Mechanism of Action

Adenosine produces a direct negative chronotropic, dromotropic and inotropic effect on the heart, presumably due to A1-receptor agonism, and produces peripheral vasodilation, presumably due to A2-receptor agonism. The net effect of adenosine in humans is typically a mild to moderate reduction in systolic, diastolic and mean arterial blood pressure associated with a reflex increase in heart rate. Rarely, significant hypotension and tachycardia have been observed.

Pharmacokinetics

Intravenously administered adenosine is rapidly cleared from the circulation via cellular uptake, primarily by erythrocytes and vascular endothelial cells. This process involves a specific transmembrane nucleoside carrier system that is reversible, nonconcentrative, and bidirectionally symmetrical. Intracellular adenosine is rapidly metabolized either via phosphorylation to adenosine monophosphate by adenosine kinase, or via deamination to inosine by adenosine deaminase in the cytosol. Since adenosine kinase has a lower K_M and V_max than adenosine deaminase, deamination plays a minor role only when cytosolic adenosine saturates the phosphorylation pathway. Inosine formed by deamination of adenosine can leave the cell intact or can be degraded by hypoxanthine, xanthine, and ultimately uric acid. Adenosine monophosphate formed by phosphorylation of adenosine is incorporated into the high-energy phosphate pool. While extracellular adenosine is primarily cleared by cellular uptake with a half-life of less than 10 seconds in whole blood, excessive amounts may be deaminated by an ecto-form of adenosine deaminase. As adenosine requires no hepatic or renal function for its activation or inactivation, hepatic and renal failure would not be expected to alter its effectiveness or tolerability.

Clinical Trials

In two crossover comparative studies involving 319 subjects who could exercise (including 106 healthy volunteers and 213 patients with known or suspected coronary disease), adenosine and exercise thallium images were compared by blinded observers. The images were concordant for the presence of perfusion defects in 85.5% of cases by global analysis (patient by patient) and up to 99% of cases based on vascular territories. In these two studies, 193 patients also had recent coronary arteriography for comparison (healthy volunteers were not catheterized). The sensitivity (true positive adenosine divided by the number of patients with positive (abnormal) angiography) for detecting angiographically significant disease (≥50% reduction in the luminal diameter of at least one major vessel) was 64% for adenosine and 64% for exercise testing, while the specificity (true negative divided by the number of patients with negative angiograms) was 54% for adenosine and 65% for exercise testing. The 95% confidence limits for adenosine sensitivity were 50% to 78% and for specificity were 27% to 71%.

INSTRUCTIONS AND USAGE

Intravenous adenosine injection is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately (See WARNINGS).

CONTRAINDICATIONS

Intravenous adenosine injection should not be administered to individuals with:

1. Second- or third-degree AV block (except in patients with a functioning artificial pacemaker).
2. Known or suspected bronchospastive or bronchospastic lung disease (e.g., asthma).
3. Known hypersensitivity to adenosine.

WARNINGs

Fatal Cardiac Arrest, Ventricular Arrhythmias, and Myocardial Infarction

Fatal and nonfatal cardiac arrest, sustained ventricular tachycardia (malignant reversion), and myocardial infarction have occurred following adenosine infusion. Avoid use in patients with symptoms or signs of acute myocardial ischemia, for example, unstable angina or cardiovascular instability; these patients may be at greater risk of serious cardiovascular reactions to adenosine. Appropriate resuscitative measures should be available.

Sinusoidal and Atrioventricular Nodal Block

Adenosine injection 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. Adenosine can cause sinus bradycardia. Adenosine should be used with caution in patients with preexisting 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 injection 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, pectoral 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 lasted spontaneously within several minutes, but in some cases, hypertension lasted for several hours.

Bronchoconstriction

Adenosine injection is a respiratory stimulant (probably through activation of cardiac body chemoreceptors), and intravenous administration in man has been shown to increase minute ventilation (Ve) and reduce arterial PCO2, 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.

Atrial fibrillation

Atrial fibrillation has been reported in patients (with and without a history of atrial fibrillation) undergoing myocardial perfusion imaging with adenosine infusion. In these cases, atrial fibrillation began 1.5 to 3 minutes after initiation of adenosine, lasted for 15 seconds to 6 hours, and spontaneously converted to normal sinus rhythm.

PRECAUTIONS

Drug Interactions

Intravenous adenosine injection has been given with other cardiovascular 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 vasodepressor effects of adenosine are inhibited by adenosine receptor antagonists, such as methyloxanthines (e.g., caffeine and theophylline). The safety and efficacy of adenosine in the presence of these agents has not been systematically evaluated.

The vasodepressor effects of adenosine are potentiated by nucleoside transport inhibitors, such as diprydamole. The safety and efficacy of adenosine in the presence of diprydamole has not been systematically evaluated.

C_{6}H_{10}N_{2}O_{6} 267.24

Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in alcohol.

CLINICAL PHARMACOLOGY

Mechanism of Action

Adenosine is a potent vasodilator in most vascular beds, except in renal afferent arterioles and hepatic veins where it produces vasoconstriction. Adenosine is thought to exert its pharmacological effects through activation of purine receptors (cell-surface A1 and A2 adenosine receptors). Although the exact mechanism by which adenosine receptor activation relaxes vascular smooth muscle is not known, there is evidence to support both inhibition of the slow inward calcium current reducing calcium uptake, and activation of adenylate cyclase through A2 receptors in smooth muscle cells. Adenosine may also lessen vascular tone by modulating sympathetic neurotransmission. The intracellular uptake of adenosine is mediated by a specific transmembrane nucleoside transport system. Once inside the cell, adenosine is rapidly phosphorylated by adenosine kinase to adenosine monophosphate, or deaminated by adenosine deaminase to inosine. These intracellular metabolites of adenosine are not vasoactive.

Myocardial uptake of thallium-201 is directly proportional to coronary blood flow. Since adenosine significantly increases blood flow in normal coronary arteries with little or no increase in stenotic arteries, adenosine causes relatively less thallium-201 uptake in vascular territories supplied by stenotic coronary arteries i.e., a greater difference is seen after adenosine between areas supplied by normal and areas supplied by stenotic vessels than is seen prior to adenosine.

Adenosine produces a direct negative chronotropic, dromotropic and inotropic effect on the heart, presumably due to A1-receptor agonism, and produces peripheral vasodilation, presumably due to A2-receptor agonism. The net effect of adenosine in humans is typically a mild to moderate reduction in systemic, diastolic and mean arterial blood pressure associated with a reflex increase in heart rate. Rarely, significant hypotension and tachycardia have been observed.
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.

Central Nervous System
Dizziness; emotional instability; tremors

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
Fatality, heart arrest, myocardial infarction, ventricular arrhythmia

Central Nervous System
Seizure activity, including tonic clonic (grand mal) seizures, and loss of consciousness

Digestive
Nausea and vomiting

Respiratory
Respiratory arrest, throat tightness

To report SUSPECTED ADVERSE REACTIONS, contact Sagent Pharmaceuticals, Inc. at 1-866-625-1618 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE
The half-life of adenosine is less than 10 seconds and side effects of adenosine (when they occur) usually resolve rapidly when the infusion is discontinued, although delayed or persistent effects have been observed. Methyloxanthines, 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 to 125 mg slow intravenous injection) was needed to abort adenosine side effects in less than 2% of patients.

DOSAGE AND ADMINISTRATION
For intravenous infusion only.

Adenosine injection 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 injection). 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 injection administered by the intracoronary route have not been established.

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

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Infusion Rate (mg/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1</td>
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<tr>
<td>30</td>
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<td>80</td>
<td>4</td>
</tr>
<tr>
<td>90</td>
<td>4.5</td>
</tr>
</tbody>
</table>

This nomogram was derived from the following general formula:

\[
\text{Infusion Rate (mg/kg/min)} = \frac{250 \times \text{Weight (kg)}}{\text{Body Surface Area (m²)}}
\]

Adenosine concentration (3 mg/mL)

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED
Adenosine Injection, USP is supplied as 20 mL and 30 mL single-dose vials of sterile, nonglycoextran solution in normal saline as follows:

NDC Adenosine Injection, USP (3 mg per mL) Package Factor
25021-307-20 60 mg per 20 mL Single-Dose Vial 1 vial per carton
25021-307-21 60 mg per 20 mL Single-Dose Vial 10 vials per carton
25021-307-30 90 mg per 30 mL Single-Dose Vial 1 vial per carton
25021-307-31 90 mg per 30 mL Single-Dose Vial 10 vials per carton

Storage Conditions
Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F). [See USP Controlled Room Temperature.] Do not refrigerate as crystallization may occur. If crystallization has occurred, dissolve crystals by warming to room temperature. The solution must be clear at the time of use. Discard unused portion.

Sterile, Nonglycoextran, Preservative-free.
The container closure is not made with natural rubber latex.