Original Article

Regadenoson as a new stress agent in myocardial perfusion imaging. Initial experience in The Netherlands

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Abstract

Objective: Regadenoson is a recently approved selective adenosine-2A receptor agonist to induce pharmacological stress in myocardial perfusion imaging (MPI) procedures using a single bolus injection.

Material and methods: We included 123 patients referred for MPI because of suspected coronary arterial disease (CAD). Of these, 66 patients underwent a regadenoson stress test and 57 patients underwent an adenosine stress test preceding standard myocardial SPECT imaging. Technicians, physicians and patients were asked to report their experience using questionnaires.

Results: As compared to adenosine, regadenoson did not produce any atrio-ventricular block (0 vs. 10% with adenosine), but did produce minor tachycardia and minimal blood pressure changes while all other side effects were milder and shorter. There were fewer patients with severe complaints after taking regadenoson than adenosine (17% vs. 32%, respectively, p<0.01). The most frequent complaint reported was dyspnea, followed by flushing and chest pain. However, when they did occur, they usually disappeared rapidly. The overall symptom score, including severity and duration of side effects, was significantly lower after regadenoson than after adenosine (6.7 ± 6.3 vs. 10.0 ± 7.9, respectively; p<0.01.) SPECT imaging results were similar. The regadenoson procedure was faster and more practical.

Conclusion: Regadenoson, the new selective adenosine-2A receptor agonist, is a stress agent for MPI with a patient- and department-friendly profile.

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El regadenosón como nuevo agente de estrés para la adquisición de imágenes SPECT de perfusión miocárdica. Experiencia inicial en Holanda

Resumen

Objetivo: El regadenosón es un agonista selectivo para los receptores adenosínicos-2A recientemente aprobado para inducir estrés farmacológico con una sola inyección en bolo para la adquisición de imágenes SPECT de perfusión miocárdica (IPM).

Material y Métodos: Se incluyeron 123 pacientes consecutivos referidos para IPM por sospecha de enfermedad arterial coronaria (EAC). A 66 pacientes se les hizo una prueba de estrés con regadenosón y a 57 con adenosina, ambas seguidas por SPECT de manera estándar. A los técnicos, médicos y pacientes se les pidió que reportaran sus experiencias mediante cuestionarios.

Resultados: En comparación con la adenosina, el regadenosón no produjo ningún bloqueo auriculo-ventricular (frente al 10% tras adenosina), pero produjo una taquicardia menor y cambios de la presión arterial más leves que tras adenosina (17% vs. 32%, respectivamente, p<0.01). El efecto secundario más frecuente fue la disnea, seguido por rubor y angina, pero todos estos efectos se resolvieron rápidamente. La puntuación global de los síntomas, que incluye tanto la severidad como la duración, fue significativamente más baja tras regadenosón que tras adenosina (6.7 ± 6.3 vs. 10.0 ± 7.9, respectivamente, p<0.01). Las imágenes SPECT fueron similares. El procedimiento con el regadenosón fue más rápido y práctico.

Conclusión: El regadenosón es un nuevo agente de estrés conveniente para IPM con un perfil muy favorable para los pacientes y los departamentos de cardiología nuclear.

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**Introduction**

The use of single photon emission computed tomography (SPECT) with tracers such as $^{99m}$Tc-sestamibi or $^{99m}$Tc-tetrofosmin in myocardial perfusion imaging (MPI) is one of the basic procedures performed in patients suspected of having coronary artery disease (CAD). The principle of MPI is based on comparing the myocardial activity between stress and rest acquisitions. The activity is reduced in tissue irrigated by the stenotic artery compared to myocardial activity between stress and rest acquisitions. The activation is reduced in tissue irrigated by the stenotic artery compared to the normal blood flow in tissues irrigated by a normal epicardial coronary artery. This difference in myocardial blood flow produces a reversible defect which is characteristic of myocardial ischemia.

Several methods can produce the optimal stress test required for MPI. Conventional stress produced by physical exercise on a static bicycle or treadmill is widely used and represents the normal daily life and also provides information on the functional capacity of the patient. However, many patients are unable to produce the level of exercise required and thus, pharmacological stress with the same diagnostic potential has been developed, including adenosine (more frequently used in The Netherlands) and dipyridamole.

Nonetheless, the use of adenosine and dipyridamol has several disadvantages. Adenosine interacts with the 4 subtypes of the adenosine receptors leading to many side effects such as atrioventricular block (AV) (subtype 1A), bronchospasm (subtype 2B), flushing and headache due to general vasodilatation (subtypes 2A and 3). Coronary vasodilatation only depends on subtype 2B. Although the side effects of adenosine are brief and reversible and disappear rapidly after discontinuation of the infusion, many patients are uncomfortable with the procedure with adenosine. Other contraindications for the use of adenosine are second-degree atrioventricular block as well as conditions such as asthma or chronic obstructive pulmonary disease (COPD) which are often present in patients assessed for diseases of the coronary arteries and have many common symptoms such as dyspnea and chest pain.

These disadvantages of adenosine may be avoided with the use of the new stress agent called regadenoson. This drug has been used in the USA for more than 5 years, and has also recently been approved for use in several countries of the European Union including The Netherlands and France. Regadenoson is a selective agonist of the adenosine receptor 2A and does not, in theory, produce either AV block or bronchospasm. In addition, coronary vasodilatation is rapidly induced by regadenoson, and it can therefore be administered with a bolus injection over 10–20 s followed by saline flush (10 s) and radiotracer injection. The procedure is both practical and rapid.

The aim of this study was, therefore, to determine patient tolerance to regadenoson as well as evaluate the opinion of the patients and the professionals involved, the side effects presented and the logistic aspects in our high-performance cardiac laboratory. To do this we used regadenoson instead of adenosine in all the patients referred to the Department of Nuclear Medicine over a 2-week period and compared the results with those obtained with adenosine over an identical time period.

**Material and methods**

We included 66 consecutive patients referred for MPI for suspicion or follow-up of CAD. Forty-three patients were male (65%), and the mean age was 62.6 years (range: 41–88 years). Over 2 consecutive weeks at the beginning of 2013, regadenoson was administered to all the patients undergoing MPI. The results were compared with those in a group of 57 patients including 31 males (54%) with a median age of 64 years (range: 34–84 years) who received adenosine during the following 2 weeks. All the patients signed informed consent to participate in the study.

All the patients underwent a $^{99m}$Tc-tetrofosmin stress-rest MPI protocol with a time interval of 4–6 h between the doses. The patients were instructed to refrain caffeine consumption for at least 24 h before the study. All the studies were conducted by a nuclear medicine technician in the presence of a cardiologist or a nuclear medicine specialist.

ECG rhythm and blood pressure were monitored with the patient in supine. A slow bolus injection (15 s) of 5 ml of a fixed dose of 400 μg of regadenoson was given followed by 10 ml saline flush (approximately 10 s). $^{99m}$Tc-tetrofosmin (standard dose of 370 or 500 MBq in patients with a body weight >100 kg) was then injected followed by 10 ml saline flush. During the next 10 min the heart rate, blood pressure and ECG were continuously recorded before the injection of regadenoson, and at 1 and 3–4 min thereafter. Patients were asked to report any sensations or discomfort during the study. The technicians (2 of a group of 6 always present) and the physician (1 of a group of 4 always present) with lengthy experience (technicians 3–10 years and physicians >15 years) recorded the information using a sensation scale of 0 (absent), 1 (very mild), 2 (mild), 3 (moderate) 4 (severe) and 5 (very severe requiring medical care). In addition, the duration of the symptoms was reported into 3 categories: 0–1 min, 1–5 min and more than 5 min. The symptoms were classified as sensations of flushing, chest pain or oppression, general feeling of tiredness, nausea and abdominal pain, dizziness and others. In addition to the evaluation by the technicians and the physician, the patients were asked to report their symptoms in a questionnaire during the waiting time (45–60 min) after the study and before the acquisition of rest SPECT images. This questionnaire asked about symptoms similar to those described previously, including the severity and duration (0–10 min, 10–30 min, >30 min).

The mean number of moderate or severe symptoms (classified as 3, 4 or 5) and the number of patients with one or more severe symptoms were registered and compared in both groups of patients. To obtain a general impression of the side effects the total rate of symptoms was calculated, being defined as the product of the degree of severity and duration of each symptom, adding up the total of the symptoms of all the patients. Statistical comparisons were performed using the Student’s t test for independent parameters, with statistical significance expressed as a bipolar p of 0.05.

**Procedure with adenosine**

With regard to the stress test with adenosine, patients were prepared as in the protocol with regadenoson. The adenosine was intravenously injected by continuous infusion of 140 μg/kg/min over at least 6 min with the patient in supine. Three times later, 370 MBq of $^{99m}$Tc-tetrofosmin (500 MBq for patients with a body weight >100 kg) was injected. For rest study, patients received 740 MBq of $^{99m}$Tc-tetrofosmin (1000 MBq in patients >100 kg). The dose injected and the follow-up and evaluation by the technicians and the patients were the same as described in the procedure with regadenoson.

**Acquisition of SPECT images**

Both stress and rest SPECT images were carried out 45–60 min after tracer injection. The images were acquired with a conventional gamma camera ($n = 25$ after regadenoson, $n = 19$ after adenosine) or with a new type of gamma camera with CZT detectors (cadmium, zinc and tellurium) ($n = 41$ after regadenoson, $n = 38$ after adenosine). The conventional gamma camera was a dedicated double-detector cardiac camera (Ventri, GE Healthcare) with
low-energy, high-resolution collimators using a symmetric window of 20% at 140 keV, a matrix of 64 × 64, and a noncircular orbit with a 180° step-and-shoot acquisition based on 30 steps of 6° from 45° right anterior oblique to 45° left posterior oblique. All the patients were evaluated in supine with the arms above the head. The acquisition time was 12 min for stress and 15 min for rest. The SPECT CZT gamma camera is a multi-pinhole camera (NM/CT 570c, GE Healthcare) containing 19 stationary detectors which are simultaneously imaging the heart. Each detector contains 32 × 32 elements of pixelated CZT (2.46 mm × 2.46 mm). A symmetric energy window of 20% at 140 keV was used. All the patients were studied in supine with the arms above the head. The acquisition time was 5 min for stress and 4 min for rest.

The quality of the SPECT images was assessed by experienced nuclear physicians and cardiologists using a scale of 2 = good, 1 = reasonable and 0 = bad. The mean of the two groups was denominated by the index of quality. Extracardiac activity was also registered using a scale of 0 = none, 1 = little but with no effect on the assessment, 2 = marked and hampering with the evaluation of myocardial activity. Lastly, the results of the studies in both groups were registered.

Results

Regadenoson was well tolerated by all the 66 patients, with no other medications such as aminophylline, salbutamol or nitroglycerin being required.

ECG, blood pressure and heart rate

Atrio-ventricular block was not observed in the group receiving regadenoson but was found in those administered adenosine; 6/57 patients (10%) presented episodes of first- or second-degree AV block (p < 0.01). Only one patient receiving regadenoson and 2 patients with adenosine presented ECG changes associated with ischemia.

The systolic blood pressure increased slightly in the first minute after the administration of regadenoson but decreased slightly over the following 3 min to a post-stress value similar to baseline (p = ns). Diastolic blood pressure decreased during the first minute after the injection of regadenoson but remained stable, showing a slight global decrease of 6 mmHg (SD 21).

The global reduction in the adenosine group was significantly greater than in the regadenoson group; the initial decrease was 9 ± 27 mmHg with adenosine versus an increase of 1 ± 15 mmHg with regadenoson. The decrease in diastolic blood pressure was similar in the two groups (4 mmHg and 1 mmHg, respectively, p = NS).

The maximum heart rate clearly increased from 68 ± 11 to 94 ± 15 bpm 4 min after the injection of regadenoson, being slightly greater than that observed after adenosine (26 ± 10 versus 22 ± 11 bpm, respectively; p < 0.05). The maximum heart rate in the regadenoson group was 131 bpm versus 133 bpm in the adenosine group.

Symptoms

In general the technicians and the patients reported few, mild and short lasting side effects with regadenoson, being significantly less frequent, milder and shorter compared to those reported in the adenosine group (Table 1 and Fig. 1).

According to the technicians and the physicians, the average number of moderate or severe symptoms was 0.67 ± 0.83 with regadenoson and 1.44 ± 1.50 for adenosine (p < 0.001). The number of patients with one or more severe symptoms was 11/66 (17%) after regadenoson versus 18/57 patients (32%) after adenosine (p < 0.01). This difference was the same as that in the questionnaires answered by the patients, albeit with an even higher percentage; 31 patients (45%) considered their symptoms to be “severe” after regadenoson versus 50 patients (76%) after adenosine (p < 0.001).

Table 1 shows a subdivision of the side effects presented. Dyspnea was the symptom most frequently observed followed by flushing and chest pain after regadenoson, while flushing was more frequent followed by chest pain and dyspnea in the adenosine patients.

Interestingly, the severity of the side effects was reportedly mild or moderate according to the technicians but was always more severe in the evaluation by the patients. The duration of the side effects with regadenoson was generally short, with most of the symptoms disappearing within 30 min. Flushing, chest pain, dyspnea, headache, tiredness, and nausea were described in 11, 14, 11, 31, 36 and 20% of the patients, respectively and, according to the patients, lasted longer than 30 min. The percentages reported in the evaluations by the technicians were somewhat lower. The side effects with adenosine also disappeared rapidly, although 10–20% of the patients reported a duration of >30 min.

A global index of all the symptoms (including the presence, duration and severity) was calculated, being significantly lower with regadenoson than adenosine (6.7 ± 6.3 vs. 10.0 ± 7.9, p < 0.01).

One of the 6 patients with previously known asthma or COPD or who received drugs related to pulmonary disease presented grade 4 dyspnea which rapidly reversed within a few minutes. None of the other patients presented pulmonary symptoms of greater than grade 1 (very mild).

SPECT results

No differences were observed in the quality of the SPECT images with the two stress agents (the index of image quality was 1.91 ± 0.27 for regadenoson vs. 1.89 ± 0.31 for adenosine, p = ns).

Neither were differences found in the frequency and severity of extracardiac activity: 54 patients with grade 0, 8 with grade 1, and 4 with grade 2 (6%) after regadenoson and 44, 10 and 3 [7%] respectively, after adenosine, p = ns). SPECT showed ischemia in

### Table 1

<table>
<thead>
<tr>
<th>Stress agent Evaluated by</th>
<th>Technicians/physician</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>41*</td>
<td>71</td>
</tr>
<tr>
<td>Chest pain</td>
<td>23*</td>
<td>56</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>Headache</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Tiredness</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>27</td>
</tr>
<tr>
<td>Global symptom score</td>
<td>0.67 ± 0.83*</td>
<td>1.67 ± 1.09</td>
</tr>
</tbody>
</table>

AD: adenosine; REG: regadenoson.

* Significance p < 0.05.
Technical: Severity of symptoms

Patients: Severity of symptoms

Technical: Duration of symptoms

Patients: Duration of symptoms

Fig. 1. Bar graph showing the severity and duration of the side effects after regadenoson (REG) and adenosine (AD), according to evaluation by the technicians and the patients themselves. Mean values are shown for the category of severity using a scale from 1 to 5 (very mild, mild, moderate, severe, very severe) and the category of duration with a scale from 0 to 3 (absent, 5–10 min, 10–30 min, >30 min).

14 patients (21%), fixed defects in 16 (24%), being normal in 39 patients (59%) in the regadenoson group versus 8 (14%), 11 (19%) and 28 patients (49%), respectively in the adenosine group (p = ns).

An example is demonstrated in Fig. 2.

In summary, it was impossible to determine whether the images had been made with regadenoson or adenosine as the stress agent, with no differences regarding reliability among the observers. Small differences are usually observed between images with the

Fig. 2. Example of stress (row 1 and 3) and rest (row 2 and 4) myocardial SPECT after regadenoson showing anteroseptal and inferior ischemia.
The use of this drug has also been approved in several European countries. Regadenoson is the first selective adenosine receptor agonist 2A. It is a potent vasodilator with a favorable safety profile, producing fewer side effects. In addition, it is easy to use, with only a single bolus injection and a mild profile of side effects was considerably more rapid and more convenient for both the patients and the personnel. Adenosine requires time for correct dose preparation, infusion volume and 6 min of infusion pump. In addition, it took several minutes for the symptoms to resolve. Many patients did not report symptoms with regadenoson. After tracer administration only a few minutes of observation were needed, and additional or other symptoms were not reported after leaving the stress room.

Logistic aspects

Similar to the adenosine procedure, patients received regadenoson in the stress room for a period of 20 min. The time from the beginning until the end of the procedure was not measured. However, it was clear that the intervention with regadenoson with a bolus injection and a mild profile of side effects was considerably more rapid and more convenient for both the patients and the personnel. Adenosine requires time for correct dose preparation, infusion volume and 6 min of infusion pump. In addition, it took several minutes for the symptoms to resolve. Many patients did not report symptoms with regadenoson. After tracer administration only a few minutes of observation were needed, and additional or other symptoms were not reported after leaving the stress room.

Discussion

Our results on the use of regadenoson were quite positive in that, on comparison with adenosine, fewer patients presented side effects and these were reportedly milder and shorter in length. The quality of the SPECT images and the capacity to induce ischemia were identical and the procedure was more rapid and more practical. The use of regadenoson was approved in the USA in 2006 and, to date, many articles have described the results obtained with this new stress agent.\textsuperscript{5–10} The use of this drug has also been approved in several European countries. Regadenoson is the first selective adenosine receptor agonist 2A. It is a potent vasodilator with a favorable safety profile, producing fewer side effects. In addition, it is easy to use, with only a single bolus injection the quantity of which does not depend on the patient’s body weight.\textsuperscript{6} Although adenosine and dipyridamole are also generally well tolerated, they may produce severe side effects such as bronchospasm and AV block. These symptoms are much less frequent with regadenoson and many studies have reported its application to be safe.\textsuperscript{7,11–13} The affinity of regadenoson with the adenosine receptor 2A is somewhat lower than that of adenosine, and thus, regadenoson adheres to the receptor longer and does not require the constant administration needed with adenosine. Several PET studies have demonstrated that the large number of adenosine receptors 2A present in the coronary vasculature ensures that vasodilatation with regadenoson is similar to that of adenosine.\textsuperscript{10}

Although the objective of this study was not to compare the capacity of regadenoson and adenosine to induce ischemia, which would have implied the need for larger groups and intra-individual comparisons, the percentages of ischemia, fixed defects and normal results did not differ between the two study groups. Moreover, the images did not indicate which stress agent had been used. The first studies with regadenoson in the USA did not show any difference in the induction of ischemia. Lastly, we did not observe any differences in the frequency of extracardiac activity.

As expected, our results were similar to those published in the USA. Regadenoson did not induce AV block and the changes in blood pressure were small. We only observed a moderate, short duration, increase in heart rate in most of the patients. Adenosine more frequently induced AV block and the changes in blood pressure were more severe, albeit with less marked tachycardia. The percentage of patients presenting severe symptoms after adenosine was almost two-fold greater than that found with the use of regadenoson (32% vs. 17%, respectively). The most common side effect was dyspnea followed by flushing and chest pain, all of which disappeared in less than 30 min. Neither aminophylline nor nitroglycerine was needed in any patient.

In the present study regadenoson was administered without the need for supplemental stress test (i.e. treadmill) which has been used in other studies to further increase stress levels or in cases in which the desired heart rate had not been achieved. This application of regadenoson seems to be safe and without severe side effects and also has the advantage of determining the functional capacity of the patients which cannot be achieved with only pharmacologically induced stress.\textsuperscript{14,15} Moreover, several groups reportedly use aminophylline routinely to further reduce the side effects.\textsuperscript{16}

The increasing use of regadenoson has provided more information regarding the safety of this stress agent, and it has also been described to be safe in end-stage renal insufficiency and liver disease.\textsuperscript{17,18} In addition, the safety profile of regadenoson is not related to age, genre, obesity and diabetes.\textsuperscript{19} Nonetheless, several publications have reported myocardial infarction during stress with regadenoson possibly due to a reduction in myocardial blood flow in territories dependent on collateral circulation.\textsuperscript{20} Epileptic seizures have also been associated with the use of regadenoson.\textsuperscript{21}

This study has several limitations which include the reduced sample size, the non-randomized nature and the low number of patients with lung diseases. However, European patients probably do not respond differently from those in the USA and therefore it should not be necessary to repeat all the American studies in Europe. Another limitation of our study was that the groups were compared separately instead of performing an intra-individual comparison in which the same patients would have received both adenosine and regadenoson.

The most important disadvantage seems to be the price of regadenoson. In several countries adenosine and dipyridamole only cost a few euros, making it difficult for regadenoson to compete. On the other hand, the high price of regadenoson may be compensated by its efficiency, shorter intervention time and less patient discomfort. Perhaps regadenoson can be used only in patients with pulmonary disease who cannot receive adenosine or dipyridamole, thereby avoiding the use of dobutamine. Several authors have described this latter use of regadenoson as safe, although further studies are needed.\textsuperscript{7,11–13}

In conclusion, the selective adenosine agonist 2A, regadenoson has shown to have a beneficial safety profile and few side effects for patients and in nuclear cardiology laboratories when used in MPI.

Conflict of interest

The authors declare no conflict of interest.

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