Initial Clinical Experience With Regadenoson, a Novel Selective A_{2A} Agonist for Pharmacologic Stress Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging

Robert C. Hendel, MD,* Timothy M. Bateman, MD,† Manuel D. Cerqueira, MD,‡
Ami E. Iskandrian, MD,§ Jeffrey A. Leppo, MD,‖ Brent Blackburn, PhD,¶ John J. Mahmarian, MD#

Chicago, Illinois; Kansas City, Missouri; Cleveland, Ohio; Birmingham, Alabama; Pittsfield, Massachusetts; Palo Alto, California; and Houston, Texas

OBJECTIVES	Regadenoson, a selective A_{2A} adenosine receptor agonist, was evaluated for tolerability and effectiveness as a pharmacological stress agent for detecting reversible myocardial hypoperfusion when combined with single-photon emission computed tomography (SPECT).
BACKGROUND	Adenosine and dipyridamole are nonselective adenosine agonists currently used as pharmacologic stressors. Despite proven safety, these agents often cause undesirable side effects and require a continuous infusion.
METHODS	This Phase II, multicenter, open-label trial was conducted in 36 patients who had demonstrated ischemia on a 6-min adenosine SPECT imaging study within the previous 2 to 46 days. Patients received regadenoson as a rapid intravenous bolus dose of 400 μg (n = 18) or 500 μg (n = 18). The radiopharmaceutical was then delivered within one minute. The SPECT images were acquired in a standard manner and uniformly processed at a central laboratory. Regadenoson and adenosine studies were presented in random order and interpreted blindly with a 17-segment model by three observers. Additionally, quantitative analysis was performed with 4D-MSPECT software (University of Michigan, Ann Arbor, Michigan).
RESULTS	Overall agreement for the presence of reversible hypoperfusion was 86%. The 400-μg dose was better tolerated. Overall, regadenoson was well-tolerated; side effects (e.g., chest discomfort, flushing, dyspnea) were generally mild in severity and self-limiting. High-grade atrioventricular block and bronchospasm were not observed.
CONCLUSIONS	Regadenoson is well-tolerated and seems as effective as adenosine for detecting and quantifying the extent of hypoperfusion observed with SPECT perfusion imaging. Phase III clinical trials are now underway, given the promise of regadenoson's reduced side effects and simplicity of bolus administration. (J Am Coll Cardiol 2005;46:2069–75) © 2005 by the American College of Cardiology Foundation

The continued growth and expanding role of stress myocardial perfusion imaging (MPI) mandates the development of newer pharmacologic stressor agents that are simpler to administer, have an improved side effect profile, and offer greater accessibility to patients who currently have contraindications to other agents. Although exercise remains the

preferred modality of stress testing, many patients are limited from completing a maximum stress test for a variety of reasons. Presently, almost 50% of MPI performed in the U.S. is done with pharmacologic stress testing (1,2).

Pharmacologic single-photon emission computed tomography (SPECT) MPI is most commonly performed with vasodilators to induce heterogeneous coronary blood flow patterns in the setting of a hemodynamically significant coronary artery stenosis (1–5). Adenosine and dipyridamole increase coronary blood flow by coronary arteriolar vasodilatation, through stimulation of adenosine A_{2A} receptors (6). Although these nonselective agonists have well-established safety, the activation of adenosine A_1, A_{2B}, and A_3 receptors can result in side effects, such as high-degree atrioventricular (AV) block and bronchospasm in susceptible patients (7,8). Less serious side effects, such as flushing, shortness of breath, and chest pain are bothersome in the majority of patients. In addition, the very short half-life of adenosine requires continuous infusion with a computerized pump.

> **Abbreviations and Acronyms**
> AV   = atrioventricular
> IV   = intravenous
> MPI   = myocardial perfusion imaging
> SBP   = systolic blood pressure
> SDS   = summed difference score (SSS − SRS)
> SPECT = single-photon emission computed tomography
> SRS   = summed rest score
> SSS   = summed stress score

The selective A_{2A} agonist regadenoson (Fig. 1) has a rapid onset of action and, as a result of its low affinity, a short duration of effect (9,10). Upon rapid intravenous (IV) bolus administration, regadenoson increased coronary blood flow velocity by more than 2.5-fold above baseline values for at least two minutes (11), which is adequate for radionuclide uptake. Owing to selective A_{2A} adenosine receptor stimulation and selective coronary vasodilatation, regadenoson is anticipated to have a lower incidence of significant side effects and less effect on blood pressure than adenosine (9,11), and the bolus administration eliminates the need for an infusion pump.

The current pilot study was performed to evaluate the potential use of regadenoson as a new agent for pharmacologic stress in conjunction with SPECT MPI and to determine the optimal dose for use in Phase III trials.

METHODS

Study design. This Phase II, open-label, multicenter, non-randomized pilot study was designed to evaluate the tolerability of regadenoson when administered by IV bolus for use as a pharmacological stress agent in conjunction with SPECT MPI and to determine the comparability with images obtained with adenosine. Eligible patients had documented reversible hypoperfusion on a clinically indicated 6-min adenosine MPI study performed within 2 to 46 days. No significant changes in clinical status or in medications were permitted during the interval between the adenosine scan and trial entry. Two non–weight-dependent rapid IV bolus doses were used: 400 μg in the first 18 patients and 500 μg in the second 18 patients.

Entry criteria. All imaging procedures were performed in accordance with guidelines established by the American Society of Nuclear Cardiology (12). Subjects were ≥18 years of age and, if female, were not of child-bearing potential. Institutional review board approval was obtained at each institution, and all subjects provided written informed consent.

Subjects were excluded for any of the following reasons: percutaneous coronary intervention or coronary artery bypass graft surgery within one month or documented unstable angina or acute myocardial infarction within three months of study entry, greater than first degree AV block, left bundle branch block or electronic ventricular pacemaker, decompensated heart failure, hemodynamic instabil-

ity, left ventricular ejection fraction <35%, sick sinus syndrome, cardiac transplantation, weight >250 lbs, contraindication to adenosine, currently receiving dipyridamole, or had theophylline within 24 h of either scan. Subjects were not allowed methylxanthine-containing products (e.g., caffeinated beverages) within 12 h of the study.

Stress techniques. A 6-min adenosine protocol was performed with the radiopharmaceutical injection at three minutes into the infusion. No adjunctive exercise was performed. Regadenoson was administered as a single peripheral IV bolus (<10 s), followed by a 5-ml saline flush. Tc-99m sestamibi or Tc-99m tetrofosmin (25 to 40 mCi) was then administered IV over one to two seconds, 10 to 20 s after the 5-ml saline flush.

Clinical evaluation. Baseline assessment included a complete medical history, physical examination, and laboratory evaluations including hematology, serum chemistry, and a 12-lead electrocardiogram (ECG). Blood pressure, heart and respiratory rates, and a 12-lead ECG were measured again before regadenoson administration and each minute for 10 min and then at 15, 30, and 45 min after regadenoson injection. The clinical assessment was repeated 24 to 72 min later. Tolerability was evaluated by collection of adverse events, laboratory profile, vital signs, and ECG measurements during the study, with a telephone follow-up contact 14 to 18 days after study completion. Adverse events reported by two or more subjects are included.

Imaging protocols. All commonly performed imaging protocols were permitted as long as the same radiopharmaceutical and sequence were used for both studies. The dose of the radiopharmaceutical and time to imaging between studies had to be within 10%. The SPECT acquisition was to be performed within 90 min after drug administration. Camera and acquisition parameters were to be identical between studies. All gamma cameras were dual detector systems, with a 90° orientation.

SPECT image analysis. Image data were transferred to the nuclear cardiology core laboratory, which blinded each study and performed uniform processing and display. Three readers evaluated the blinded images independently and, then, with a consensus (majority) interpretation. To reduce potential bias, three normal studies and three studies with fixed defects were added to the study group images. The
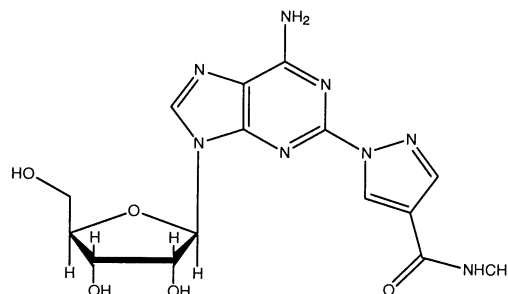

Figure 1. The molecular structure of regadenoson (CVT-3146; (1-{9-[(4S, 2R, 3R, 5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2yl]-6aminopurin-2-yl}pyrazol-4-yl)-N-methylcarboxamide).

perfusion patterns were assessed with a 17-segment model and a semi-quantitative visual score on a five-point scale from zero (normal) to four (no activity) (13). Summed scores for stress (SSS) and rest (SRS) were determined, and summed scores for differences (SDS = SSS − SRS) were calculated to represent the extent and severity of reversible perfusion defects. Additionally, a blinded, direct, same-screen comparison of the adenosine and regadenoson stress images was performed to determine relative differences in the extent and severity of ischemic defects using five regions (apical, anterior, inferior, lateral, and septal), with a single resting study (from the adenosine examination). Quantitative analysis was also done with 4D-MSPECT (University of Michigan, Ann Arbor, Michigan).

Statistical analysis. The current trial was designed as a pilot study; 18 subjects per dose group were considered adequate to provide an initial assessment of safety and tolerability. All analyses were performed with SAS Release 8.1 for Windows (SAS Institute, Cary, North Carolina) (14). Regadenoson/adenosine image agreements were determined; square tables that cross-classified patients by their adenosine and regadenoson image assessments were prepared, and the assessment pairs falling in the diagonal cells of the table were considered to be in agreement. Agreement rates were tabulated by regadenoson dose group, and 90% Clopper-Pearson confidence intervals for agreement rates were computed (15).

RESULTS

Between August 2002 and January 2003, 36 subjects were enrolled from four study sites and received one of two different doses of regadenoson, 400 μg (n = 18) or 500 μg (n = 18). Baseline demographics and medical history are summarized in Table 1. Protocols used were single day stress/rest Tc-99m sestamibi (n = 16), single day rest/stress

Table 1. Demographics and Baseline Medical History

Characteristic	All Patients (n = 36)	400 μg Regadenoson (n = 18)	500 μg Regadenoson (n = 18)
Age, yrs, mean (SD)	67.3 (9.5)	66.0 (10.5)	68.5 (8.6)
Male	27 (75)	13 (72)	14 (78)
Race			
Caucasian	25 (69)	10 (56)	15 (83)
African American	5 (14)	4 (22)	1 (6)
Hispanic	5 (14)	3 (17)	2 (11)
Asian	1 (3)	1 (6)	0 (0)
Weight, kg, mean (SD)	90.2 (19.5)	89.3 (22.2)	91.1 (17.0)
BMI, kg/m², mean (SD)	30.3 (5.9)	30.1 (5.8)	30.6 (6.2)
Pre-existing condition or procedure			
CAD	35 (97)	18 (100)	17 (94)
Hypertension	34 (94)	17 (94)	17 (94)
Angina	28 (78)	13 (72)	15 (83)
PCI	22 (61)	10 (56)	12 (67)
CABG	19 (53)	10 (56)	9 (50)

Values are n (%) unless otherwise indicated.
  BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; PCI = percutaneous coronary intervention.

Table 2. Mean Maximum Hemodynamic Changes With Regadenoson

Variable	Combined (n = 36)	400 μg Regadenoson (n = 18)	500 μg Regadenoson (n = 18)
Heart rate, beats/min*	+24 (11)	+21 (10)	+26 (12)
Systolic blood pressure, mm Hg†	−14 (10)	−11 (8)	−17 (12)
Diastolic blood pressure, mm Hg	−10 (7)	−11 (6)	−9 (8)

Values are means (SD). *Maximum heart rate observed at 1 min. †Maximum decrease in systolic blood pressure at 4 min.

Tc-99m sestamibi (n = 7), rest thallium/stress Tc-99m sestamibi (n = 12), and rest thallium/stress Tc-99m tetrofosmin (n = 1). One patient (500-μg group) was excluded from image analysis, because adenosine images were inadvertently erased and were unavailable for comparison. Time between radiopharmaceutical injection and image acquisition was 45 to 147 min.

Hemodynamic effects of regadenoson. Table 2 summarizes the hemodynamic changes that occurred with regadenoson administration. Heart rate increased for both dose groups; a greater, but not statistically different effect was observed in the 500-μg group. A heart rate >100 beats/min was noted in seven subjects (19%), with a maximum observed heart rate of 115 beats/min. The mean maximum change from baseline was 21 and 24 beats/min for the 400-μg and 500-μg groups, respectively. The maximum change occurred within approximately two minutes after regadenoson administration (Fig. 2A). Two-thirds of the patients returned to near-baseline (within 10 beats/min) heart rate within 15 min after regadenoson administration.

The mean systolic blood pressure (SBP) and diastolic blood pressure decreased in both dose groups, with 500-μg subjects showing a trend (p = 0.091) for a greater and more sustained mean decrease in SBP (Table 2; Fig. 2B). Decreases in SBP >25 mm Hg were observed in six patients: one patient in the 400-μg group and five patients in the 500-μg group. Hypotension (SBP <90 mm Hg) was noted in one subject (500-μg dose). For SBP, the greatest mean decrease from baseline occurred at three minutes after dose in the 400-μg group and at four minutes after dose in the 500-μg group.

SPECT imaging. The blinded consensus interpretation of the adenosine SPECT images confirmed the presence of myocardial ischemia in all 35 subjects, as compared with 89% (16 of 18) and 82% (14 of 17) of the scans obtained with 400 or 500 μg regadenoson, respectively. Agreement for the presence of reversible hypoperfusion was calculated on the basis of the majority of the three independent ratings, which demonstrated 89% agreement with the 400-μg dose and 76% for the 500-μg group. An example of the images obtained with adenosine and regadenoson is shown in Figure 3.

When the two regadenoson doses are combined, agreement rates between adenosine- and regadenoson-induced
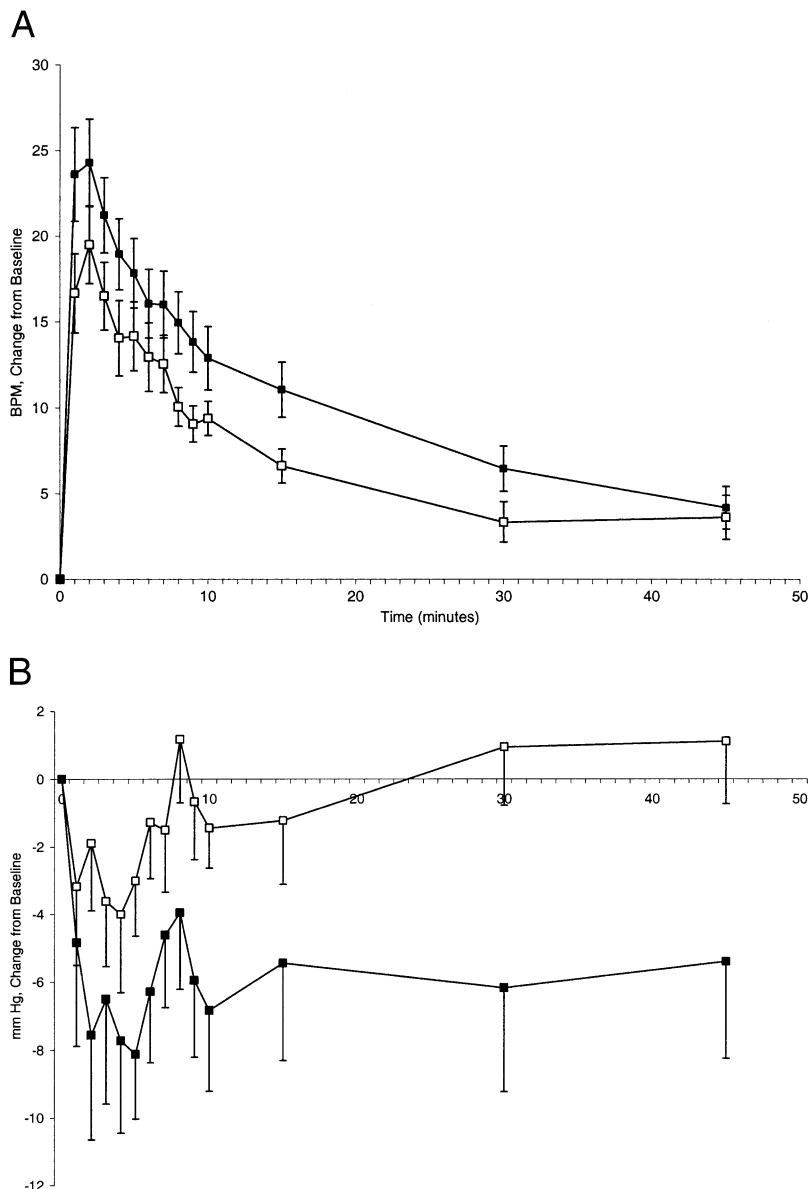
Figure 2. Change in heart rate in beats/min **(A)** and in systolic blood pressure in mm Hg **(B)** from baseline after regadenoson administration; values are means with standard errors. **Open squares** = 400 μg; **solid squares** = 500 μg.

perfusion defects by coronary artery vascular territory are as follows: 86% for the right coronary artery, 80% for the left anterior descending coronary artery, and 77% for the left circumflex coronary artery.

The severity of the defect, as determined by the SSS, was assessed both visually, on the basis of the average of the independent reviews, and quantitatively, by 4D-MSPECT (Table 3). By both methods, the summed scores were grouped as follows: 0 to 3, 4 to 7, 8 to 11, and ≥12. For the visual SSS assessment, the overall regadenoson/adenosine agreement was 57%. The computerized software assessment showed an overall regadenoson/adenosine agreement of 69%. No significant difference was present in the visual or quantitative summed scores between adenosine and regadenoson (Table 3).

In the same-screen comparison of the 175 regions (5 regions per patient, n = 35) on the regadenoson and adenosine stress images, the extent of the ischemic region was less in 9 regions and greater in 15 regions, yielding an overall rate of agreement of 86%.

Safety and tolerability. Reported side effects are summarized in Table 4. Most side effects were considered mild and transient, resolving spontaneously within 10 min. Of the 26 subjects experiencing any symptoms, 77% categorized their symptoms as mild, with 88% of all reported adverse events being mild (83 of 94). A higher proportion of patients receiving the 500-μg dose group reported flushing, dyspnea, and dizziness compared with the 400-μg group, although these differences were not statistically significant. Two subjects receiving regadenoson (400 μg), experienced severe adverse
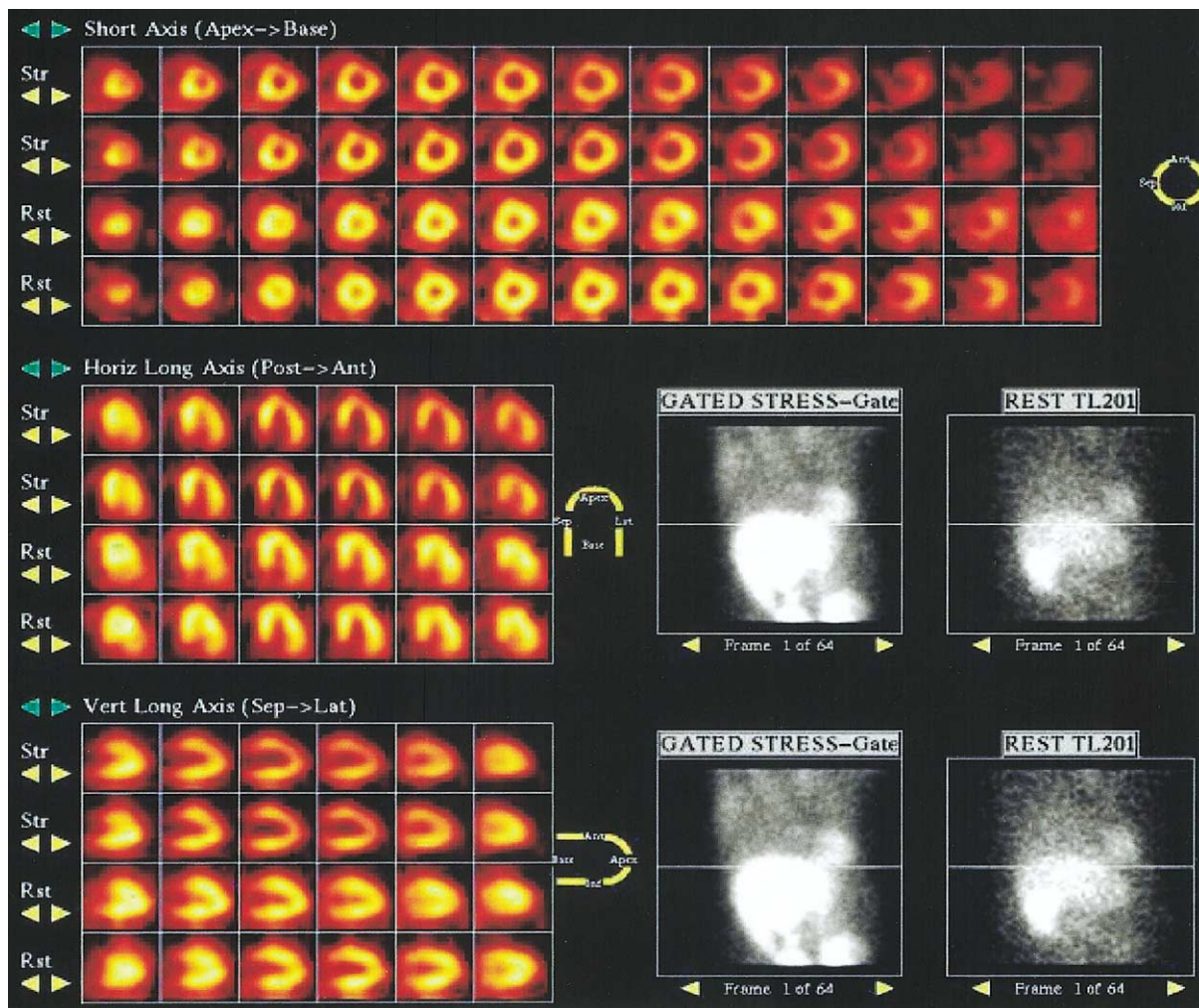
Figure 3. Direct comparison of adenosine and regadenoson images using a dual-isotope protocol (rest: thallium-201, stress: Tc-99m tetrofosmin). These images reveal a large, mild, reversible perfusion defect in the anterior, apical, and lateral walls. Similar findings were noted on the adenosine and regadenoson stress images. **Upper panel** is the regadenoson study.

effects, which were not reported as occurring with adenosine. One subject reported a worsening of migraine headache, requiring a hospital stay. A second subject had chest pain and headache, which quickly subsided after treatment with 100 mg of IV aminophylline. The clinical laboratory profile (hematology, serum chemistry, and urinalysis) for all patients was either normal during the study or reflected changes in laboratory values that were not clinically significant.

Electrocardiographic findings. Six patients had episodes of transient ST-segment depression (range of 0.5 to 3 mm),

occurring within one minute after dose and resolving by 30 min. No second- or third-degree AV block occurred with regadenoson; one patient (in the 400-μg group) developed first-degree AV block. No clinically significant or sustained ectopy was noted after regadenoson.

DISCUSSION

This is this first study examining the clinical utility of regadenoson, a selective adenosine A_{2A} agonist, in conjunc-

Table 3. Imaging Visual and Quantitative Summed Scores by Pharmacologic Stress Agent

Summed Score*	Visual†		Quantitative‡	
	Regadenoson	**Adenosine**	**Regadenoson**	**Adenosine**
Rest (SRS)	5.0 (4.8)	4.8 (5.2)	6.2 (6.8)	6.4 (6.8)
Stress (SSS)	13.2 (7.7)	13.9 (8.8)	13.6 (9.5)	13.7 (9.0)
Difference (SDS)	8.2 (5.9)	9.1 (6.4)	8.0 (5.6)	7.9 (5.3)

Values are means (SD); all pair-wise comparisons are not statistically significant. *Summed scores for stress (SSS) and rest (SRS) were measured; summed scores for differences (SDS) were calculated (SSS−SRS). †Visual analysis used a 17-segment model and a semiquantitative visual score on a five-point scale from zero (normal) to four (no activity). ‡Quantitative analysis was performed by 4D-MSPECT.

Table 4. Adverse Events Associated With Regadenoson Administration

	Both Doses (n = 36)	400 μg Regadenoson (n = 18)	500 μg Regadenoson (n = 18)
Chest pain	12 (33)	6 (33)	6 (33)
Headache	9 (25)	4 (22)	5 (28)
Abdominal pain	4 (11)	3 (17)	1 (6)
Flushing	11 (31)	3 (17)	8 (44)
Palpitation	2 (6)	2 (11)	0 (0)
Dyspnea	11 (31)	3 (17)	8 (44)
Dizziness	7 (19)	2 (11)	5 (28)
Hypesthesia	3 (8)	2 (11)	1 (6)
Totals	26 (72)	11 (61)	15 (83)

Values are n (%).

tion with SPECT MPI. These results demonstrate that regadenoson is well-tolerated and yields images comparable to those obtained with adenosine. Agreement between regadenoson and adenosine for detecting ischemia was good and not dose-dependent. Regional agreement for detection of stress perfusion defects in all three major vascular territories was also good (76% to 89%) and comparable to that reported for adenosine and exercise stress in a large pivotal trial (5).

The hemodynamic effects and their temporal changes with regadenoson are consistent with earlier animal experiments (9,11) and indicate a rapid physiological response (16). The magnitude of blood pressure decrease with regadenoson was less than that commonly observed for adenosine or other vasodilators (1,2,7,17), presumably owing to its preferential effects on the coronary vasculature. A SBP of <100 mm Hg was observed in three 500-μg dose subjects. The increase in heart rate with regadenoson of 20 to 24 beats/min is similar to that reported for both adenosine and dipyridamole (1,2,7) as well as with binodenoson (17). The increase of heart rate is greater than can be accounted for by the blood pressure decrease with regadenoson. The physiological basis for the increase in heart rate is likely to be direct neurohumoral activation through stimulation of postganglionic norepinephrine release (18).

Adverse events associated with regadenoson administration were generally mild in severity and short in duration. Notably, the absence of AV block and bronchospasm suggest that regadenoson might serve as an alternative stressor to adenosine in at-risk patients. The higher dose of regadenoson used in this study was associated with a greater incidence of adverse effects, although these differences were not statistically significant. Overall, side effects noted with regadenoson were less frequent than previously reported with adenosine (7) and similar to those recently reported with binodenoson (17), although no direct comparison between these compounds and regadenoson has been performed.

The agreement between adenosine and regadenoson was slightly lower in this trial than noted in a recently published study comparing adenosine with binodenoson (17). In that study, the agreement for comparing the extent and severity of ischemia was between 79% and 85%; however, this latter study simultaneously compared the stress/rest adenosine and binodenoson images from a single screen display rather than performing independent image interpretation, which likely improved the agreement. Furthermore, the binodenoson protocol did not restrict subjects to those who have ischemia; examining subjects with an SDS ≥2 in that study provided an agreement rate of 56% to 73%, comparable to that noted in the current regadenoson trial (17).

Finally, the higher dose of regadenoson used in this study was associated with a greater incidence of adverse effects, although these differences were not statistically significant. Because the concordance with adenosine was similar for both doses (400 and 500 μg), the 400-μg dose was selected for phase III clinical trials.

The current study was a pilot, dose-ranging trial and was not powered to demonstrate efficacy. Another potential limitation of the study is that the subjects were not randomly assigned to dose groups and, therefore, bias might be present. Other limitations include the use of multiple imaging protocols and a lack of gender and racial diversity. **Conclusions.** Regadenoson, a selective A_{2A} receptor agonist, is a well-tolerated, pharmacologic stress agent for SPECT MPI and seems to produce similar regions of hypoperfusion as noted with adenosine. Regadenoson increases heart rate in a similar magnitude to that reported for adenosine, but with less impact on SBP. Side effects are generally mild in severity and short in duration, with no associated high-degree AV block or bronchospasm. The 400-μg dose of regadenoson seems to be better tolerated than the 500-μg dose. Because the agreement with adenosine was similar for both doses studied, our findings support additional clinical investigation with the 400-μg dose of this novel pharmacologic stress agent.

Reprint requests and correspondence: Dr. Robert C. Hendel, 912 Northwest Highway, Suite 7, Fox River Grove, Illinois. E-mail: rhendel@midwestheart.org.

REFERENCES

1. Hendel RC, Jamil T, Glover DK. Pharmacologic stress testing: new methods and new agents. J Nucl Cardiol 2003;10:197–204.
2. Verani MS, Mahmarian JJ. Pharmacological stress nuclear cardiology imaging. Am J Card Imaging 1994;8:223–30.
3. Gould KL. Noninvasive assessment of coronary stenosis by myocardial perfusion imaging during pharmacologic coronary vasodilatation: I. Physiologic basis and experimental validation. Am J Cardiol 1978;41:267–78.
4. Levine MG, Ahlberg A, Mann A, et al. Comparison of exercise, dipyridamole, adenosine, and dobutamine stress with the use of Tc-99m tetrofosmin tomographic imaging. J Nucl Cardiol 1999;6:389–96.
5. Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Equivalence between adenosine and exercise thallium-201 myocardial tomography: a multicenter, prospective, crossover trial. J Am Coll Cardiol 1992;20:265–75.
6. Belardinelli L, Shryock JC, Snowdy S, et al. The A2a adenosine receptor mediates coronary vasodilation. J Pharmacol Exp Ther 1998;284:1066–73.

7. Cerqueira MD, Verani MS, Schwaiger M, Heo J, Iskandrian AS. Safety profile of adenosine stress perfusion imagining: results from the Adenoscan Multicenter Trial Registry. J Am Coll Cardiol 1994;23: 384–9.

8. Ranhosky A, Kempthorne-Rawson J, Intravenous Dipyridamole Thallium Imagining Study Group. The safety of intravenous dipyridamole thallium myocardial perfusion imagining. Circulation 1990;81: 1205–9.

9. Gao Z, Li Z, Baker SP, 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.

10. Palle VK, Elzein EO, Gothe SA, et al. Structure-affinity relationships of the affinity of 2-pyrazolyl adenosine analogues for the adenosine A2a receptor. Biorganic Med Chem Lett 2002;12:2935–9.

11. Trochu JN, Zhao G, Post H, et al. Selective A2a rector agonist as a coronary vasodilator in conscious dogs: potential for use in myocardial perfusion imaging. J Cardiovasc Pharmacol 2003;41:132–9.

12. American Society for Nuclear Cardiology. Imaging guidelines for nuclear cardiology procedures, pt 2. J Nucl Cardiol 1999;6:G47–84.

13. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002 105:539–42.

14. SAS/STAT User's Guide, Version 8. Cary, NC: SAS Institute, Inc, 1999.

15. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404–13.

16. Shryrock JC, Snowdy S, Baraldi PG, et al. A2a-adenosine receptor reserve for coronary vasodilation. Circulation 1998;98:711–8.

17. Udelson JE, Heller GV, Wackers FJT, et al. Randomized controlled dose-ranging study of the selective adenosine A2a receptor agonist binodenoson for pharmacological stress as an adjunct to myocardial perfusion imaging. Circulation 2004;109:457–64.

18. Dhalla AK, Wong MY, Wang WQ, Biaggioni I, Belardinelli L. Tachycardia caused by A2A adenosine receptor agonists is mediated by direct sympathoexcitation in awake rats. J Pharmacol Exp Ther 2005. In press.