PHARMACOTHERAPY

ORIGINAL RESEARCH ARTICLE

Regadenoson versus Dipyridamole: A Comparison of the Frequency of Adverse Events in Patients Undergoing Myocardial Perfusion Imaging

Kallie A. Amer,[1] Jeff R. Hurren,[1]* Stephanie B. Edwin,[1] and Gerald Cohen[2]

[1]Department of Pharmacy Services, St John Hospital and Medical Center, Detroit, Michigan; [2]Non-Invasive Cardiology Laboratory, St John Hospital and Medical Center, Detroit, Michigan

STUDY OBJECTIVE To compare the frequency of adverse events in patients undergoing myocardial perfusion imaging (MPI) with either regadenoson or dipyridamole.

DESIGN Single-center, retrospective cohort study.

SETTING Large community teaching hospital.

PATIENTS A total of 568 adults who underwent single-photon emission tomography MPI with either regadenoson (284 patients) or dipyridamole (284 patients) as a vasodilator agent, following an institution conversion from regadenoson to dipyridamole in the MPI protocol on July 15, 2013, for cost-saving purposes.

MEASUREMENTS AND MAIN RESULTS Data were collected from the patients' electronic medical records. The primary endpoint was the composite occurrence of any documented adverse event in each group. Secondary endpoints were individual components of the primary endpoint, reason for termination of the MPI examination (protocol completion or premature end due to an adverse event), use of an interventional agent to an treat adverse event, and cost-related outcomes. A higher proportion of patients in the regadenoson group experienced an adverse event than those who received dipyridamole (84.9% vs 56.7%, $p<0.0001$). None of the patients in either group required early MPI study termination due to an adverse event. No significant differences were noted between groups regarding use of aminophylline or other interventions to treat adverse events. The overall drug cost savings in the postconversion dipyridamole group was $51,526.

CONCLUSION Dipyridamole was associated with fewer adverse events than regadenoson in patients undergoing MPI. Dipyridamole offers a safe and cost-effective alternative to regadenoson for cardiac imaging studies.

KEY WORDS dipyridamole, regadenoson, cardiac stress test, myocardial perfusion imaging.

(**Pharmacotherapy 2017;37(6):657–661) doi: 10.1002/phar.1940**

Nuclear myocardial perfusion imaging (MPI) is a diagnostic aid for differentiation of various cardiac complaints. Providers use MPI to detect cardiac perfusion deficits, wall motion abnormalities, and flow changes.[1] During MPI, pharmacologically induced or exercise-induced stress normally increases blood flow to the myocardium while imaging is performed. Coronary artery disease is associated with relative myocardial hypoperfusion.[2]

The most common medications used in pharmacologically induced stress testing are

Disclosures: Kallie Amer, Stephanie Edwin, and Jeff Hurren have no disclosures to report. Gerald Cohen has received funding as a consultant for Lantheus Medical Imaging.

Funding: No sources of funding were granted for this work.

This work was presented as a poster at the American Society of Health-System Pharmacists Midyear Clinical Meeting, New Orleans, LA, December 6–10, 2015.

*Address for correspondence: Jeff Hurren, Department of Pharmacy, St John Hospital & Medical Center, G-20, 22101 Moross, Detroit, MI 48236; e-mail: jeff.hurren@ascension.org.

vasodilators, which increase blood flow in the heart through action at the adenosine receptors.[3] Adenosine, dipyridamole, and regadenoson (Lexiscan; Astellas Pharma US, Inc., Northbrook, IL) are all approved by the United States Food and Drug Administration for use in MPI and work through different mechanisms. Although MPI is generally safe and well tolerated, up to 80% of patients will experience at least one adverse event or discomfort regardless of the vasodilator used.[4–7] Because adenosine receptors are not specific to myocardial tissue, adverse events can be noncardiac in nature. Minor reactions include nausea, dizziness, flushing, and chest pain; serious adverse events include bronchospasm, myocardial infarction, and seizures.[3–8] Depending on severity, the event may require reversal with aminophylline; other agents such as benzodiazepines, nitroglycerin, or β-blockers are infrequently used.[1]

Although most studies show similar sensitivity of dipyridamole and regadenoson for the detection of obstructive coronary artery disease, to our knowledge, their comparative adverse event profiles and a cost analysis has not been examined.[9, 10] More adverse events might be anticipated with dipyridamole for two reasons: the greater time to effect and longer half-life of dipyridamole compared with regadenoson, which may result in a longer duration of adverse events; and the lack of adenosine receptor subtype specificity of dipyridamole compared with regadenoson.[3, 6, 7, 11]

To our knowledge, there are no published studies that have primarily assessed adverse events with regadenoson compared with those of dipyridamole in patients undergoing single-photon emission tomography (SPECT) MPI. Thus, the objective of this study was to compare the frequency of adverse events in patients undergoing MPI with either regadenoson or dipyridamole. Secondary objectives were to compare the reasons for termination of the MPI examination and use of interventional agents to treat adverse events and to perform a medication cost analysis to assess the impact of converting from regadenoson to dipyridamole.

Methods

Study Design, Setting, and Patient Cohorts

This retrospective cohort study was performed at St John Hospital and Medical Center, a 772-bed community teaching hospital in Detroit, Michigan. Institutional review board approval was granted prior to the start of data collection; informed consent was waived due to the retrospective nature of the study. Patients older than 18 years were included if they underwent SPECT MPI with either regadenoson or dipyridamole as a vasodilator agent. An institution conversion was undertaken on July 15, 2013, for cost-saving purposes. MPI protocols used regadenoson as the agent of choice before this date, and dipyridamole was used after the conversion. Patients were identified by using pharmacy information systems. Both inpatient and outpatient MPI studies were included. For patients who had more than one stress protocol, only the first was included in the analysis. Patients with missing information on adverse events or reason for protocol conclusion were excluded.

Data Collection

Demographic and clinical information was collected for each patient from the electronic medical record. A standardized recording form was used to document events of the stress test, including adverse events and any interventional agents used. Data on the following adverse events were collected: headache, gastrointestinal upset (including nausea), and dyspnea, chest pain, flushing, dizziness, nodal block or arrhythmia, and throat, neck, or jaw pain. In addition, adverse events collected included hypotension (blood pressure <90/50 mm Hg) and electrocardiogram (ECG) abnormalities, such as flat or downsloping ST-segment depression of at least 1 mm from baseline interpreted by a cardiologist as indicative of ischemia from a diagnostic ECG. The use of aminophylline and other interventional agents such as nitroglycerin, β-blockers, oxygen, and transcutaneous pacing were recorded. Finally, the reason for termination of the MPI study was noted as either protocol completion or premature end due to an adverse event. The same MPI procedural consent form was used throughout the study for patients receiving either regadenoson or dipyridamole. Cost-related outcomes were based on the actual drug acquisition price at the study site; cost avoidance was calculated by multiplying the difference in drug acquisition price between the two agents by the number of cases in which the drug was used in the postconversion (dipyridamole) period.

Endpoints

The primary endpoint of this study was the composite adverse event occurrence in each group, which was defined as the occurrence of any documented adverse event. Secondary endpoints included the reason for the termination of examination, use of an interventional agent to treat an adverse event, and cost-related outcomes.

Statistical Analysis

Based on previous data, the predicted composite adverse event rate for dipyridamole was 62%, compared to 73% for regadenoson.[10, 12] To detect a difference of this size or larger, we calculated that a sample size of 284 patients in each group (a total of 568 patients) would provide an α error rate of 0.05 and 80% power. Descriptive statistics were used to characterize the study population with respect to demographic and clinical factors. Continuous variables were calculated as means with standard deviations or medians with ranges. Categorical variables were described as frequency distributions. Differences in demographic and clinical characteristics between the two study groups were assessed by using the Student *t* test or analysis of variance, and the χ^2 test, as appropriate. The difference in the proportion of patients experiencing an adverse event was compared by using χ^2 analysis. All analyses were completed by using SPSS statistical analysis software, version 23.0 (IBM Corp., Armonk, NY).

Results

Baseline characteristics were similar between groups, except the regadenoson group had a higher proportion of patients with coronary artery disease (38.4% vs 30.3%, p=0.04) and chronic obstructive pulmonary disease (20.8% vs 13.0%, p=0.01; Table 1). A higher proportion of patients in the regadenoson group experienced an adverse event than those who received dipyridamole (84.9% vs 56.7%, p<0.0001). This result was primarily driven by dyspnea (52.5% vs 2.1%, p<0.0001), gastrointestinal upset (27.8% vs 8.1%, p<0.0001), and chest pain (15.8% vs 3.9%, p<0.0001). Three patients in the regadenoson group experienced hypotension compared with none in the dipyridamole group. No significant differences between the two groups were noted for occurrence of heart block, arrhythmias, ischemic ST-segment depression, and other symptoms (Table 2).

Table 1. Baseline Demographic and Clinical Characteristics of the Study Patients

Characteristic	Regadenoson Group (n=284)	Dipyridamole Group (n=284)	p Value
Age (yrs)	62.1 ± 13.4	62.2 ± 13.0	0.93
Weight (kg)	90.8 ± 25.9	89.9 ± 22.9	0.66
African American	169 (59.5)	167 (58.8)	0.98
Male	119 (41.9)	137 (48.2)	0.13
Congestive heart failure	34 (12.0)	35 (12.3)	0.90
Coronary artery disease	109 (38.4)	86 (30.3)	0.04
Hypertension	256 (90.1)	243 (85.6)	0.10
Angina	10 (3.5)	7 (2.5)	0.46
Diabetes mellitus	101 (35.6)	109 (38.4)	0.49
Chronic kidney disease	42 (14.8)	43 (15.1)	0.91
Chronic obstructive pulmonary disease	59 (20.8)	37 (13.0)	0.01
Asthma	42 (14.8)	43 (15.1)	0.91

Data are mean ± SD values or no. (%) of patients.

No significant differences in the interventional agents used to treat adverse events were noted between the groups. Aminophylline was infrequently used, administered to 4.2% of patients receiving regadenoson versus 4.6% of patients receiving dipyridamole (p=0.838). Nitroglycerin was administered to 1.1% of patients receiving regadenoson compared with 0.7% of patients in the dipyridamole group (p=0.653). Oxygen (0.4%), β-blockers (0.7%), and other medications (ondansetron and fluids) were also used in the regadenoson group. All MPI studies were completed by reaching the end of the protocol or meeting target values. Using the acquisition costs of the medications, regadenoson cost $181.43 more per unit than dipyridamole. For the cohort in this study, the overall drug cost savings in the postconversion dipyridamole group was $51,526 for the 284 patients in that group.

Discussion

In contrast to common perceptions, patients in this study experienced a higher rate of adverse events during MPI when receiving regadenoson compared with dipyridamole. This was primarily driven by differences in dyspnea, gastrointestinal upset, and chest pain. Despite these noted differences in adverse events, medications

Table 2. Adverse Events

Adverse event	Regadenoson Group (n=284)	Dipyridamole Group (n=284)	p Value
Any adverse event	241 (84.9)	161 (56.7)	<0.0001
Dyspnea	149 (52.5)	6 (2.1)	<0.0001
Gastrointestinal upset	79 (27.8)	23 (8.1)	<0.0001
Chest pain	45 (15.8)	11 (3.9)	<0.0001
Headache	33 (11.6)	36 (12.7)	0.69
Dizziness	22 (7.7)	16 (5.6)	0.31
Ischemic ST-segment depression	20 (7.1)	9 (3.2)	0.35
Flushing	16 (5.6)	10 (3.5)	0.23
Supraventricular tachycardia	3 (1.1)	6 (2.1)	0.31
Heart block	3 (1.1)	1 (0.4)	0.32
Hypotension	3 (1.1)	0 (0)	—
Ventricular tachycardia	1 (0.4)	1 (0.4)	p>0.99
Throat, neck, or jaw pain	1 (0.4)	1 (0.4)	p>0.99

Data are no. (%) of patients.

used to attenuate effects were used with similar frequency. Furthermore, none of the patients required early termination due to an adverse event, regardless of the agent used. We achieved a significant cost savings for our health system by using dipyridamole rather than regadenoson, based on our drug acquisition costs. Cost savings for other institutions may vary based on contracted pricing and patient volume.

Our study is limited by its retrospective nature and reliance on documentation. However, the standardized documentation form remained consistent throughout the study period, and patients with missing information were excluded. All data were collected from a single site with a small pool of physicians ordering the MPI. The patient population studied included both inpatients and outpatients, which resulted in various indications for the test. Patients and exercise physiologists were not blinded to the medication used, which could have caused bias. However, when we first switched agents, our exercise physiologists and cardiologists anticipated more adverse events with dipyridamole because of the ease of use and short half-life of regadenoson, as well as their high comfort level with regadenoson. Although there was a greater proportion of patients with baseline coronary artery disease and chronic obstructive pulmonary disease in the regadenoson group, the increased incidence of shortness of breath and chest pain in these patients cannot be fully explained by these baseline differences. Although not measured, it is possible that there were qualitative aspects of the adverse events that we were unable to characterize due to differences in the pharmacokinetics or pharmacodynamics of the two agents. These qualitative aspects may be important to patients and are more adequately assessed in prospective trials.

At our institution, the initial proposal to switch to dipyridamole was met with some physician concern that it would decrease patient throughput and/or increase adverse events. Regadenoson has some clear operational advantages, including a single standardized dose and intravenous push route of administration. Our success may be, in part, due to the preparation surrounding workflow and medication delivery to minimize impact on process and throughput. Pharmacy workflow changes were planned and implemented before the change from regadenoson to dipyridamole to assist with a smooth transition.

Our switch to dipyridamole did not result in a meaningful increase in labor and materials. Previous studies estimated that the difference in total time to perform MPI could be up to 15 minutes longer when using dipyridamole.[13] Locations without 24-hour pharmacy services may have more barriers to implementation due to the weight-based dosing, sterile compounding, and infusion devices required by dipyridamole. A prospective comparison in a randomized controlled trial to control for these factors would be of benefit.

Recent changes in the United States health care system have emphasized implementation of value-based medicine. At the core of many of the reforms are adjustments to payment mechanisms, and pressures for cost control are increasingly being transferred to the providers of patient care. This is particularly true in cardiac diagnostic testing, where costs for some procedures are being bundled into a single payment.[14] These changes are challenging organizations to consider the most efficient and cost-effective way to improve patient outcomes and preserve patient experiences, including implementing initiatives such as the one described in this study.

Conclusion

Dipyridamole was associated with fewer overall adverse events than regadenoson in patients

undergoing MPI. Dipyridamole offers a safe and cost-effective alternative to regadenoson for cardiac imaging studies.

Acknowledgments

We are grateful to Rachel Davis, Mary Manoogian, Stefanie Nadolski, and Julie Simon for their contributions in implementing the changes described in this study.

References

1. **Druz RS.** Current Advances in vasodilator pharmacological stress perfusion imaging. Semin Nucl Med 2009;39(3):204–9.
2. **Badheka AO, Hendel RC.** Radionuclide cardiac stress testing. Curr Opin Cardiol 2011;26:370–8.
3. **Johnson SG, Peters S.** Advances in pharmacologic stress agents: focus on regadenoson. J Nucl Med Technol 2010;38: 163–71.
4. **Leaker BR, O'Connor B, Hansel TT, et al.** Safety of regadenoson, an adenosine A2A receptor agonist for myocardial perfusion imaging, in mild asthma and moderate asthma patients: a randomized, double-blind, placebo-controlled trial. J Nucl Cardiol 2008;15(3):329–36.
5. **Astellas Pharma US, Inc.** Adenoscan (adenosine) package insert. Northbrook, IL; 2014.
6. **Astellas Pharma US, Inc.** Lexiscan (regadenoson) package insert. Northbrook, IL; 2017.
7. **Hospira, Inc.** Dipyridamole package insert. Lake Forest, IL; 2015.
8. **Page RL, Spurck P, Bainbridge JL, Michalek J, Quaife RA.** Seizures associated with regadenoson: a case series. J Nucl Cardiol 2012;19(2):389–91.
9. **Bravo PE, Pozios I, Pinheiro A, et al.** Comparison and effectiveness of regadenoson versus dipyridamole on stress electrocardiographic changes during positron emission tomography evaluation of patients with hypertrophic cardiomyopathy. Am J Cardiol 2012;110(7):1033–9.
10. **Goudarzi B, Fukushima K, Bravo P, Merrill J, Bengel FM.** Comparison of the myocardial blood flow response to regadenoson and dipyridamole: a quantitative analysis in patients referred for clinical 82Rb myocardial perfusion PET. Eur J Nucl Med Mol Imaging 2011;38(10):1908–16.
11. **Palani G, Ananthasubramaniam K.** Regadenoson: review of its established role in myocardial perfusion imaging and emerging applications. Cardiol Rev 2012;21(1):1.
12. **Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE.** 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 (3):307–16.
13. **Friedman M, Spalding J, Kothari S, et al.** Myocardial perfusion imaging laboratory efficiency with the use of regadenoson compared to adenosine and dipyridamole. J Med Econ 2013;16(4):449–60.
14. **American Society of Nuclear Cardiology.** Medicare Hospital Outpatient Prospective Payment System HOPPS (APC), nuclear cardiology procedures, radiopharmaceuticals, and drugs. Final 2016 payment rates compared to 4Q 2015 final rates. Available from http://www.asnc.org/Files/Advocacy/ASNC%20HOPPS%20Final%20payment%20chart%202016%2011_02_2015.pdf. Accessed August 1, 2016.