ADENOSINE b (Systemic)

Introduction

Revised: 08/21/2000

VA CLASSIFICATION (Primary/Secondary)¾CV300/DX900

Commonly used brand name(s):Adenocard; Adenoscan.

Category

Antiarrhythmic; diagnostic aid adjunct (ischemic heart disease).

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Tachycardia, supraventricular, paroxysmal (treatment)¾Adenosine is indicated for conversion to sinus rhythm of paroxysmal supraventricular tachycardia, including those due to atrioventricular (AV) node reentry 52 and associated with accessory bypass tracts (Wolff-Parkinson-White syndrome), after appropriate vagal maneuvers (e.g., Valsalva maneuver) have been attempted 1, 3, 7, 15, 49.

Myocardial perfusion imaging, radionuclide (adjunct) * 85 ; or

[Stress echocardiography (adjunct)] *¾In patients unable to exercise adequately, adenosine is used to induce coronary artery vasodilation in conjunction with myocardial perfusion imaging (i.e., thallium-201 myocardial perfusion scintigraphy) 85 or two-dimensional echocardiography for the detection of perfusion defects or regional contraction abnormalities 56 associated with coronary artery disease. 85, 25, 26, 27, 28, 29, 30, 31, 32, 33

Mechanism of action/Effect:

Antiarrhythmic¾Slows impulse formation in the sinoatrial (SA) node, slows conduction time through the atrioventricular (AV) node, and can interrupt reentry pathways through the AV node. 1, 3, 7, 19, 20, 21, 41 Adenosine depresses left ventricular function, but because of its short half-life, the effect is transient, allowing use in patients with existing poor left ventricular function 7.

Diagnostic aid¾The precise mechanism of coronary vasodilation is not completely understood. 34 However, it is speculated that adenosine may have a direct effect on smooth muscle receptors and may influence cellular calcium dynamics. 85, 34 Coronary vasodilation by adenosine contributes to the creation of heterogeneity of myocardial blood flow. 35, 36 The difference in coronary reserve in the vascular bed distal to a critical coronary stenosis versus that supplied by normal coronary arteries accounts for a significantly greater, 3- to 5-fold, increase in regional myocardial blood flow to normal epicardial vessels. 35, 36

Other actions/effects:

Administration of doses larger than 12 mg by intravenous infusion decreases blood pressure by reducing peripheral vascular resistance 1, 3.

Physiologically, naturally occurring adenosine functions as an intermediate metabolite in a number of processes including regulation of coronary and systemic vascular tone, platelet function, lipolysis in fat cells, and intracardiac conduction 2.

Biotransformation:

Very rapid, by circulating enzymes 2 in erythrocytes and vascular endothelial cells 1, 9 , by deamination 2, 19 , primarily to inactive inosine (further degraded to hypoxanthine and then to uric acid) 19 and by phosphorylation to adenosine monophosphate (AMP) 1, 3, 9.

Half-life:

Less than 10 seconds [1, 3, 7, 9, 21, 38, 39].

Onset of action:

Immediate.

Elimination:

Principal elimination routes are cellular uptake, primarily by erythrocytes and vascular endothelial cells, and metabolism. [85, 19] Metabolites excreted renally. [19] The predominant final excretory metabolite is uric acid. [19]

Precautions to Consider

Carcinogenicity

Studies have not been done [1, 15, 85].

Mutagenicity

Mutagenicity tests in the Salmonella/mammalian microsome assay (Ames test) were negative [1, 15, 85].

However, adenosine causes chromosomal alterations [1, 15, 85].

Pregnancy/Reproduction

Fertility¾In rats and mice, intraperitoneal administration of 50, 100, and 150 mg per kg of body weight (mg/kg) per day for 5 days caused decreased spermatogenesis and increased numbers of abnormal sperm [1, 3, 15, 85].

Pregnancy¾Studies have not been done in humans. Because adenosine occurs naturally in the body, problems are not expected [1, 4].

Scant reports of adenosine use in pregnant women have not revealed fetal or maternal sequelae. [17, 18, 40, 41]

Studies have not been done in animals. [15]

FDA Pregnancy Category C.

Breast-feeding

Because of rapid removal from circulation, adenosine is not expected to be distributed into breast milk [10].

Pediatrics

Studies performed to date on adenosine's use as an antiarrhythmic have not demonstrated pediatrics-specific problems that would limit the usefulness of this medication in the pediatric population. [2, 6, 8, 16, 22, 23, 24, 50, 51]

The safety and effectiveness of adenosine, when used as an adjunct to myocardial perfusion imaging, have not been established in patients less than 18 years of age [85].

Geriatrics

Appropriate studies on the relationship of age to the effects of adenosine have not been performed in the geriatric population. However, geriatrics-specific problems that would limit the usefulness of this medication in the elderly are not expected [11].

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Carbamazepine

(may increase heart block caused by adenosine 1, 3, 15, 21)

Dipyridamole

(potentiates the effects of adenosine by inhibiting cellular uptake; dosage reduction is recommended 1, 2, 3, 9, 15, 21, 38, 85)

Xanthines, especially caffeine and theophylline

(antagonize the effects of adenosine; larger doses of adenosine may be required or alternative therapy should be used 85, 57, 1, 2, 3, 9, 15, 21, 46)

(concurrent use with xanthines may invalidate test when adenosine is used as a diagnostic aid 53, 54)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problem exists

>> Atrioventricular (AV) block, pre-existing second or third degree without pacemaker 1, 3, 35, 85

(risk of complete heart block)

Risk-benefit should be considered when the following medical problems exist

Angina pectoris, unstable 85

(may increase risk of developing fatal cardiac arrest, life threatening ventricular arrhythmias, and myocardial infarction)

Asthma 1, 3, 7, 9, 35, 45, 85

(although problems have not been reported with adenosine injection, inhaled adenosine has been reported to cause bronchoconstriction in asthmatic patients but not in normal individuals)

Hypotension 85

(patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, or uncorrected hypovolemia are at a greater risk of hypotensive complications)

Sensitivity to adenosine 1, 3, 85

>> Sick sinus syndrome 1, 3, 9, 35, 42, 49, 85

(sinus node recovery time prolonged; sinus bradycardia, sinus pause, or sinus arrest may occur)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):

>> Blood pressure and

>> Heart rate

(determinations recommended every 15 to 30 seconds for several minutes 13)

>> Electrocardiogram (ECG) 12

(recommended to confirm efficacy of adenosine)

Side/Adverse Effects

Note: Side/adverse effects are usually transient, generally lasting less than one minute. 1, 7, 9, 48 However, loss of consciousness and prolonged hypotension have been reported rarely. 42

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:

Those indicating need for medical attention

Incidence more frequent

Arrhythmias, new 1, 2, 4, 5, 6, 7, 9, 44, 47, 48, 49 , including premature ventricular contractions, atrial premature contractions, sinus bradycardia, sinus tachycardia, and skipped beats 1, 9; chest, 1, 3, 5, 21, 44, 48 jaw, throat, or arm pain 54; dyspnea (shortness of breath) 1, 2, 3, 4, 5, 6, 7, 9, 44

Note: New arrhythmias usually last only a few seconds 3, 5, 7.

Incidence rare

Heart block, first-, second-, or third-degree 1, 3, 4, 5, 14, 49

Note: Heart block is usually of short duration 3, 49 and may occur more frequently in patients who receive a rapid intravenous dose of adenosine 53.

Episodes of transient asystole have been reported 49.

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Flushing of face 1, 2, 3, 5, 6, 7, 9, 21, 47, 48, 49, 54; gastrointestinal discomfort 85 (abdominal or stomach pain; diarrhea; nausea ; vomiting); headache 1, 3, 5, 6, 9, 54

Incidence less frequent

Cough 9; dizziness or lightheadedness 1, 3; nausea 1, 3, 6, 9; numbness or tingling in arms 1, 3

General Dosing Information

If high-level heart block occurs after one dose of adenosine, it is recommended that additional doses not be given 1, 3.

The effect usually resolves quickly because of adenosine's short duration of action 1.

Rapid intravenous administration of adenosine is recommended for the treatment of paroxysmal supraventricular tachycardia in order to achieve the desired negative chronotropic and dromotropic activity 9.

Slow administration may result in an increase in heart rate in response to vasodilation 9.

During myocardial perfusion imaging, adenosine should be given as a continuous peripheral intravenous infusion 85.

Safety and efficacy of adenosine administered by the intracoronary route have not been established 85.

For treatment of adverse effects and/or overdose

Because of adenosine's extremely short duration of action, adverse effects are usually self-limiting 1, 3, 15, 85.

Treatment of prolonged adverse effects should be individualized 1, 3.

Xanthines (e.g., caffeine, theophylline) are competitive antagonists of adenosine 1, 3, 85.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

ADENOSINE INJECTION

Usual adult dose

Antiarrhythmic¾Intravenous, rapid (over one to two seconds), 6 mg 1, 3, 15.

If the first dose is not effective within one to two minutes, a rapid intravenous dose of 12 mg may be given, and repeated if necessary 1, 3, 15.

Diagnostic aid adjunct *¾Intravenous, 140 mcg (0.14 mg) per kg of body weight per minute given for six minutes. 85, 26, 27, 28, 29, 30, 31

Note: The following adenosine infusion nomogram may be used to determine the appropriate infusion rate corrected for total body weight 85 :

Patient Weight kg	Patient Weight lbs	Infusion Rate mL/min
45	99	2.1
50	110	2.3
55	121	2.6
60	132	2.8
65	143	3.0
70	154	3.3
75	165	3.5
80	176	3.8
85	187	4.0
90	198	4.2

This nomogram was derived from the following general formula: 0.140 (mg/kg/min) ´ total body weight (kg) adenosine concentration (3 mg/mL) = infusion rate (mL/min) 85.

In patients at increased risk for side/adverse effects, the dose may be titrated from 50 mcg (0.05 mg) per kg of body weight per minute up to 140 mcg (0.14 mg) per kg of body weight per minute at one-minute intervals. 25, 53, 54, 55 If side/adverse effects are severe, the infusion rate may be reduced to a more tolerable level. 35, 53 Doses of 75 and 100 mcg (0.075 and 0.1 mg) per kg of body weight per minute can adequately increase coronary blood flow. 35

Thallium is physically compatible with adenosine and may be injected directly into the adenosine infusion set 85 ; however, it has been suggested that thallium should be injected into a separate vein 53.

Thallium is usually injected at the three- or four-minute mark (midpoint) of the adenosine infusion 85, 26, 29, 30, 53.

Note: To ensure that adenosine injection reaches the systemic circulation, it should be given directly into a vein or, if given into an intravenous line, be given as proximally as possible and followed by a rapid saline flush 1, 3, 85.

Usual adult prescribing limits

Up to 12 mg per dose 1, 3.

Usual pediatric dose

Antiarrhythmic¾Intravenous, 50 mcg (0.05 mg) per kg of body weight. Dose may be increased in increments of 50 mcg (0.05 mg) per kg of body weight given every two minutes up to a maximum dose of 250 mcg (0.25 mg) per kg of body weight. 50

Diagnosis and treatment of supraventricular tachycardia in neonates¾Intravenous, 100 mcg (0.1 mg) to 300 mcg (0.3 mg) per kg of body weight 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80

Diagnostic aid adjunct¾Safety and effectiveness of adenosine in patients less than 18 years of age have not been established 85.

Strength(s) usually available

U.S.¾3 mg per mL (Rx)[Adenocard]

3 mg per mL (Rx)[Adenoscan (20 mL and 30 mL vials) (sodium chloride (9 mg/mL)) (water for injection)]

Canada¾Not commercially available.

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Do not refrigerate 1, 85.

Protect from freezing.

Stability:

Because adenosine injection contains no preservatives, any unused portion should be discarded 1, 3, 85.

Crystallization may occur if adenosine injection is refrigerated. If that occurs, the crystals may be dissolved by warming the injection to room temperature. The solution must be clear before use. 1, 3, 85.

References

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85 Product Information: AdenoscanÒ, adenosine. Fujisawa Healthcare, Inc., Deerfield, IL, (PI revised 1/1999) reviewed 8/2000.