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Original article

Prevalence and significance of electrocardiographic changes and side effect profile of regadenoson compared with adenosine during myocardial perfusion imaging

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ABSTRACT

Background: Significance of electrocardiogram (EKG) changes associated with regadenoson as well as side effects compared to adenosine in a real world, unselected population is unknown.
Methods and results: Three hundred ninety six consecutive patients undergoing either adenosine or regadenoson-based single-isotope (Technetium 99c) nuclear images were evaluated. A standard form documenting side effects was filled immediately following administration. The EKGs and nuclear scans were reviewed in a blinded-fashion. Commonest symptoms reported were flushing (64%), chest pain (36%) and dyspnea (36%). Flushing and chest pain were significantly more common with adenosine (73% vs. 57%, $P < 0.01$ and 53% vs. 47%, $P = 0.06$) and dyspnea more with regadenoson (40% vs. 31%, $P = 0.05$). Sixty (29%) patients carried a diagnosis of chronic bronchitis or asthma but only 4 (2 with each) required aminophylline. There was no significant correlation between chest pain induced by either agent or ischemia on nuclear imaging. EKG changes occurred infrequently (16% with regadenoson and 10% with adenosine), and had low sensitivity for detecting ischemia (7% for regadenoson and 11% for adenosine).
Conclusions: EKG changes with adenosine and regadenoson occur infrequently and have low sensitivity for detecting ischemia. Chest pain is frequently induced by both, and is not predictive of ischemia on nuclear imaging.

1. Introduction

Pharmacological agents, like dipyridamole, adenosine, dobutamine and now regadenoson, are utilized in almost greater than 50% of out-patients undergoing a stress test, either because of inability to exercise, inability to achieve target heart rate or presence of left bundle branch block. This number trends toward being even higher in the in-patient population, approaching 75%, and rises with increasing age of the patient population.[1] Vasodilators employed clinically increase coronary perfusion 3–5 fold by binding to adenosine receptors, activating G-coupled proteins, leading to increase in intracellular adenylyl cyclase activity resulting in increased intracellular cAMP levels, inhibition of calcium channels and hence, smooth muscle relaxation leading to vasodilation. Dipyridamole indirectly, and adenosine directly acts on all four adenosine receptor subtypes; A1, A2a, A2b and A3. In contrast, regadenoson is the first in its class of selective A2a receptor agonist approved for clinical use.

Since gaining FDA approval for use as a pharmacological stressor in May 2008, regadenoson has been adopted into widespread clinical use. Initial clinical trial showed regadenoson to be well-tolerated[2] with phase III clinical trials showing its diagnostic ability to be comparable to standard adenosine infusion,[3] in detecting ischemia on gated single photon emission computed tomography (SPECT) imaging. Although EKG changes were reported in 6 out of 36 (16.7%) patients in the first study,[2] and 17% of patients tested with regadenoson in the second study,[3] no data was provided regarding the sensitivity or specificity of these EKG changes (range of ST-segment depression of 0.5–3 mm in the initial trial[2] or ST-segment depression or elevation in second trial[3]) for predicting ischemia on the SPECT images. In the current study, we provide the incidence of ST-segment changes with use of adenosine or regadenoson in consecutive patients in a real world, unselected

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population, and compare the sensitivity and specificity of these changes in predicting ischemia on SPECT imaging. We further compare the incidence of side effects induced by either agent. As chest pain was frequently induced by both regadenoson and adenosine, we correlate it with the presence of ischemia on SPECT imaging to see if it is of clinical relevance.

2. Materials and methods

The study was approved by Excela Health Institutional Review Board. A total of 396 patients, undergoing either adenosine or regadenoson-based SPECT stress testing at a single community hospital were evaluated. At this community hospital, regadenoson was introduced in January 2009 and 209 consecutive patients undergoing regadenoson-based stress testing from 1/1/2009 to 12/31/2010 were entered into the study. For comparison purposes, 187 consecutive patients undergoing adenosine-based stress test prior to the introduction of regadenoson were selected.

All patients had a standardized form listing reason for stress test, co-morbidities, cardiac risk factors and medication use, filled by a nuclear stress lab dedicated nurse. Weight-based adenosine infusion over 4-min was used, with radio-isotope injection given at 2 min. Regadenoson was given as a fixed-dose, 400 ug bolus injection over 20 s with radio-isotope injection at 30 s. A standardized form listing side effects induced by the agent as well as use of aminophylline was filled immediately following the completion of the stress test. All patients underwent single-isotope Technetium-99m-Sestamibi, one-day imaging protocol. A two-day protocol was utilized in patients over 350 lbs in weight.

The EKGs were reviewed by a board-certified cardiologist blinded to the clinical or nuclear images findings. EKG changes were considered to be indicative of ischemia if there were 0.5 mm or more ST-segment deviations in two or more contiguous leads. Patients with paced rhythms or complete left bundle branch (LBBB) were excluded. However, these patients were included for the purpose of documenting adenosine or regadenoson infusion associated side effects. The SPECT images were analyzed using a 17-segment model, again blinded to the EKG findings.

Patient demographics and baseline data were compared between adenosine and regadenoson group using the unpaired student's *t*-test and chi-square statistic for continuous and categorical data respectively. Prevalence of side effects in the two groups was compared using the chi-square statistic. Data was analyzed using statistical package Stata 8.0.

3. Results

Two hundred and nine patients underwent regadenoson-based stress tests and were compared to 187 patients undergoing adenosine-based stress test prior to the introduction of regadenoson at a single, community-based hospital. The majority of the study population was Caucasian (98.0%) and female (63.6%), with a mean age of 71.8 yrs (±12.3; range 33–98). There were no significant differences between patients receiving adenosine versus regadenoson, with the exception that the latter group more frequently carried the diagnosis of chronic obstructive pulmonary disease, and had a higher prevalence of being on a beta-blocker, calcium-channel blocker or statin therapy [Table 1].

Side effects were very common with both adenosine infusion (81.8%) and regadenoson bolus injection (83.7%) and not significantly different between the two agents [Table 2]. Flushing was the commonest symptom reported with both adenosine and regadenoson though it was significantly more common with adenosine (73.2% versus 56.7%; $P = 0.001$). Chest pain was also more common with adenosine infusion, as opposed to dyspnea which was significantly more common with regadenoson (40.3% versus 30.7%; $P = 0.049$). AV-conduction abnormalities occurred in only one patient with regadenoson and consisted of transient first degree AV-block. In contrast, AV-block was seen in 11.2% of patients with adenosine infusion, and consisted largely of transient second degree AV-blocks, though one octogenarian developed transient complete heart block. Women were significantly more likely than men to experience headaches, dyspnea, flushing and nausea with adenosine infusion (all *P*-values <0.05). However, with regadenoson, although the side effects were just as common as with adenosine, there were no statistically significant gender differences seen.

Patients were continuously monitored for at least 6 min with adenosine infusion and 4 min with regadenoson. EKGs of 10 patients in regadenoson group and 12 in the adenosine group could not be evaluated due to underlying paced rhythm or complete LBBB, and hence, were excluded from the sensitivity/specificity analysis. Out of the evaluable EKGs, 31 (15.4%) patients receiving regadenoson had ST-segment depressions, whereas only 18 (10.4%) of patients in the adenosine group had ST-segment depressions. None of the patients in the study experienced ST-segment elevations. As shown in Table 3, the EKG changes with both agents had low sensitivity for predicting ischemia on nuclear imaging, and low positive predictive value. As there were few false positives with

Table 1
Patient demographics by stress type.

Patient characteristic	Regadenoson ($N = 209$) *N* (%)	Adenosine ($N = 187$) *N* (%)	*P*-value
Age (mean ± st. dev.)	72.3 yrs (±12.1)	71.1 yrs (±12.7)	Ns
Caucasian	206 (99.5%)	180 (96.3%)	Ns
Sex (female)	133 (63.6%)	119 (63.6%)	Ns
Prior stress test (yes)	160 (76.6%)	133 (71.5%)	Ns
History of myocardial infarction	39 (18.7%)	24 (12.9%)	Ns
Coronary artery bypass grafting	48 (23.0%)	39 (21.0%)	Ns
Prior catheterization/PCI	98 (46.9%)	74 (40.0%)	Ns
Chronic obstructive pulmonary disease	37 (17.7%)	21 (11.3%)	0.07
Asthma	23 (11.0%)	13 (7.0%)	Ns
Hypertension	141 (67.5%)	118 (63.8%)	Ns
Cerebrovascular accident	26 (12.4%)	33 (17.7%)	Ns
Diabetes mellitus	67 (32.1%)	57 (30.7%)	Ns
Hyperlipidemia	117 (56.5%)	94 (50.8%)	Ns
Current tobacco abuse	28 (13.4%)	19 (10.2%)	Ns
Aspirin	112 (53.9%)	94 (50.5%)	Ns
Plavix	35 (16.8%)	30 (16.1%)	Ns
Beta-blockers	89 (42.8%)	63 (33.9%)	0.07
Nitrates	19 (9.1%)	10 (5.4%)	Ns
Calcium channel blockers	42 (20.2%)	16 (8.6%)	0.001
Lipid lowering therapy-statin	90 (43.5%)	62 (33.3%)	0.04
Lipid lowering therapy-nonstatin	18 (8.7%)	10 (5.4%)	Ns

Ns = Not Significant.

Table 2
Side effects associated with regadenoson versus adenosine.

Symptom	Regadenoson	Adenosine	*P*-value
Flushing	115 (56.7%)	131 (73.2%)	0.001
Dyspnea	82 (40.4%)	55 (30.7%)	0.049
Chest pain	65 (32.0%)	74 (41.3%)	0.059
Headache	44 (21.7%)	38 (21.2%)	Ns
Nausea	35 (17.2%)	29 (16.2%)	Ns
Dizziness	12 (5.9%)	12 (6.7%)	Ns
AV-block	1 (0.5%)	21 (11.2%)	<0.001
Use of aminophylline	2 (1.0%)	2 (1.1%)	Ns

Table 3
Sensitivity and specificity of regadenoson versus adenosine associated EKG changes.

Stressor agent	Ischemia nuclear-study	Ischemic changes-EKG	Sensitivity	Specificity	PPV	NPV
Regadenoson	43 (21.7%)	31 (15.7%)	7%	81.9%	9.7%	76.0%
Adenosine	28 (17.9%)	16 (10.2)	10.7%	89.8%	18.8%	82.1%

either adenosine or regadenoson, the specificities were higher with both agents. The induction of chest pain with either adenosine infusion or regadenoson injection had poor correlation with findings of ischemia on nuclear imaging ($R^2 = -0.13$, $P = 0.08$ for regadenoson and $R^2 = 0.007$, $P =$ ns for adenosine).

4. Discussion

Since gaining approval by the FDA in 2008 as a pharmacological stressor, regadenoson has been rapidly incorporated into clinical use. Initial clinical studies compared it to patients undergoing a myocardial perfusion stress test with adenosine and showed that it was well-tolerated and as effective as adenosine for detecting ischemia with an agreement for reversible defects of 86%.[2] Phase III studies following this initial report established regadenoson as having comparable performance to adenosine as a chemical stressor.[3,4] These reports were followed by a number of studies establishing the safety of regadenoson in patients with chronic obstructive pulmonary disease and bronchial asthma,[5,6] chronic kidney disease,[7–9] post-heart transplant,[10] as well as patients with end-stage liver disease.[11] The initial study comparing regadenoson to adenosine reported 6 out of 36 patients (16.7%) having ST-segment depressions that occurred within 1 min of the regadenoson infusion and resolving by 30 min.[2] The largest study to date comparing regadenoson to adenosine, the ADVANCE trial, showed very similar incidence of ST-segment changes (depression or elevation) with regadenoson and adenosine (17% with either agent). However, in neither of these studies was the relevance of these ST-segment changes associated with regadenoson was reported. Hence, the rationale for our current study was to look at the prevalence and significant of ST-segment changes with regadenoson, and to compare it with adenosine associated EKG changes. Further, we compared the prevalence of side effects associated with regadenoson infusion and compared it with adenosine administration.

In the current study, ST-segment depression of $\geq$0.5 mm in two or more contiguous leads was seen in 15.7% of patients receiving regadenoson and 10.2% of patients receiving adenosine in a real-world clinical population undergoing pharmacological SPECT study. Our definition of ST-segment deviations is similar to that used in prior studies with regadenoson.[2] None of the patients developed ST-segment elevations with either agent. Consecutive patients receiving adenosine (187) or regadenoson (209) had their EKGs evaluated retrospectively by a board-certified cardiologist blinded to the nuclear imaging findings. The sensitivity and specificity of ST-segment depressions with either agent for predicting ischemia on the nuclear images was evaluated. The sensitivity of ST-segment depressions in predicting ischemia was low with both regadenoson (7.0%) and adenosine (10.7%), making these findings of little clinical value. Additionally, chest pain was induced frequently by both agents (regadenoson 32.0%; adenosine 41.3%), with little correlation with ischemia on nuclear imaging, also leaving this finding of little clinical value. Similar to prior reports, regadenoson affected AV-conduction to a statistically significantly lesser extent than adenosine with only one patient developing a first degree AV-block, which resolved spontaneously. In contrast most of the AV-block induced by adenosine was second degree, with one case of self-limited third degree AV-block. In none of the cases, did the conduction abnormality last long or require any intervention.

In contrast to regadenoson, significance of EKG changes with adenosine has been reported before as the agent has been in use for a much longer time.[12,13] In one study, the prevalence of EKG changes was 17% using criteria of $\geq$1 mm ST-depression.[13] Adenosine associated ST-depression was an independent marker of adverse clinical events over a follow-up period of 1–3 years. Similarly, Nishimura and colleagues studied a selected population of 65 patients with reversible perfusion defects of which one-third displayed ischemic ST-depression with adenosine infusion.[12] The three independent variables associated with ST-depression were presence of collateral vessels, baseline systolic blood pressure and adenosine induced angina chest pain. Interestingly, other researchers have reported adenosine associated ST-segment depression in the presence of normal perfusion imaging to be associated with significantly more adverse cardiovascular events over a mean follow-up of just over 2 years.[14] Our study population is significantly different from these studies. Our 187 patients that underwent pharmacological stress testing with adenosine were consecutive patients with both ischemia and no ischemic changes on SPECT imaging. Furthermore we used a less stringent definition of ST-depression of $\geq$0.5 mm to keep interpretations of EKG consistent with that of regadenoson and what is published as far as prevalence of EKG change is concerned in the literature. Lastly, we made no attempt to correlate ST-depression with either agent with clinical outcome. Rather the goal of our study was to correlate EKG findings with ischemia on SPECT imaging.

The presence of side effects with either regadenoson or adenosine were collected prospectively using a standardized form at the time of the stress test. It is interesting to note that the frequency of side effects induced by either agent were very similar (81.8% with adenosine versus 83.7% with regadenoson). This is in contrast to the ADVANCE trial where a summed score utilizing flushing, chest pain and dyspnea showed less side effects with regadenoson compared with adenosine.[3] When we utilized a similar analysis incorporating only flushing, dyspnea or chest pain into a summed score, the prevalence of side effects were nearly identical (80.4% with regadenoson versus 80.8% with adenosine). It may be that the intensity, severity or duration of symptoms may be less so with regadenoson as compared to adenosine, rather than the presence of any of these symptoms. As we did not employ a severity score or quantification of side effects, other than mere presence or lack thereof, we cannot compare severity of side effects between the two agents. Since our patient population is relatively old, the possibility of elderly patients being more prone to side effects with either agent has to be entertained. It should be noted that the two groups of patients receiving regadenoson versus adenosine were not significantly different in any baseline clinical measure other than use of statins and calcium channel blockers. Differences in medication use are unlikely to increase the prevalence of side effects noted with either agent.

Another interesting finding was the gender differences seen in terms of adenosine-induced side effects. Women were significantly more likely to experience side effects with adenosine compared to men. These gender differences were not seen with regadenoson,

showing it to be equally well-tolerated among the two groups. Additionally aminophylline was utilized in only two patients each with adenosine and regadenoson. However, presence of COPD and asthma was higher in patients getting regadenoson denoting the relatively higher comfort level clinicians have with use of this agent in this particular population.

Our study shows the poor correlation of EKG findings of ST-segment depression in patients receiving regadenoson or adenosine with ischemic changes on nuclear imaging. To the best of our knowledge, this is the first report looking at the significance of ST-segment deviations with regadenoson in a real-world patient population. Furthermore, in this relatively older population, the prevalence of side effects with regadenoson was quite high and similar to adenosine. Whereas there was a gender difference noted with side effects with adenosine, no such difference was seen with regadenoson.

Our study has several limitations. We do not have cardiac catheterization data to serve as our gold standard. Also we correlate ST-segment depressions with SPECT findings and not clinical outcome as this was not the goal of the study. However, we acknowledge that perhaps adverse cardiac outcomes would be more clinically relevant endpoints.

Conflicts of Interest

All authors have none to declare.

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