by Astellas Pharma US, Inc.

Deerfield, IL 60015

Manufactured by Hospira Inc.

Lake Forest, IL 60045 USA

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Phone Calls Improve Post-CABG Depression

BY MARY ANN MOON

A collaborative-care intervention delivered by telephone improved mental and physical functioning in patients who developed depression after undergoing coronary artery bypass grafting, according to a study published online in JAMA simultaneously with its presentation at the annual scientific sessions of the American Heart Association.

The treatment's benefits became evident within 2 months of surgery and persisted through 8 months of follow-up. Overall, half of the 150 patients who received the intervention reported a 50% or more reduction in mood symptoms, compared with 30% of patients who received usual post-CABG care, said Dr. Bruce L. Rollman of the Uni-

At 8 months' follow-up, the intervention group showed significant clinical improvement on the Short Form-36 of 3.2 points, with an effect size of 0.30.

versity of Pittsburgh and his associates.

The investigators described their study as the first clinical trial to assess a collaborative-care strategy for treating depression following an acute cardiac event.

"Collaborative care emphasizes a flexible real-world treatment package that involves active follow-up by a nonphysician care manager who adheres to evidence-based treatment protocols, supports patients with timely education about their illness, considers patients' prior treatment experiences and current preferences, teaches self-management techniques, actively involves primary care physicians in their patients' care through regular exchanges of real-time information, proactively monitors treatment responses and suggests adjustments when indicated, and facilitates co-management or transfer of care to local mental health specialists when patients do not respond to treatment or have clinically complicated cases, or upon request by the patient or primary care physician," they explained.

For this intervention, 2,485 post-CABG patients were first screened for depression before hospital discharge, then screened again 2 weeks later to determine whether depression symptoms persisted. A total of 302 were found to have moderate depression and agreed to participate in the study.

The patients had been treated at two university-affiliated and five community hospitals in the Pittsburgh area between 2004 and 2007. They were randomly assigned to the intervention group (150 subjects) or to usual care (152 subjects). A comparison group of 151 post-CABG patients who did not have depression was included in the study.

The intervention was run by a nurse care manager who reported weekly to

a study psychiatrist and internist. The care manager contacted patients by phone in 15- to 45-minute sessions, providing "basic psychoeducation" about depression and its effect on cardiac disease, initiating and adjusting antidepressant pharmacotherapy through the patients' primary care physicians, closely monitoring mood symptoms, and coordinating care with a local psychiatrist or psychologist as necessary.

The care manager also performed serial assessments with the 36-item Short Form health survey (SF-36) to measure general mental and physical health, the

Duke Activity Status Index to measure disease-specific physical functioning, and the Hamilton Rating Scale for Depression to measure mood symptoms.

After 8 months, the intervention group showed significant clinical improvement on the SF-36 of 3.2 points, with an effect size of 0.30. Improvements of at least 3 points or an effect size of 0.25 on these measures are considered "minimally clinically important," Dr. Rollman and his colleagues said (JAMA 2009;302:2095-103).

Men showed a better treatment response than did women.

For men in the intervention group, there was a nearly 6-point rise on the SF-36. Moreover, 61% of the men who received the intervention reported a 50% or more reduction in depression scores, compared with only 33% of men who received usual care.

In contrast, 38% of women who received the intervention reported that degree of reduction in depression scores, compared with 23% of women who received usual care.

The study subjects who responded well to the intervention showed better outcomes than did those who received usual care, but both groups of patients with post-CABG depression had poorer outcomes than did the comparison group of patients without depression. Overall, 33% of intervention patients and 32% of usual care patients required rehospitalization, compared with only 25% of the control group.

Noting that "a substantial minority of patients," particularly women, did not benefit from the collaborative-care intervention, "it is vital to identify post-CABG patients most likely to become treatment resistant so as to develop more effective treatments for them," the researchers added.

This study was supported by the National Institutes of Health and the University of Pittsburgh.

Dr. Rollman reported no financial conflicts of interest. ■