Asystole following regadenoson infusion in stable outpatients

Jeffrey Rosenblatt, MD, FACC, FASNC,[a,b] Deirdre Mooney, MD, MPH,[a] Timothy Dunn, CNMT, NMTCB,[b] and Mylan Cohen, MD, MPH, FACC, FASNC[a,b]

[a] Maine Medical Center, Department of Cardiac Services, Tufts University School of Medicine, Portland, ME
[b] Maine Medical Partners Maine Health Cardiology, South Portland, ME

Received Jan 15, 2014; accepted Mar 25, 2014
doi:10.1007/s12350-014-9898-0

Regadenoson is a selective A2A receptor agonist approved for use as a pharmacologic stress agent for myocardial perfusion imaging after several multicenter trials demonstrated its equivalence in diagnostic accuracy for the detection of coronary artery disease and a decreased incidence of serious side effects as compared to adenosine. Recently, the FDA released a safety announcement advising of the rare but serious risk of heart attack and death associated with regadenoson and adenosine in cardiac stress testing, particularly in patients with unstable angina or cardiovascular instability. We report two cases of asystole with hemodynamic collapse in stable outpatients soon after receiving a standard regadenoson injection. The prevalence of potentially life threatening bradycardia, including asystole, associated with the use of regadenoson may be greater than previously expected. These cases highlight the need for cardiac stress labs to anticipate the potential for serious side effects with all patients during the administration of coronary vasodilators. (J Nucl Cardiol 2014;21:862–8.)

Key Words: A2A adenosine receptor agonists • pharmacologic stress • vasodilator stress • adenosine

See related editorial, pp. 871–876

INTRODUCTION

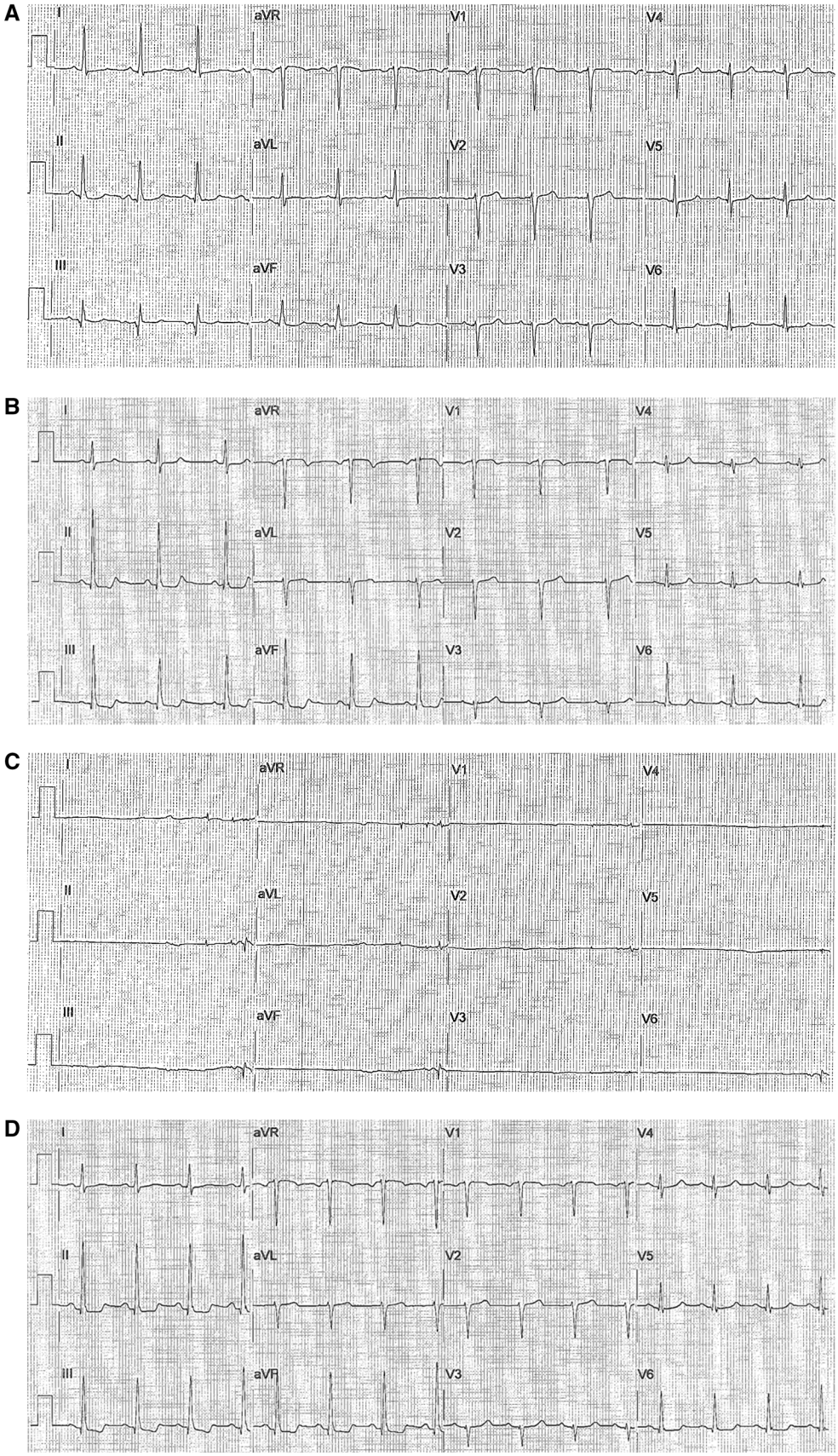
Regadenoson is a selective A2A receptor agonist approved for use as a pharmacologic stress agent for myocardial perfusion imaging (MPI) in 2008 after several multicenter trials demonstrated its equivalence to adenosine in diagnostic accuracy for the detection of coronary artery disease (CAD).[1,2] Based on the molecule's designed selectivity to the A2A receptor compared to the A1, A2B, and A3 receptors, fewer undesirable side effects such as flushing, dyspnea, hypotension, and bronchospasm were expected. Results of the Advance MPI Trial reported the incidence of serious side effects was significantly lower in the regadenoson vs the adenosine group.[3] Based on a tenfold reduction in affinity for the A1 receptor, the incidence of symptomatic bradycardia was also expected to be minimal. Phase 3 trials did not report episodes of high grade atrioventricular (AV) block. However, post-marketing surveillance has identified a case of complete heart block and a case of asystole.[3,4] Recently, the FDA released a safety announcement advising of the rare but serious risk of heart attack and death associated with regadenoson and adenosine in cardiac stress testing, particularly in patients with unstable angina or cardiovascular instability.[5-7] We report two cases of life threatening asystole with hemodynamic collapse in stable outpatients soon after receiving a standard regadenoson injection.

Reprint requests: Jeffrey Rosenblatt, MD, FACC, FASNC, Maine Medical Center, Department of Cardiac Services, Tufts University School of Medicine, 22 Bramhall St, 119 Gannett Drive, Portland, ME 04106; *jrosedeb@maine.rr.com, Jeffrey.Rosenblatt@mhcardio.com*

1071-3581/$34.00

Case 1

A 65-year-old female with a history of heart failure with preserved ejection fraction, hypertension,


A
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
B
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
C
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
D
I
aVR
V1
V4
II
aVL
V2
V5
III
aVR
V3
V6

◀ **Figure 1.** (**A**) Case 1. The baseline electrocardiogram shows normal sinus rhythm without evidence of specific conduction abnormalities or prior infarct. (**B**) Case 1. Electrocardiogram from 30 seconds after administration of regadenoson demonstrates sinus rhythm with 0.5 mm downsloping ST depression in leads II, III, and aVF. (**C**) Case 1. Electrocardiogram from 45 seconds after infusion of regadenoson which demonstrates severe sinus bradycardia with first degree atrioventricular delay and subsequent development of asystole. Subtle rhythmical undulation of the baseline corresponds to chest compressions from cardiopulmonary resuscitation. Case 1. Electrocardiogram from 8 minutes and 20 seconds after infusion showing sinus rhythm at 86 bpm with 1 mm horizontal ST depression in leads II, III, and aVF.

dyslipidemia, bilateral knee osteoarthritis, and diabetes mellitus was seen in follow-up for CAD 3 years after drug eluting stent placement in the left anterior descending, right, and posterior descending coronary arteries. Prior stress tests had all been exercise echocardiograms, the most recent of which was over 3 years ago, prior to her PCI. Due to easy fatigability, pharmacologic MPI was requested to evaluate for ischemia. The patient's medications at the time of evaluation were carvedilol, lisinopril, aspirin, rosuvastatin, fenofibrate, furosemide, fish oil, liraglutide, subcutaneous insulin, ferrous sulfate, and levothyroxine. Her baseline electrocardiogram (ECG) showed normal sinus rhythm with nonspecific ST-T wave abnormalities and nondiagnostic q waves in the inferior leads (Figure 1A). Carvedilol was held the day of the exam.

Utilizing a standard protocol, 0.4 mg of regadenoson was injected over 15 seconds while the patient was walking at a 1 mph on a 0% incline treadmill. Within seconds, she felt lightheaded, her heart rate (HR) decreased from 87 to 60 bpm, and her blood pressure (BP) from 144/98 to 103/40 mm Hg. Thirty seconds after regadenoson infusion, downsloping ST depression were noted in leads II, III, and aVF (Figure 1B). Forty-five seconds after infusion, she developed severe sinus bradycardia with first degree atrioventricular delay and subsequent asystole (Figure 1C). Cardiopulmonary resuscitation was performed for 2 minutes. Circulation was restored prior to the administration of aminophylline or other medications. She was pale and diaphoretic yet alert, oriented and without focal neurologic deficit. Intermittent nonsustained ventricular tachycardia was noted. Over 8 minutes after infusion, she continued to demonstrate nonspecific ST depression (Figure 1D). She was emergently transported for inpatient monitoring.

Upon arrival to the hospital, she was hemodynamically stable and her serum electrolytes, creatinine and CK-MB were within normal limits. Troponin T was undetectable. Thyroid stimulating hormone level was within normal limits 3 months prior to admission. Stress imaging was performed and demonstrated a subtle anterior and anteroseptal defect (Figure 2A). Coronary angiography showed modest progression of native coronary artery disease, patent stents, mildly elevated filling pressures, and normal left ventricular systolic function (Figure 2B, C). Subsequent merging of the outpatient and inpatient SPECT scans suggested no significant ischemia. She was managed with an adjusted medical regimen.

In follow-up 1 week later, she was doing well except for some mild sternal discomfort which was attributed to the CPR. Twenty-four-hour Holter monitoring revealed rare supraventricular ectopic beats and one ventricular ectopic beat. Two months after her stress test, was back working full time.

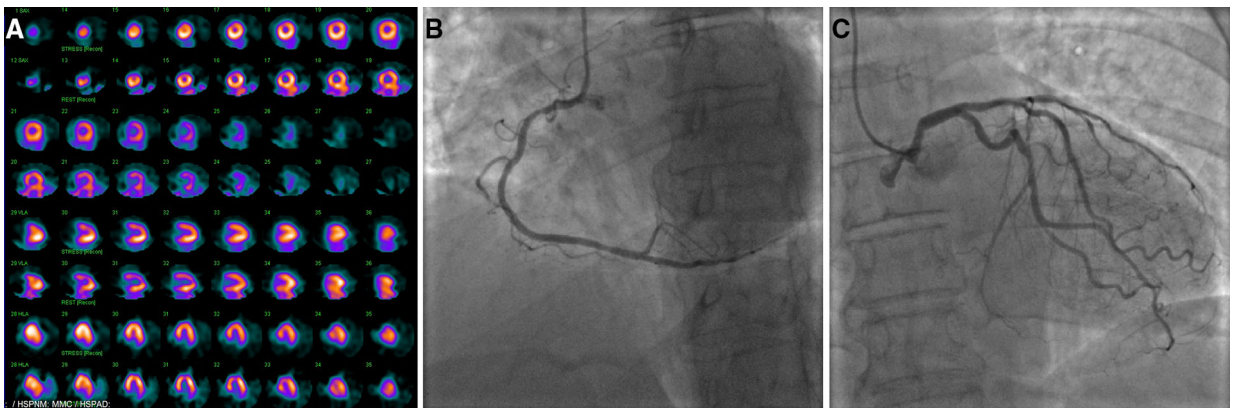
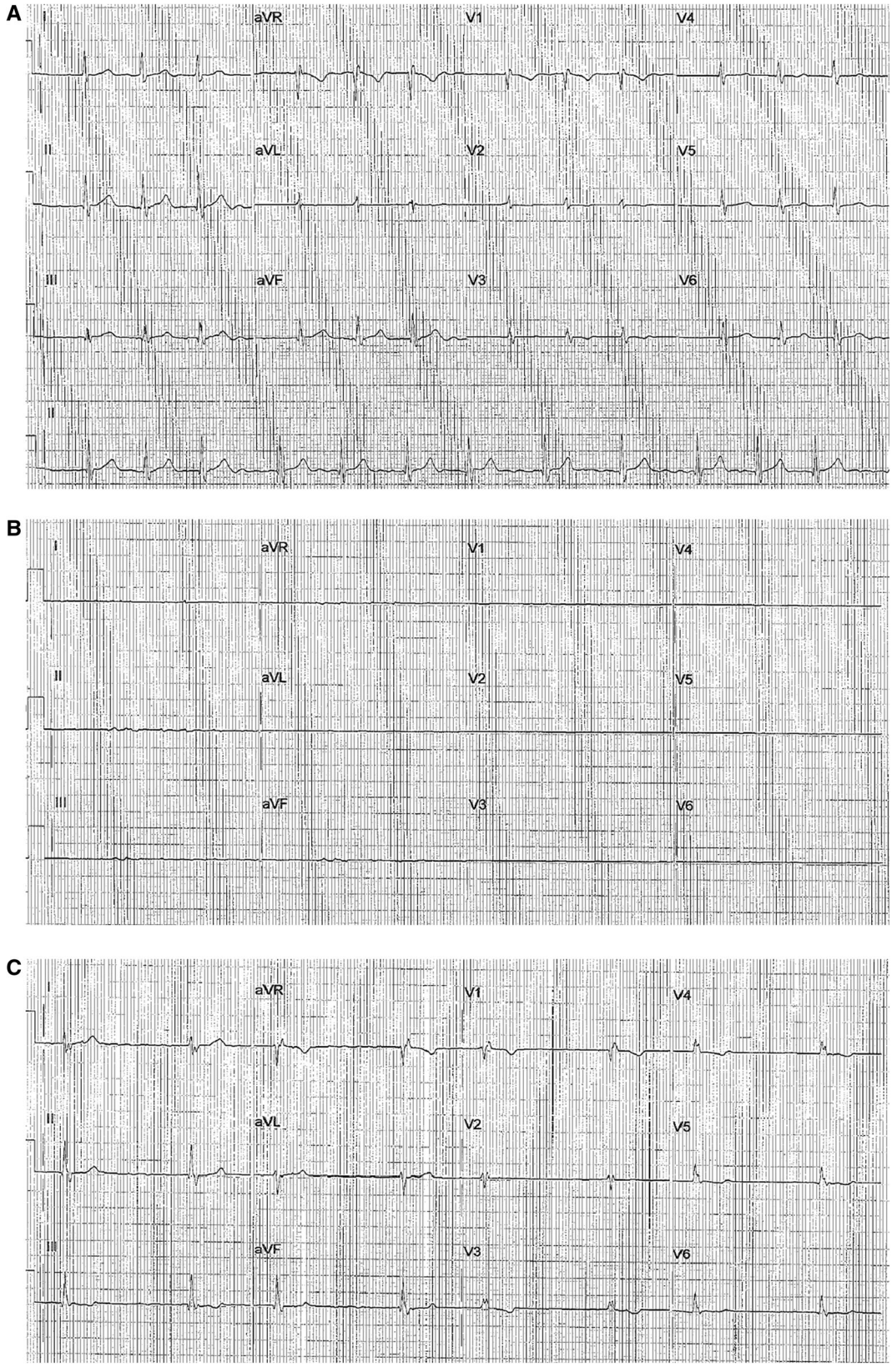


Figure 2. (**A**) Case 1. Merged outpatient and inpatient nuclear perfusion rest and stress images demonstrating a fixed subtle anterior and anteroseptal perfusion abnormality. (**B**) Case 1. Diagnostic coronary angiography of the right coronary artery (RCA) demonstrating patent RCA stent with a 50% stenosis proximal to the previously placed stent. (**C**) Case 1. Diagnostic coronary angiography of the left coronary system demonstrating a patent LAD stent, a long 50% stenosis proximal to the mid-LAD stent, and a 70% stenosis in the proximal portion of a modest-sized bifurcating diagonal branch.


A
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II
B
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
C
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

◀ **Figure 3.** (**A**) Case 2. The baseline electrocardiogram shows atrial fibrillation with an average ventricular rate of 72 bpm. (**B**) Case 2. Electrocardiogram from 42 seconds after infusion of regadenoson demonstrating asystole. (**C**). Case 2. Electrocardiogram from 4 minutes after administration of regadenoson shows atrial fibrillation with an estimated ventricular rate of 39 bpm.

Case 2

A 73-year-old male with history of hypertension, paroxysmal atrial fibrillation, mild obstructive sleep apnea effectively treated with continuous positive airway pressure ventilation, and osteoarthritis was referred for regadenoson Tc99m sestamibi SPECT to evaluate 2 months of progressive dyspnea on exertion and fatigue. Stress echocardiography 8 years prior had been unremarkable. His baseline medications included aspirin, fish oil, finasteride, folic acid, and vitamins A, C, and B12. He held his atenolol the morning of the test.

The resting ECG showed atrial fibrillation at 72 bpm (Figure 3A). Thirty seconds after injection of 0.4 mg of regadenoson while at rest, he felt warm and lightheaded. The ECG at that time showed atrial fibrillation with a ventricular rate of 69 bpm and was without significant change from baseline. Forty-two seconds after injection, he became unresponsive and continuous ECG monitoring showed asystole (Figure 3B). After several chest compressions, circulation returned with a ventricular rate in the 30-40 bpm range. He was responsive, diaphoretic, and had borderline hypotension. His consciousness waxed and waned for several seconds. Aminophylline 75 mg IV and a normal saline bolus were administered. Two minutes after regadenoson administration, there was one further abrupt asystolic event that spontaneously resolved with restoration of atrial fibrillation with a ventricular response of 30-40 bpm (Figure 3C). No ischemic changes were noted on the ECG. Normal perfusion was demonstrated with Tc99m sestamibi SPECT. He was monitored in the cardiology clinic until complete resolution of his symptoms. He remained hemodynamically stable and neurocognitively intact, and was released with close outpatient follow-up.

One week later, he reported improved exertional capacity on adjusted rate controlling agents for his atrial fibrillation. Four months later, after several weeks of therapeutic oral anticoagulation, he underwent direct current cardioversion to restore sinus rhythm. One month after cardioversion, he reported intermittent mild palpitations and was noted to be back in atrial fibrillation. He elected to continue with a rate control and anticoagulation strategy.

DISCUSSION

The receptor affinity profile for the A2A receptor agonist regadenoson was intended to affect coronary vasodilation by achieving coronary hyperemia while minimizing undesirable side effects associated with activation of other adenosine receptors. Despite no episodes of serious bradycardia during large-scale multicenter clinical trials, multiple cases of high grade AV block have been identified since its approval by the FDA.[3,4] Recently, the FDA has released warnings of heart attack and death during vasodilator stress testing as reported in Table 1.[5] Due to limitations in the data, it was unable to discern a difference in risk between regadenoson and adenosine. The warning highlights that some cases of myocardial infarction and death occurred in patients with pre-existing unstable angina or cardiovascular instability.

We report two cases of asystole and hemodynamic collapse soon after regadenoson administration necessitating emergent intervention and medical stabilization. In the combined experience of our three outpatient cardiology offices over 18 months (April 2012-September 2013), 2,732 doses of regadensoson have been administered as a cardiac stress agent and two patients have developed asystole and hemodynamic collapse shortly after injection. All of these patients were clinically stable and presenting for outpatient testing. The two episodes were separated by 2 months, and thus are unlikely to be due to a contaminated batch of regadensoson, technetium, or medical supplies. In these same offices, it is conservatively estimated that over 9,000 adenosine MPI studies were done over 10 years (2003-2012) without a single case of hemodynamic collapse or asystole.

The exact mechanism by which regadenoson could cause profound bradycardia or asystole remains uncertain. Adenosine is believed to exert its cardiac electrophysiologic effects mainly through activation of A1 adenosine receptor and to have both direct and indirect effects in the supraventricular tissues but only indirect effects in the ventricle.[8] In the aforementioned cases, the mechanism cannot simply be explained by AV block via activation of the A1 receptor since both patients developed apparent atrial standstill with no reliable ventricular escape. It has been postulated that

Table 1. FDA reported cases of death and MI

	Adenosine (5/18/1995)	Regadenoson (6/24/2008)
Myocardial infarction	6	26
Death	27	28

FDA approval date of the pharmacologic agents are listed in parentheses. Data from the FDA Adverse Event Reporting System (FAERS) database.[5]

the mechanism may be due to an accentuated vasovagal response (Bezold Jarish Reflex) in susceptible individuals, possibly due to A2A receptor activation at the level of the hypothalamus resulting in excessive bradycardia and hypotension.[9]

In a recent European review of over 1,764 consecutive patients receiving regadenoson as a stress agent, two patients were reported to have developed transient asystole.[10] The only significant variable associated with any adverse event was significant drop of HR and BP after Regadenoson injection. However, the very low incidence in that study (0.0013) would make it difficult to determine whether there is a particularly unique risk factor for developing asystole. A2A adenosine receptors are expressed in human supraventricular myocardium and believed to modulate spontaneous sarcoplasmic reticulum calcium release.[11] Their presence in ventricular myocytes remains controversial.[12,13] While it has been reported that there is no significant SA node or other myocardial cell effect of A2A activation, other studies have contradicted this finding and have demonstrated direct A2A effect at the level of the sarcoplasmic reticulum in SA nodal and other myocardial cells directly affecting calcium efflux and subsequent myocardial cell depolarization; however, such inhibitory effect has not yet been demonstrated.[11,14,15]

Given the 2- to 4-minute-long first phase half-life of regadenoson yet relatively short lived duration of asystole in the previously discussed cases, a vasovagal mechanism, including subsequent rebound sympathetic output through the baroreceptor reflex, seems to be the most plausible explanation.[16] Additionally, similar to the previous reported cases, our patients exhibited premonitory vasodepressor-like signs and symptoms. Furthermore, one of the patient's baseline rhythm was atrial fibrillation which would also suggest a profound vasovagal effect rather through inhibition of spontaneous SA node depolarization via activation A2A receptor in atrial myocytes.

NEW KNOWLEDGE GAINED

Asystole with hemodynamic collapse was not previously recognized as an adverse effect of regadenoson in stable patients. The risk factors for and mechanism behind these events remain undefined but might involve a heightened vasovagal response in susceptible individuals, possibly in combination with an as yet undefined effect on hypothalamic and cardiac A2A receptors.

CONCLUSION

Currently, the FDA warning on use of these cardiac nuclear stress-testing agents applies to patients with unstable angina or cardiovascular instability; however, the cases in this report represented outpatient stress tests in stable patients without angina. Until further data is available, we emphasize the importance of having readily available resuscitation equipment during and after administration of vasodilators for MPI. Staff must be trained and knowledgeable about the rare but potentially serious side effects of either of these vasodilator pharmacologic stress agents.

References

1. Iskandrian AE, Bateman TM, Belardinelli L, Blackburn B, Cerqueira MD, Hendel RC, et al. Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: Results of the ADVANCE phase 3 multicenter international trial. J Nucl Cardiol 2007;14:645-58.
2. Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE, ADVANCE-MPI Trial Investigators. Effects of age, gender, obesity, and diabetes on the efficacy and safety of the selective A2A agonist regadenoson versus adenosine in myocardial perfusion imaging integrated ADVANCE-MPI trial results. JACC Cardiovasc Imaging 2008;1:307-16.
3. Pandit A, Unzek-Freiman S. Complete heart block associated with regadenoson: A real side effect. J Nucl Cardiol 2012;19:1236-9.
4. Grady EC, Barron JT, Wagner RH. Development of asystole requiring cardiac resuscitation after the administration of regadenoson in a patient with pulmonary fibrosis receiving *n*-acetylcysteine. J Nucl Cardiol 2011;18:521-5.
5. U.S. Food and Drug Administration. Drug Safety Communications: FDA warns of rare but serious risk of heart attack and death with cardiac nuclear stress test drugs Lexiscan (regadenoson) and Adenoscan (adenosine). http://www.fda.gov/downloads/Drugs/DrugSafety/UCM375668. Accessed February 13, 2014.
6. Shah S, Parra D, Rosenstein RS. Acute myocardial infarction during regadenoson myocardial perfusion imaging. Pharmacotherapy 2013;33:90-5.
7. Hsi DH, Marreddy R, Moshiyakhov M, Luft U. Regadenoson induced acute ST-segment elevation myocardial infarction and multivessel coronary thrombosis. J Nucl Cardiol 2013;20:481-4.
8. Mustafa SJ, Morrison RR, Teng B, Pelleg A. Adenosine receptors and the heart: Role in regulation of coronary blood flow and cardiac electrophysiology. Handb Exp Pharmacol 2009;193:161-88.
9. Kang MJ, Park MS, Shin IC, Koh HC. Modification of cardiovascular response of posterior hypothalamic adenosine A(2) receptor stimulation by adenylate cylase, guanylate cyclase and by K(ATP) channel blockade in anesthetized rats. Neurosci Lett 2003;344:57-61.
10. Brinkert M, Reyes E, Walker S, Latus K, Maenhout A, Mizumoto R, et al. Regadenoson in Europe: First-year experience of regadenoson stress combined with submaximal exercise in patients undergoing myocardial perfusion scintigraphy. Eur J Nucl Med Mol Imaging 2014;41:511-21.
11. Hove-Madsen L, Prat-Vidal C, Llach-Ciruela F, Casado V, Lluis C, Bayes-Genis A, et al. Adenosine A2A receptors are expressed in human atrial myocytes and modulate spontaneous sarcoplasmic reticulum calcium release. Cardiovasc Res 2006;72:292-302.
12. Marala RB, Mustafa SJ. Immunological characterization of adenosine A2A receptors in human and porcine cardiovascular tissues. J Pharmacol Exp Ther 1998;286:1051-7.

13. Kilpatrick EL, Narayan P, Mentzer RM Jr, Lasley RD. Cardiac myocyte adenosine A2a receptor activation fails to alter cAMP or contractility: Role of receptor localization. Am J Physiol Heart Circ Physiol 2002;282:H1035-40.
14. Gao Z, Li Z, Baker SP, Lasley RD, Meyer S, Elzein E, et al. Novel short-acting A2A adenosine receptor agonists for coronary vasodilation: Inverse relationship between affinity and duration of action of A2A agonists. J Pharmacol Exp Ther 2001;298:209-18.
15. Llach A, Molina CE, Prat-Vidal C, Fernandes J, Casadó V, Ciruela F, et al. Abnormal calcium handling in atrial fibrillation is linked to up-regulation of adenosine A2A receptors. Eur Heart J 2011;32:721-9.
16. Gordi T, Frohna P, Sun HL, Wolff A, Belardinelli L, Lieu H. A population pharmacokinetic/pharmacodynamic analysis of regadenoson, an adenosine A2A-receptor agonist, in healthy male volunteers. Clin Pharmacokinet 2006;45:1201-12.