Research Brief

Regadenoson administration and QT interval prolongation during pharmacological radionuclide myocardial perfusion imaging

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ABSTRACT

The objective of our study is to assess change in QTc interval with Regadenoson administration during myocardial perfusion imaging (MPI). We conducted a retrospective, observational analysis of 1497 consecutive patients who underwent pharmacological radionuclide MPI. On multivariate logistic regression analyses, there was no statistical significance of QTc prolongation when adjusted for ischemia/fixed perfusion defect on MPI and QT prolonging medications being taken prior to stress testing. However, a positive stress ECG after Regadenoson injection had a statistical significance (p value 0.0004). Regadenoson is a safe drug for use in MPI with little, if any, side effects of major clinical significance.
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1. Introduction

Prolongation of QT interval and all-cause cardiovascular mortality has been correlated to arrhythmogenic cardiac death.[1,2] Myocardial perfusion imaging (MPI) is increasingly used to detect coronary artery disease using pharmacological agents, Regadenoson being more commonly used since April 2008. Initial clinical trials showed no evidence of increased risk for adverse events with its use. However, many case reports and post-marketing surveillance reports have shown incidence of multiple side effects including advanced heart block, transient corrected-QT (QTc) interval prolongation and seizures.[3] Our study aims at determining the association of regadenoson use and incidence of QTc prolongation during radionuclide single-photon emission computed tomography (SPECT) MPI.

2. Study design and methods

We conducted a retrospective, observational analysis of 1497 consecutive patients who underwent pharmacological radionuclide SPECT MPI in our hospital between 2012 and 2014. Patients that were included are both inpatient admissions and referrals from outpatient clinics, above 18 years of age. Exclusion criteria included patients with acute myocardial infarction or unstable angina within 3 months, coronary revascularization procedure within 6 months, pre-excitation or bundle branch block on electrocardiogram (ECG), history of sinus node or atrioventricular (AV) nodal disease, history of serious uncontrolled ventricular arrhythmia, uncontrolled hypertension, cardiac transplant, structural heart disease (including congenital heart disease, hypertrophic obstructive cardiomyopathy, amyloidosis, etc.), acute pericarditis or myocarditis, symptomatic valvular heart disease, patients with artificial pacemakers, active asthma or bronchospastic reactive airway disease, patients on dipyridamole, theophylline or have had aminophylline in the last 24 hours. 1293 patients were included in the analysis. Protocol was approved by the Institutional Review Board (IRB) of BronxCare Health System, New York, USA.

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Standardized electrocardiograms (ECGs) at sensitivity of 10 mm/mV and paper speed of 25 mm/s were recorded for all patients. QT interval was measured from the start of the QRS complex to the point where the tangent meets the TP segment. QT interval was corrected with the preceding cycle length (RR interval) using the Bazett formula ($QTc = QT/\sqrt{RR}$).[4] Prolonged QTc interval was defined as >470 msec in women and >450 msec in men.[5] The criteria for positive stress ECG after Regadenoson injection included horizontal or downsloping ST depression ≥1 mm (0.1 mV) at 60–80 ms after the J point as per standard guidelines.

Medications that were being taken by patients were categorized depending on their pharmacologic effect of prolonging QT interval. This was based on a commonly consulted internet-based registry of QTc prolonging medications from Woosley et al.[6]

Change in QTc during the study was divided into tertiles to assess the association with baseline variables. *P* values were obtained from *t*-test for continuous variables and chi-square test for categorical variables. Analyses were conducted to see the association of change in QTc intervals with Regadenoson to anthropometric variables, clinical parameters, medical comorbidities, and QTc prolonging medications. Based on prior published literature, variables that were individually associated with QTc change were then entered into multivariate logistic regression analysis to see association of baseline variables to QTc change. All analyses were completed using SAS, version 9.4 (SAS institute Inc, Cary, NC). All *p*-values were 2-tailed and significance level was set at an alpha of 0.05.

3. Results

Baseline characteristics of all patients after applying our exclusion criteria are presented in Tables 1 and 2. We analyzed 1293 patients with mean age of 62 ± 11.5 years. Around 29% of our patients ($n = 379$) were on medications known to cause QTc interval prolongation. Overall 70.5% ($n = 912$) patients in our study were seen to have QTc interval prolongation after Regadenoson injection with a mean change in QTc of 18.8 ± 43.14 msec. Others were seen to have some degree of decrease in QTc interval.

Our analysis showed no statistical significance of QTc prolongation when adjusted for different variables. Prolongation of QT interval was seen regardless of whether patients were on medications which affect QT interval or not, however *p*-value was insignificant. Multivariate logistic regression analyses showed that patients who had a positive stress ECG after Regadenoson injection, QTc prolongation had a statistical significance (Table 3). Interestingly, ischemia on perfusion images itself (regardless of ECG changes) had no statistical significance with QTc prolongation. Frequent arrhythmias in the form of premature ventricular contractions (PVCs) were seen in around 30% of our patients. This was also not statistically significant between our tertiles.

4. Discussion

Animal studies and human clinical trials have so far failed to show any significant QT interval prolongation with administration of this Regadenoson.[7,8] In our analysis, we found an increase in QTc

Table 1
Clinical characteristics of all patients included in the study.

Patient characteristics ($n = 1293$)	QTc tertiles			*P*-value
	Q1 ($n = 431$)	Q2 ($n = 431$)	Q3 ($n = 431$)	
Age (years)	61.4 ± 12.2	62.2 ± 11.4	61.3 ± 11.1	0.41
Race (%)				0.39
• Caucasian	7.7	7.4	6.7	
• African-American	32.8	32.0	29.5	
• Hispanic	57.2	60.1	62.4	
• Others	2.3	0.5	1.4	
Ischemic heart disease (%)	24.2	22.1	26.2	0.37
Diabetes mellitus (%)	51.7	51.3	50.4	0.71
Hypertension (%)	90.7	92.8	89.6	0.33
Chronic kidney disease (%)	31.2	31.6	27.8	0.43
Patients on QT prolonging medications (%)	27.4	30.8	29.8	0.53
MPI normal (%)	60.6	66.6	59.6	0.07
MPI with ischemia (%)	30.9	27.5	30.9	0.50
MPI with scar (%)	9.3	6.0	11.6	0.02
Positive stress ECG with Regadenoson (%)	18.3	10.4	10.7	0.0005
LVEF on MPI at stress	58 ± 16	61 ± 15	58 ± 15	0.02
PVC after Regadenoson at 2 min (%)	10.9	9.1	9.5	0.64
PVC after Regadenoson at recovery* (%)	14.8	12.1	11.8	0.34

Abbreviations: MPI: myocardial perfusion imaging, LVEF: left ventricular ejection fraction, PVC: premature ventricular contraction. Recovery ECG is taken at 5 minutes after Regadenoson injection.

Table 2
QTc interval prolongation among different groups.

Characteristic	Mean QTc interval at baseline (msec)	Mean QTc interval at 2 min (msec)	Mean QTc interval at recovery (msec)
Male	434.8 ± 40.5	455.9 ± 40.8	447.6 ± 35.7
Female	441.1 ± 44.8	457.9 ± 44.8	452.4 ± 43.0
Ischemia on SPECT MPI	437.8 ± 46.6	458.1 ± 46.0	448.3 ± 39.9
Scar on SPECT MPI	436.3 ± 57.8	458.9 ± 56.4	450.3 ± 55.1
On QTc interval prolonging medication	435.1 ± 42.7	455.7 ± 47.5	450.7 ± 44.7
Not QTc interval prolonging medication	439.5 ± 43.0	457.5 ± 41.1	450.1 ± 37.7

Table 3
Multivariate logistic regression analysis evaluating the effect of baseline variables on QTc change.

Patient characteristics	QTc tertiles[a]			p-value
	Q1	Q2	Q3	
Patients on QT prolonging medications	Ref	0.87 (0.63–1.20)	0.99 (0.71–1.38)	0.64
MPI result with scar	Ref	1.52 (0.90–2.57)	0.82 (0.52–1.31)	0.06
Positive Stress ECG	Ref	1.99 (1.32–3.02)	2.06 (1.35–3.15)	0.0004

[a] Values reported as odds ratio (OR) with 95% confidence interval.

interval regardless of whether patients were on QTc prolonging medications or not. QT prolongation improved in recovery period with no adverse effects. We did find a statistically significant correlation between prolongation of QTc interval and positive stress ECG after Regadenoson injection. There are studies in literature demonstrating a positive correlation between QTc prolongation, cardiac ischemia and adverse outcomes. However, very few patients had ST changes associated with QT prolongation and ischemia.[9–11] Different mechanism have been suggested which can lead to prolongation of QTc interval in ischemia.[12] It is debatable whether it was ischemia that caused QTc interval prolongation with Regadenoson or a direct effect of Regadenoson itself in our study.

Food and Drug Administration (FDA) database had documented episodes of bradycardia, QT interval prolongation, complete AV block, cardiac arrest and episodes of unresponsiveness attributed to Regadenoson injections.[13] Clinical trials during development of Regadenoson showed around 3% patients having first degree and 0.1% patients having second degree AV nodal block. Around 26% patients developed rhythm or conduction abnormalities with Regadenoson and 14% of patient were seen to PVCs.[14] Our study did not identify in any life-threatening arrhythmias.

We did not measure PR interval which is a limitation of our study. However we did not find any incidence of second or third degree heart block in our patients. New PVCs were noted in around 8% of our patients after regadenoson injection. Around 30% had PVCs at baseline, seen to occur more frequently after injection. However, these were not statistically significant.

5. Conclusion

Patients who undergo MPI are mostly patients at intermediate risk for adverse cardiovascular events. Our study is one of the largest studies to assess the effects of Regadenoson in pharmacological MPI stress testing. The QTc interval prolongation seen in majority of our patients after Regadenoson injection failed to show any statistical significance. Interestingly we did find a positive correlation with QTc interval prolongation and positive stress ECG. It can be concluded that Regadenoson is a safe drug for use in MPI with little, if any, side effects of major clinical significance.

5.1. Study limitations

We used Bazett's formula in our study which is one of the commonly used formulas for QT interval correction. However it has been shown to overestimate and over-diagnose prolonged QTc interval in few studies with no increase in associated mortality when compared to those with normal QT interval.[15] There was no comparison group in our study to assess the causal relationship of QTc prolongation with Regadenoson.

Declaration of competing interest

There are no disclosures to report by any author of this manuscript.

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