

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

**CONTRAINDICATIONS:**

Intravenous Adenosine 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 Adenosine infusion. Patients with unstable angina may be at greater risk. Appropriate resuscitative measures should be available.

**Sinoatrial and Atrioventricular Nodal Block**

Adenosine 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 Adenosine, 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. Adenosine can cause sinus bradycardia. Adenosine 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). Adenosine 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**

Adenosine 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 Adenosine by increasing heart rate and cardiac output. However, Adenosine 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. Adenosine 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 Adenosine infusion; most increases resolved spontaneously within several minutes, but in some cases, hypertension lasted for several hours.

**Bronchoconstriction**

Adenosine is a respiratory stimulant (probably through activation of carotid body chemoreceptors) and intravenous administration in man has been shown to increase minute ventilation (V<sub>e</sub>) and reduce arterial PCO<sub>2</sub>, causing respiratory alkalosis. Approximately 28% of patients experience breathlessness (dyspnea) or an urge to breathe deeply with Adenosine. 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. Adenosine 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. Adenosine 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). Adenosine should be discontinued in any patient who develops severe respiratory difficulties.

**PRECAUTIONS:****Drug Interactions**

Intravenous Adenosine 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, Adenosine should be used with caution in the presence of these agents. The vasoactive effects of Adenosine are inhibited by adenosine receptor antagonists, such as methylxanthines (e.g., caffeine and theophylline). The safety and efficacy of Adenosine in the presence of these agents has not been systematically evaluated. The vasoactive effects of Adenosine are potentiated by nucleoside transport inhibitors, such as dipyridamole. The safety and efficacy of Adenosine 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 Adenosine.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Studies in animals have not been performed to evaluate the carcinogenic potential of Adenosine. 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 Adenosine can cause fetal harm when administered to pregnant women, Adenosine should be used during pregnancy only if clearly needed.

**Pediatric Use**

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

**Geriatric Use**

Clinical studies of Adenosine 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 Adenosine 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 Adenosine 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 Adenosine 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 Adenosine (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 Adenosine side effects in less than 2% of patients.

**DOSE AND ADMINISTRATION:**

For intravenous infusion only.

Adenosine 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 Adenosine infusion (i.e., after the first three minutes of Adenosine).

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

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

The safety and efficacy of Adenosine 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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# Hypertension Treatment Can't Explain Stroke Rates

BY MITCHEL L. ZOLER

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NEW ORLEANS — Low levels of hypertension awareness and treatment do not explain why African Americans and people who live in the Stroke Belt have a high incidence of stroke and stroke mortality, based on findings from a nationwide epidemiologic study of more than 11,000 people.

But African Americans do show a substantial shortfall in hypertension control, compared with whites, which provides a major explanation for the large excess of strokes among blacks, George Howard, Dr.P.H., said at the annual International Stroke Conference.

In contrast, hypertension is as well controlled among residents in the southern Stroke Belt as in other regions of the United States, indicating that factors other than hypertension must explain this disparity, said Dr. Howard, chairman of the department of biostatistics at the University of Alabama, Birmingham.

Dr. Howard also reported on results from a second epidemiologic study by that showed that the risk of stroke death faced by African Americans who live in the Stroke Belt far exceeds their expected risk based on race or residence alone.

"There is an interaction of race and geography that causes an extra 15%-20% of risk that we don't understand," said Dr. Howard at the conference, sponsored by the American Stroke Association. "Whatever causes African Americans to have more strokes, African Americans who live in the South have more of it."

In fact, Dr. Howard and his associates have launched an epidemiologic study that's designed to examine possible explanations for this unexpectedly high risk among Southern African Americans, and it was the initial phase of this study that produced the findings on hypertension awareness, treatment, and control. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study is recruiting 30,000 volunteers, aged 55 or older, from across the United States. The aim is to have a group in which 20% reside in the regions where stroke rates are highest (the "buckle of the Stroke Belt," which includes North and South Carolina and Georgia), 30% reside in other areas of the Stroke Belt, and 50% live elsewhere in the United States. Half the participants will be African American and half will be white, with equal gender representation.

The initial analysis of hypertension was done on the first 11,701 people enrolled, minus 95 whose blood pressure records were missing. (As of early February, more than 15,000 people had been enrolled in REGARDS). Among the initial group, 6,023 had hypertension.

Hypertension awareness was defined as

a correct self-report of the disease by the hypertensive participants. Hypertension treatment was positive if patients with high blood pressure were able to show their interviewer a medication supply. And hypertension control was based on whether the hypertensive participants had a pressure of less than 140/90 mm Hg when examined for the study.

In an analysis that controlled for socioeconomic status and risk factors, African Americans with hypertension were 30% more likely to be aware of their disease than whites, 75% more likely to be on treatment for hypertension than whites, and 30% less likely to be controlled by their treatment. All of these differences were statistically significant.

In the analysis by region, which again controlled for potential confounders, residents of the Stroke Belt had essentially the same level of hypertension awareness and control as people who lived elsewhere. Treatment frequency was about 25% higher among Stroke Belt residents, but this difference was not statistically significant.

"The implication for the Stroke Belt is that something other than hypertension awareness, treatment, and control must cause the disparity in stroke rates," said Dr. Howard. Many alternative factors have been hypothesized, including differences in diet, physical activity, infection rates, and quality of health care. For African Americans, the focus will now fall on trying to determine why hypertension control is so much worse than among whites.

The second study by Dr. Howard and his associates looked at stroke mortality data collected by the Centers for Disease Control and Prevention during 1997-2001. These data showed higher rates among African Americans and Stroke Belt residents. What was surprising, said Dr. Howard, was the way that race and residence location interacted.

In Florida, where residents had the highest stroke mortality, the rate among African Americans aged 65-74 years old was 150% higher than in similarly aged whites. In contrast, in New York, the state with the lowest stroke mortality rates in the country, African Americans aged 65-74 years old had a rate of stroke deaths that was 50% higher than in whites. In other words, the increased rate of stroke death associated with being African American was three times as high in Florida as it was in New York.

"The interaction between race and geography that we see is more than additive, and more than multiplicative," said Dr. Howard. The stroke mortality rate in Florida was 15%-20% higher than would be predicted based on race alone or location alone.

Researchers need to uncover what causes this excess risk of stroke mortality so that appropriate interventions can be applied, Dr. Howard said. ■