

# Supraesophageal Signs of GERD Tricky to Treat

BY SHARON WORCESTER

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ORLANDO, FLA. — Supraesophageal manifestations of reflux disease pose a treatment challenge, Reza Shaker, M.D., said at the annual meeting of the American College of Gastroenterology.

There is a misperception that when reflux is treated, other related disorders—such as laryngitis—will disappear as well, but that's not always the case, said Dr.

Shaker, chief of gastroenterology and hepatology at the Medical College of Wisconsin, Milwaukee.

When faced with a patient who has lingering laryngitis, throat clearing, and other conditions presumed to be associated with gastroesophageal reflux disease, he recommends the following:

► **Interview the patient carefully.** A thorough history is imperative for ensuring the correct diagnosis. Most patients won't present with cut-and-dried signs

and symptoms of GERD. More often, there is a little redness in the area of the supraesophageal structures. Studies show that the presence or absence of symptoms may not be as specific for diagnosis as previously thought.

► **Evaluate the therapeutic options.** Reevaluate the use and value of therapy; the treatment must be tailored to individual patient needs. Although some patients need simple acid suppressive therapy, others with mild disease could respond well to reflux precautionary measures, such as having an empty stomach at bedtime, he said. Others need a combination approach, and still others will require surgery.

Surgeons, however, are increasingly requiring that patients have shown a prior response to medical therapy, indicating that the diagnosis is correct.

In evaluating the effectiveness of the current therapy, check to see if acid has been adequately suppressed. The use of esophageal acid monitoring can be helpful. Also, ensure proper timing of medication dosing. "How many patients do we encounter who take their medicine at the

wrong time in the morning and then drink a cup of coffee?" he asked.

In addition, confirm that the dosage is adequate.

► **Recommend the use of precautionary measures.** A key difference between the esophageal and supraesophageal structures is that nonacidic and minimally acidic materials can cause injury to the supraesophageal structures. Having an empty stomach before bedtime is an important preventive strategy.

Patients should be evaluated for delayed gastric emptying, which occurs in about 40% of GERD patients. This may not be important when dealing with complications of the esophagus in this age of proton pump inhibitors, but it can create a reservoir for acid and nonacid material that can be harmful to the supraesophageal area.

► **Consider referral to an ear, nose, and throat specialist.** Remember that reflux is not exclusive for aerodigestive tract disorder, and consider referring patients who fail to respond to therapy to an ENT physician for additional evaluation, he advised. ■

## 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.

#### Sinotrial 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<sub>E</sub>) and reduce arterial P<sub>CO2</sub> causing respiratory alkalosis. 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 Adenoscan 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 Chromosome 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	35%	SI 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%	Parosmia	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; 1-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.

#### DOSE 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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## Combo Therapy Cuts Risk of Rebleeding in Clotted Ulcers

BY JEFF EVANS

Senior Writer

ORLANDO, FLA. — A combination of endoscopic and medical treatment of bleeding peptic ulcers with adherent clots results in a significantly lower rebleeding rate than does medical therapy alone, according to findings from a metaanalysis of randomized clinical trials.

Peptic ulcers with adherent clots are problematic because of highly variable rebleeding rates that range from 8% to 36%, Charles J. Kahi, M.D., said at the annual meeting of the American College of Gastroenterology.

In the metaanalysis, patients who received combination therapy had about a 60% lower risk of rebleeding than did those who received medical therapy alone.

During a search of four databases (Medline, Embase, Thomson Biosis, and Brown University Cochrane Center's Central) for trials published during 1966-2003, Dr. Kahi and his colleagues located six randomized trials that compared the combination of endoscopic and medical therapies with medical therapy alone for bleeding peptic ulcers with adherent clots. They contacted the primary authors of the studies, obtained the raw data from each of the trials, and combined all the data into one database.

Four studies were fully published reports, and two were published in abstract

form. The six studies included a total of 240 patients.

Overall, three of the trials found no difference in rebleeding rates, whereas the remaining three trials found that the combination treatment gave a significantly lower rebleeding rate than did medical therapy alone, said Dr. Kahi of Indiana University, Indianapolis.

In the four fully published studies, rebleeding occurred in significantly fewer patients (8% [5 of 61 patients]) who received endoscopic plus medical therapy than in those who received medical therapy alone (25% [21 of 85 patients]).

The two groups did not differ in their length of hospital stay, number of transfusions, or mortality.

In each of the studies, endoscopic therapy consisted of clot removal and treatment of the underlying lesion with thermal energy, electrocoagulation, and/or injection of sclerosing agents. Medical therapy included supportive care, ICU monitoring, and acid suppressive medications, such as histamine-2 receptor antagonists or proton-pump inhibitors.

Dr. Kahi cautioned that the meta-analysis might include publication bias because reports of negative studies might not have been published. He also noted that the trials included patients from the United States, Hong Kong, Spain, and South Korea, who may have different responses to medical therapy because of genetic differences. ■

**Patients who received a combination of endoscopic and medical treatment had a 60% lower risk of rebleeding than those who received medical therapy alone.**