

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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Rise in *E. coli* Resistance In UTIs Starting to Slow

BY ELIZABETH MEHCATIE

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WASHINGTON — The prevalence of urinary tract infections in women resistant to standard treatment has been increasing, but there are indications that the increase has begun to level off, Patricia D. Brown, M.D., said at an update on sexually transmitted infections.

Emerging uropathogenic *Escherichia coli* antimicrobial resistance—particularly to the front-line, first choice treatment of urinary tract infections (UTIs), trimethoprim-sulfamethoxazole (TMP-SMX)—has been documented worldwide. However, much of the data are based on passive surveillance, which can overestimate prevalence, because women with acute, uncomplicated UTIs often do not have cultures performed, so these cases are not reported, said Dr. Brown of Wayne State University, Detroit.

Women who do have a culture have complicated disease and fail treatment, leading to overestimates of true prevalence, she added. Still, passive surveillance can provide information on trends.

In the United States, active surveillance has been conducted in specific geographic areas, where the true prevalence may not reflect that of other geographic areas, Dr. Brown said at the meeting, sponsored by OB.GYN. NEWS, FAMILY PRACTICE NEWS, and Boston University.

Recent studies indicate that TMP-SMX resistance “may be leveling off” after peaking at about 25%, which is probably because of the reduced use of this treatment, she said. But as the use of TMP-SMX for UTIs has decreased, resistance to other antimicrobial agents has been increasing.

In 890 isolates from women with UTIs in the United States who were a part of the North American Urinary Tract Infection Collaborative Alliance (NAUTICA) study, the prevalence of TMP-SMX resistance was about 23%. Resistance to ampicillin was 38%, and resistance to levofloxacin was nearly 7%.

As the use of TMP-SMX has dropped, the use of fluoroquinolones has increased, Dr. Brown said, noting that rates of resistance to β -lactams such as ampicillin have been high for some time.

In the NAUTICA study, resistance to nitrofurantoin was only 1.8%, which she said was “remarkable,” considering that it has been available for about 50 years. But that rate has probably remained so low because the agent has several mechanisms of action and is indicated only for cystitis, she noted.

There are several clinical implications of these resistance trends: In treatment studies of pyelonephritis, antimicrobial resistance has clearly been shown to increase the risks of both clinical and microbiologic failure, she said. She cited a retrospective

cohort study of women with acute uncomplicated cystitis, in which the risk of clinical failure was 45.4%, and a prospective study in Israel of empiric TMP-SMX in an area where the prevalence of resistance was high, in which the risk of clinical failure was 46%.

Identifying risk factors for resistance can help guide antibiotic choice, she said, referring to the difficulty facing clinicians, who usually do not have access to resistance trends and who likely will be given an overestimate of resistance if they call their local microbiology lab.

Results of retrospective case-control studies have identified potential risk factors for infection with a uropathogen resistant to TMP-SMX. Two risk factors found in every such study include recent antibiotic use and recent hospitalization, she said.

Recent travel to underdeveloped countries has been identified as an independent risk factor in several studies.

The standard treatment of uncomplicated cystitis is 3 days of double-strength formulations of TMP-SMX twice a day. Avoid empiric treatment with TMP-SMX in patients who have recently been hospitalized or have taken antibiotics in the previous 3 months, she said.

Alternative treatments for those with risk factors for resistance are a 7-day course of nitrofurantoin or a 3-day course of a fluoroquinolone. The major drawback of the former is that a full-week course is necessary.

As for the fluoroquinolones, ciprofloxacin is available in generic formulations, so the drug is less expensive. The Food and Drug Administration has approved gatifloxacin as a single-dose treatment for uncomplicated cystitis. One fluoroquinolone that should not be used for UTI is moxifloxacin, which is indicated for respiratory infections, because treatment results in low levels of the drug in the urinary tract.

A single dose of fosfomycin is another alternative, but this is considered a second-line treatment because the efficacy is not that high and it is expensive. One benefit, however, is that resistance to this agent appears to be low, Dr. Brown said.

Short-course treatment is not appropriate for complicated cystitis, which should be treated with a 7-day course of therapy, she said. Avoid empiric TMP-SMX treatment in patients who have recently been treated with antibiotics or have recently been hospitalized, as you would for patients with uncomplicated cystitis. Culture all patients, and adjust treatment based on susceptibility data, she said.

As many as 25% of women with acute cystitis can develop frequent, recurrent UTIs, which are reinfections, not relapses. (Fewer than 5% of these women have a correctable structural or functional abnormality of the urinary tract.)

Active surveillance has been conducted in specific geographic areas, where the true prevalence may not reflect that of other geographic areas.