

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 (V_e) 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%	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

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SSRIs Cut Depression Scores in Heart Failure

BY MITCHEL L. ZOLER

Philadelphia Bureau

ATLANTA — Treatment with an anti-depressant drug relieved the mild to moderate depression that often occurs in patients with heart failure in a controlled study with 26 patients.

But the reduction of depression symptoms using a selective serotonin reuptake inhibitor generally did not improve quality of life measures in these patients with heart failure, Dr. Mark R. Vesely and his associates reported in a poster at the annual meeting of the American College of Cardiology.

The findings suggest that physicians should screen for depression in patients with heart failure and then treat when depression is diagnosed, Dr. Vesely said in an interview. Treatment with an SSRI is safe and effective. The next step would be to examine whether treating depression can produce any reductions in hospitalization rates or death in heart failure patients, added Dr. Vesely, a cardiologist at the University of Maryland in Baltimore.

Results from previous studies have shown that depression occurs in 24%-48% of patients with heart failure. Despite this high prevalence, "heart failure patients usually don't get treated" for depression, said Dr. Stephen S. Gottlieb, professor of medicine and director of the heart failure service at the University of Maryland and a coinvestigator for the study.

An SSRI is the logical, first-line agent to use to treat depression in a patient with heart failure because of its presumed safe-

ty in these patients. By contrast, treatment with a tricyclic antidepressant involves the risk of producing neurohormonal activation that might exacerbate the heart failure, Dr. Vesely said.

The study included patients with New York Heart Association class II or III heart failure who were diagnosed with mild or moderate depression by a score of 10 or more on the Beck Depression Index (BDI). The average BDI score of the patients enrolled was about 21, and they were all placed on an optimal panel of heart failure medications.

The patients were randomized to treatment with either paroxetine-CR (Paxil CR) 12.5 mg daily or placebo for 12 weeks. During follow-up, three patients dropped out of the study.

After 12 weeks, the BDI score fell by an average of 12 points in the 12 patients treated with paroxetine-CR for the full study, compared with an average 0.5-point rise in 11 patients in the placebo group, a statistically significant difference.

No significant improvements were seen for most quality of life measures in the paroxetine-treated patients compared with the controls. The sole exception was the mental score on the Short Form-36, which rose by 9 points in the actively treated patients and by 1 point in the placebo-treated patients, a statistically significant difference.

GlaxoSmithKline, which markets Paxil CR, supplied the drug used in this study, but otherwise the study and investigators received no industry support. ■

Post-Myocardial Infarction Depression Severity Stabilizes After 6 Months

DENVER — Depression that occurred in adults after acute myocardial infarction decreased in severity during the first 6 months after the cardiac event, but then stabilized over the next several years, Kenneth E. Freedland, Ph.D., reported in a poster presented at the annual meeting of the American Psychosomatic Society.

Dr. Freedland, a member of the psychiatry department at Washington University, St. Louis, and his colleagues reviewed data on 1,086 adults who were randomized to the usual care arm of the Enhancing Recovery in Coronary Heart Disease (ENRICH) study, a multicenter trial sponsored by the National Institutes of Health that was designed to evaluate depression interventions in MI patients.

The patients' mean age was 43 years, 44% were female, and 35% were minorities. In addition, 55% were high school graduates, 19% were college graduates, and 26% had less than a high school education. About 60% of the patients had a history of major depression before the MI.

The patients completed a Beck Depression Inventory (BDI) at the start of the study, and again at 6-month intervals for an average follow-up period of 26 months.

The average baseline BDI score was 15.3; baseline BDI scores were lowest among older patients, non-Hispanic white patients, and patients without a history of major depression, and highest among women and patients who were taking antidepressants.

Antidepressant use was associated with worse depression in the overall ENRICH study, so its impact in this analysis must be interpreted with caution, the investigators noted.

Overall, the severity of depression decreased during the first 6 months after the MI, but depression scores then stabilized during the follow-up period, which lasted as long as 4 years for some patients. The average decrease in BDI score was -0.85 during months 0-6, compared with -0.07 during months 6-54.

Female gender, minority status, younger age, and lower levels of education were significantly associated with higher levels of depression immediately after MI, but younger female patients showed the fastest improvements in depressive symptoms over time. Additional analysis is needed to determine patterns among these subgroups, the researchers noted.

—Heidi Splete