

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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Colchicine Delays HCC in Hepatitis-Related Cirrhosis

BY MARY ANN MOON

Contributing Writer

Colchicine therapy prevents or delays the development of hepatocellular carcinoma in patients who have cirrhosis related to viral hepatitis, reported Dr. Oscar Arrieta of the National Cancer Institute, Mexico City, and his associates.

Until now, no treatment had been found effective in preventing hepatocellular carcinoma (HCC) from developing in patients with cirrhosis of any etiology.

The alkaloid and antimitotic agent colchicine has shown mixed effects on the progression of fibrosis, ascites, esophageal varices, portal vein pressure, functional status, and mortality in cirrhosis patients, but no studies had assessed its effect against HCC, the investigators said.

They evaluated colchicine in a retrospective cohort study involving 186 patients with hepatitis virus-related cirrhosis who were treated between 1980 and 2000 and who were followed every 3-6 months for a minimum of 3 years. A total of 116 of these subjects (62%) received 1 mg colchicine 5 days per week for a mean of 63 months (range 6-168 months). Almost all of these subjects (96%) were treated for at least 1 year. None discontinued the drug because of adverse effects.

Of the subjects who took colchicine, 9% developed HCC compared with 29% of

the subjects who did not take the drug, a significant difference, Dr. Arrieta and his associates said (Cancer 2006 Sept. 11 [Epub doi:10.1002/cncr.22198]).

Moreover, among subjects who did develop HCC, the cancer-free interval was significantly longer in those treated with colchicine (222 months) than in those who did not take the drug (150 months).

The exact oncogenic mechanism of viral-related HCC is not known, but virus-induced inflammation is thought to lead to hepatocyte destruction and liver fibrosis. Colchicine may decrease inflammation and may also have antimitotic properties that reduce cellular proliferation, "thereby interrupting the hyperplasia-dysplasia-metaplasia sequence of HCC and preventing mutations leading to HCC," the researchers said.

In this study, as in previous studies, colchicine showed no direct beneficial effect on the progression of cirrhosis. With colchicine, 9% of patients showed improvement on their Child-Turcotte-Pugh score during follow-up, 35% showed no change, and 56% showed disease progression. The corresponding numbers in the subjects who didn't take colchicine were 2.5%, 37%, and 60%—progression rates that were not significantly different.

The study findings indicate that colchicine prevents or delays the development of HCC independent of factors such as age, platelet count, alpha fetoprotein levels, and transaminase levels. ■

Liver Transplant Successful In Carefully Selected Elderly

BY JEFF EVANS

Senior Writer

BOSTON — Carefully selected liver transplant recipients older than 70 years can have survival rates similar to those of patients in their 50s, Dr. Gerald S. Lipshutz reported at the 2006 World Transplant Congress.

"As the older population continues to grow, more transplant centers will be forced to consider liver transplantation in the elderly," said Dr. Lipshutz of the University of California, Los Angeles.

Previous single-center studies of liver transplant recipients aged 60 years and older have reported 5-year survival rates of 52%-69%. Kaplan-Meier curve estimates have predicted 10-year survival to be about 35% in that population. But no studies so far have looked at the outcomes of septuagenarians after liver transplant, Dr. Lipshutz said.

Dr. Lipshutz compared the outcome of liver transplants performed at his center during 1988-2005 in recipients aged 70-79 years with transplants in those aged 50-59 years. The 62 liver transplant recipients in the older group had a mean age of 72 years while the 864 younger patients had an average age of 54 years.

To be put on the liver transplant wait list, patients had to undergo "aggressive cardiac clearance." If there was any evidence of significant cardiovascular disease, they had to undergo coronary artery catheterization.

Survival rates at 1, 3, 5, and 10 years were higher in the younger group than in the older group, but the difference was never statistically significant. At 1 year, survival rates were about 79% and 73%, respectively, followed by 72% and 66% at 3 years, 65% and 49% at 5 years, and 54% and 40% at 10 years.

A multivariate analysis combining both groups of patients showed that significant risk factors for death were preoperative hospitalization, longer cold ischemia times of the donor liver, a liver disease etiology of hepatitis C virus infection, and alcohol consumption. An age of 70 years or older was not a significant risk factor.

"With appropriate selection and screening, transplants in select septuagenarians may result in long-term survival," Dr. Lipshutz said at the congress, which was sponsored by the American Society of Transplant Surgeons, the American Society of Transplantation, and the Transplantation Society. ■