Performance and safety profile of regadenoson myocardial perfusion imaging: first experience in Greece

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Keywords: CAD -Imaging -Myocardial -Perfusion -Regadenoson

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Received:
19 September 2017
Accepted revised:
16 November 2017

Abstract

Objective: MPI can provide valuable information in the investigation of patients with known or suspected coronary artery disease. The stress component of the studies can be conducted with regadenoson, which was approved for clinical use in Greece in 2016. We investigated the performance and safety profile of regadenoson MPI based on our 7 months institutional experience. **Patients and Methods:** We studied 96 consecutive patients (59 males, 37 females, mean age 70.35y.o, range: 46-87y.o.) referred to our department for a clinically indicated MPI study with pharmacological stress. Eleven patients suffered from chronic obstructive pulmonary disease. Patients underwent regadenoson stress test, combined with both stress and rest imaging. Data on the symptoms and electrocardiographic changes due to regadenoson administration were recorded. Symptoms were graded as 1-mild: a symptom that did not distress the patient, 2-moderate: a symptom that distressed the patient but it was self-limiting, or 3-severe: a symptom that distressed the patient requiring medical intervention. **Results:** Regadenoson-related symptoms were reported in 56 patients and were: dyspnea, discomfort, dizziness, chest pain, epigastric pain, neck pain, headache, flushing, nausea, heartburn, weakness, and upper limbs numbness. The severity of symptoms was recorded as grade 1 in 30 patients, grade 2 in 25 patients, and grade 3 in 1 patient. Two or more different symptoms were reported in 28 patients. Ischemic electrocardiographic changes and arrhythmias were observed in 8 patients. **Conclusion:** Our findings support previously published data indicating the optimal safety profile of regadenoson MPI, even in the group of patients suffering from chronic obstructive pulmonary disease.

Hell J Nucl Med 2017; 20(3): 232-236 *Epub ahead of print: 27 November 2017* *Published online: 11 December 2017*

Introduction

Coronary artery disease (CAD) is recognized as one of the main causes of death worldwide [1, 2]. Moreover, a significant number of patients are annually hospitalized due to CAD-related symptoms and complications; based on administrative data of 75,231 patients with previous hospitalization for acute coronary syndrome, 3.3% had a major adverse cardiovascular event during a 12-month follow-up period [3]. Therefore, accurate determination of the location and severity of CAD and risk assessment of future cardiac events are of great importance in the clinical setting.

Myocardial perfusion imaging (MPI) is a well-established and cost effective non-invasive imaging procedure for the assessment of myocardial perfusion, viability and ventricular function in patients with known or suspected CAD [4-9]. Physical exercise remains the most widely used stress component in MPI studies [10]. On the other hand, the main advantage of pharmacological stress is that it can be performed when contraindications to dynamic stress are present, or in patients who are unable to exercise adequately due to non-cardiac reasons (e.g. musculoskeletal disorders, neurological conditions). Active substances that are used for MPI studies include adenosine, dipyridamole, and dobutamine. Dipyridamole and adenosine bind to A_1, A_2A, A_2B and A_3 subtypes of adenosine receptors which are located on the arteriolar vascular smooth muscle cells, inducing coronary arteries dilatation [11]. If vasodilatation is contraindicated, pharmacological testing can be performed using the inotropic agent dobutamine which also enables the detection of myocardial perfusion defects.

Regadenoson is a selective A_2A adenosine receptor agonist developed specifically to overcome certain limitations of the conventional stress agents [12, 13]. Due to the non-specific binding to A_1, A_2B and A_3 receptors, adenosine and dipyridamole may induce serious adverse effects, including bronchospasm, conduction abnormalities (grade II or III atrioventricular block) and hypotension. When compared to these agents, regadenoson

is expected to be linked to better patient tolerability, offers an option for patients at risk for adenosine-induced bronchoconstriction, and is characterized by lower potential for atrioventricular nodal prolongation [14-18]. Indeed, the efficacy and safety profile of regadenoson were determined in two double-blind, randomised clinical trials [17, 18]. Most adverse reactions recorded in patients receiving regadenoson were mild and transient, requiring no medical intervention. Furthermore, controlled trials, enrolling patients with reactive airways disease, confirmed in vitro findings suggesting a decreased potential to elicit bronchospasm in subjects with reactive airways [14-16]. Therefore, the introduction of regadenoson in the clinical setting may be related to important practical benefits in the process of performing MPI studies.

Regadenoson was approved for clinical use in Greece in 2016. At our Institution, it was introduced in December 2016. In the present study, we aimed to investigate the performance and safety profile of regadenoson MPI based on 7 months institutional experience.

Patients and Methods

The study was conducted at the Department of Nuclear Medicine, Army Share Fund Hospital in Athens, Greece, between December 2016 and July 2017. We enrolled 96 consecutive patients (59 males, 37 females, mean age 70.35y.o, range: 46-87y.o.) referred to our department for a clinically indicated MPI study using pharmacological stress. No patient met any of the contraindications for regadenoson administration such as: hypersensitivity to the active substance or to any of the excipients, second or third degree atrioventricular block or sinus node dysfunction without a functioning artificial pacemaker, unstable angina despite medical therapy, sever hypotension, or decompensated heart failure. Thirty patients had suffered a myocardial infarction (MI), 36 had undergone percutaneous coronary intervention (PCI), while in 15 cases a previous coronary artery by-pass grafting (CABG) was recorded. A significant number of participants reported one or more CAD risk factors, such as hypertension (84), increased cholesterol and/or triglyceride levels (72), family CAD history (20), and diabetes mellitus (36). Thirty eight patients were non-smokers, 37 ex-smokers and 21 smokers. Established diagnosis of chronic obstructive pulmonary disease (COPD) was recorded in 11 patients. The study was approved by the ethical committee of our hospital and informed written consent was obtained from all participants.

According to the study protocol, standard one-day stress-rest imaging was performed after technetium-99m (^{99m}Tc) methoxy isobutyl isonitrile (^{99m}Tc MIBI) administration in a weight-adjusted dose (average body mass index, BMI=29.1, range: 19-49.3). Coronary dilatation before stress MPI was induced using regadenoson-only method. Regadenoson (400 micrograms/5mL) was injected in a bolus, followed by 5 mL NaCl (0.9%). Radiotracer was administered after 30 seconds, followed by a flush of saline. Symptoms, hemodynamic parameters and ECG changes due to regadenoson were closely followed, with continuous ECG monitoring, for six minutes after the administration of the stress agent. Symptoms were graded as 1-mild: a symptom that did not distress the patient, 2-moderate: a symptom that distressed the patient but it was self-limiting, or 3-severe: a symptom that distressed the patient requiring medical intervention.

Stress images were acquired 45 minutes after radiotracer administration. Three hours later, a rest dose of ^{99m}Tc-MIBI (2.5 times the stress dose of about 370MBq) was administered (total stress-rest dose <1,295MBq), and rest imaging was performed after 45 minutes. Two independent experienced observers blindly evaluated the scintigraphic images, classifying the studies into three categories (negative, positive and non-diagnostic). In case of discordance between the two observers, the view of a third observer was requested and the disagreement was resolved by consensus.

Results

Regadenoson-related symptoms in the study sample are presented in Table 1. Figure 1 shows the number of different symptoms per patient, using three categories (none, one, more than one symptoms). The severity of the symptoms observed (Grades 1-3) is presented in Figure 2. In one patient classified as grade 3, severe dyspnea and discomfort were observed, while no ECG changes were recorded. The patient was female, 73y.o., ex-smoker without established COPD diagnosis. No active wheezing was present before the test. Due to the severity of symptoms, aminophylline (5mL) was administered, and both discomfort and dyspnea resolved.

Table 1. *Regadenoson-related symptoms in the study sample.*

Symptoms	No.	Symptoms	No.
Dyspnea	29	Flushing	04
Dizziness	12	Heartburn	04
Discomfort	11	Neck pain	03
Chest pain	09	Nausea	03
Headache	07	Weakness	01
Epigastric pain	06	Numbness (upper limbs)	01

Ischemic electrocardiographic changes (ST segment depression of up to 1mm, T-wave changes in a form of inversion) and/or premature ventricular contractions were observed in 8 patients. No atrioventricular blocks, significant hypotension, or bradycardia were recorded.

Among patients with established COPD diagnosis, no symptoms were observed in 8 patients. One patient com-

plained for discomfort, while another complained for discomfort, dizziness and dyspnea. Discomfort and nausea com-bined with ECG changes were recorded in one patient.

In the study sample, the mean heart rate at baseline, mean maximum heart rate during monitoring, and mean heart rate at the end of monitoring (approximately 6min after regadenoson administration) were 66.5±11.1 beats per minute (bpm), 93.2±15bpm and 79.7±11bpm, respectively. The mean increase of heart rate during monitoring was 26.6±10.9bpm (mean per cent increase: 41.3%±17.9%). Mean systolic blood pressure at baseline and at the end of monitoring were 142.3±21.5mmHg and 132.4±19.9mmHg, respectively ($P<0.001$), while the corresponding values for diastolic blood pressure were 79.4±12.2mmHg and 75.9±11.8mmHg ($P<0.05$).

The majority of MPI studies were interpretable; 62 were positive and 29 negative. Five studies were classified as non-diagnostic (inconclusive), mainly due to potential attenuation artefacts and high abdominal radiotracer activity. Figure 3 shows a normal MPI study in a 86 y.o. male patient without regadenoson-induced side-effects. In another patient (male, 62 y.o.), no regadenoson-induced symptoms were also reported; however, the study was positive (Figure 4).

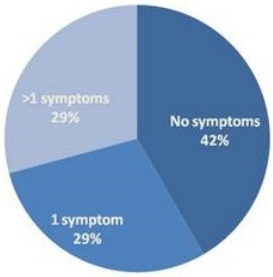

Figure 1. Clinical features associated with regadenoson administration. No symptoms were recorded in 40 patients (42%), one symptom in 28 patients (29%) and two or more symptoms in 28 patients (29%).

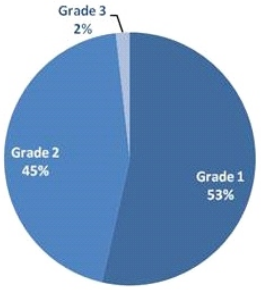

Figure 2. Severity of regadenoson-related symptoms. Thirty patients were classified as grade 1 (53%), 25 as grade 2 (45%) and 1 as grade 3 (2%).

Discussion

The efficacy and safety profile of regadenoson stress MPI were demonstrated, even in patients with reactive airways diseases, in previous randomized controlled trials [14-18]. Over a wide range of BMI, regadenoson was found to be safe, while the combination with low-level exercise tended to improve side-effects profile [19, 20]. Interestingly, the combination of regadenoson with low-level exercise was also investigated in patients with severe COPD, and was associated

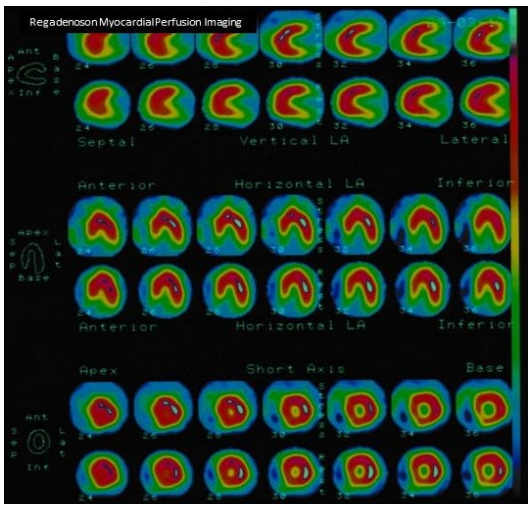

Figure 3. Normal myocardial perfusion imaging study in a 86 y.o. patient. No regadenoson-induced side-effects were reported.

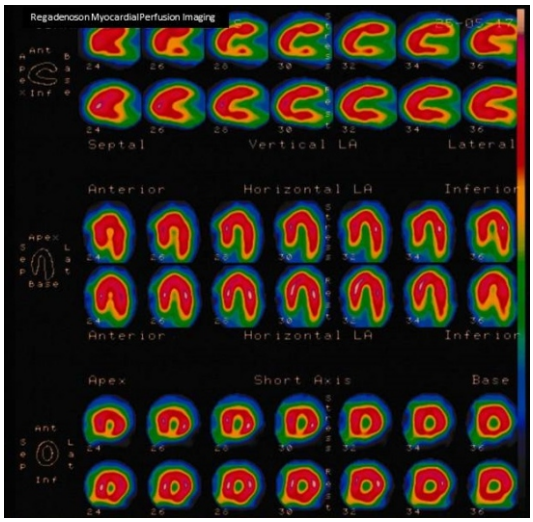

Figure 4. Positive myocardial perfusion imaging study in a 62 y.o. patient (myocardial ischemia at the inferior wall and part of the anterior wall of the left ventricle). No regadenoson-induced side-effects were reported.

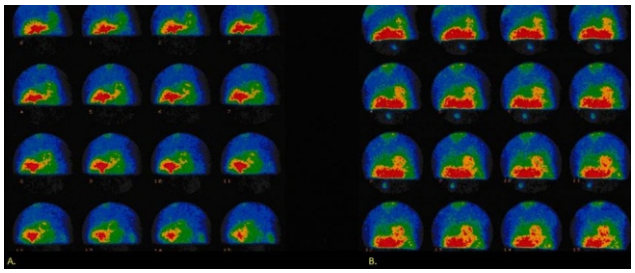

Figure 5. Stress raw images in two patients undergoing myocardial perfusion imaging, combined with regadenoson administration. A. Normal abdominal tracer uptake. B. High abdominal tracer uptake.

with adequate patient tolerance [21]. Moreover, in patients with pulmonary hypertension or severe aortic stenosis, regadenoson stress MPI was reported to be well tolerated and safe [22, 23]. patients with advance chronic kidney disease

and dialysis, there is evidence supporting the safety profile of regadenoson stress MPI, despite the fact that over 50% of regadenoson elimination occurs through the kidneys [24-26].

According to our findings, regadenoson-related symptoms were common in the study sample; dyspnoea, dizziness, and discomfort were the side-effects recorded more frequently. Notably, in 98% of the symptomatic cases, the clinical features were tolerable and of short duration, even in patients suffering from COPD. In one patient who received aminophylline, we believe that there was a psychological component of fear regarding the procedure that contributed to the severity of dyspnoea.

Previously, in a large European cohort, mild regadenoson-induced symptoms were reported in most patients; dyspnoea and chest discomfort were the commonest side effects [27]. Similarly to our study, the institutional experience regarding regadenoson administration has been reported by several centres, including those in the Netherlands, Denmark and Bosnia-Herzegovina [28-30]. In the study conducted in Bosnia-Herzegovina, more than half of the participants (66%) experienced one or more side-effects upon regadenoson administration [30]. The corresponding value in our study sample was 58%. However, in the study conducted at the Aalborg University Hospital, Denmark, one or more adverse events were reported in 90% of patients and were mainly dyspnea, headache, and chest pain [29]. Moreover, in the Dutch study, dyspnoea, followed by flushing and chest pain, was the commonest symptom [28]. Therefore, although regadenoson is a selective A_2A adenosine receptor agonist with low binding affinity for the A_2B and A_3 receptors, dyspnoea was found to be one of the commonest side-effects related to the performance of regadenoson stress MPI not only based on our results, but also in other studies [27-30].

In general, the use of regadenoson has been associated with a higher occurrence of adverse effects, in comparison to adenosine or dipyridamole [31, 32]. On the other hand, ECG changes after regadenoson administration occur infrequently and have low sensitivity for detecting ischemia [33]. In our study sample, no significant ECG changes were demonstrated.

Adjunction of handgrip exercise to regadenoson administration was reported to improve image quality [34]. Interestingly, in our study sample without low-level exercise, high abdominal radiotracer activity was noticed in some cases, posing an interpretation problem when evaluating inferior wall perfusion, and leading to non-diagnostic results (Fig. 5). However, elevated abdominal radiotracer activity can be also observed after adenosine stress test.

Regadenoson stress MPI was related to a more efficient utilization of laboratory resources, compared to adenosine or dipyridamole [35]. Given our previous institutional experience with other pharmacologic stressors (mainly adenosine), we believe that the handling and application of regadenoson proved to be easy and efficient, offering an additional option for patients at risk for adenosine-induced bronchoconstriction.

Regadenoson as a stress agent was not found to influence the prognostic significance of MPI findings, compared to adenosine stress test [36]. However, due to the short period of regadenoson application at our department, no associations with post-imaging coronary angiography findings, or future major adverse events, have been attempted so far.

In conclusion, our findings support previously published data regarding the optimal safety profile of regadenoson MPI, even in COPD patients. In the study sample, regadenoson-related symptoms were common (56/96) but transient, requiring medical intervention in only one case. In the future, we plan to enrol more patients, particularly investigating the profile of regadenoson stress MPI in subgroups with special characteristics, such as patients with end-stage renal disease [37].

The authors of this study declare no conflicts of interest

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