

Side Effects of Regadenoson Replacing Adenosine for Pharmacological Stress Tests in Real World: Prospective Evaluation in over 5000 Patients. M. Keller, M. Rippel, S. Silber, Munich Germany

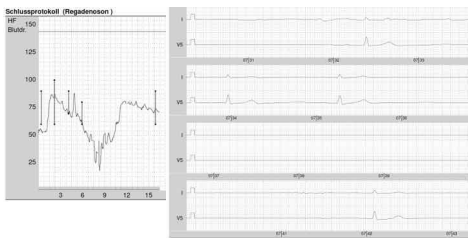
Introduction:

Pharmacological stress testing is indicated in patients who cannot be stressed adequately by physical exercise. Regadenoson is a highly selective A2A receptor agonist and approved in many countries for myocardial perfusion pharmacological SPECT stress imaging. The use of Regadenoson is much easier than the use of Adenosine without any need of an infusion pump and - in contrast to Adenosine - there is no need of body weight-related dose calculation, because a standard dose of 400 µg i.v. is applied to each patient. As a vasoactive drug, Regadenoson does have side effects, but there is only data regarding this issue available from some smaller studies, no prospectively collected data from real world application in high-volume centers.

Results: Blood Pressure

	Mean ± SD (Min - Max)
Systolic Blood Pressure	
Rest (baseline)	128.9 ± 16.2 (80 - 190) mmHg
Minimum	123.3 ± 20.3 (50 - 220) mmHg* (vs. Rest)
After 10 minutes	123.9 ± 15.5 (60 - 200) mmHg* (vs. Rest)
Diastolic Blood Pressure	
Rest (baseline)	73.7 ± 8.1 (50 - 110) mmHg
Minimum	69.3 ± 9.0 (40 - 110) mmHg* (vs. Rest)
After 10 minutes	70.8 ± 8.0 (40 - 100) mmHg* (vs. Rest)

Asystole with Regadenoson (0.3 per mill):



Methods:

Between February 16th 2012 and July 31st 2018 a total of 28351 myocardial stress tests with 99m Tc-Tetrofosmin were conducted. In patients unable to perform physical exercise, the standard dose of 400µg i.v. was injected initially over 10 seconds and after May 2012 over 20 seconds. Soon after the injection of Regadenoson, usually at a clearly visible increase of the heart rate, 99m Tc-Tetrofosmin was injected. Heart rate, blood pressure and ECG were continuously monitored before injection (rest), and up to 10 minutes after the injection of Regadenoson. All side effects were prospectively documented. SPECT perfusion scans were acquired with a double-head Anger gamma camera.

Frequent Side Effects:

	Nr. of Cases	Percentage
Shortness of Breath "Feeling of Increased Breathing"	3709	64.2 %
Headache	1199	20.7 %
Feeling of Warmth	1168	20.2 %
Pressure in the Chest	971	16.8 %
Pressure in the Stomach	935	16.2 %
Dizziness	519	9.0 %
Nausea	342	5.9 %
Sensation in the Legs	266	4.6 %

Summary and Conclusions-1:

- Pharmacologic stress testing is an important tool for making pivotal clinical decisions. In our practice, appr. 20% of all myocardial SPECT perfusion scans are with Regadenoson.
- Switching from Adenosine to Regadenoson makes sense and was immediately adopted by our nurses and technicians.
- General advantages of Regadenoson vs. Adenosine:**
 - advantage for the patients: less side effects
 - advantage for nurses / technicians: no dose calculations any more, no infusion pumps necessary
- Specific advantages of Regadenoson vs. Adenosine: In Nuclear Cardiology:**
 - for the patients: discontinuation of drug infusion after 99mTc injection
 - for technicians: easier handling, no stopcock confusion

Results: Demographic Data and Stress Tests

Due to inability of physical exercise, Regadenoson was needed in 5780/28351 cases (20.4 %). The mean age was 71.9 ± 9.7 (33 - 95) years. 2576 cases were male (44.6%) and 3204 cases were female (55.4%).

395 patients (7%) had a history of COPD, 113 patients (2%) had a history of bronchial asthma. 1051 patients (18.2%) had a pre-existing 1st degree AV-block (PQ time > 200 ms).

The vast majority of the cases (n=5011) didn't show any relevant/diagnostic ST-segment changes during the observation period of 10 minutes.

Rare Side Effects:

	Nr. of Cases	Percentage
Tightness in the Throat	200	3.5 %
Feeling of Weakness	176	3.0 %
Tussive Irritation	173	3.0 %
Feeling of Dry Throat and/or Mouth	116	2.0 %
Sensations in the Hands	99	1.7 %
Palpitations	102	1.7 %
Vomiting	39	0.7 %
Sweating	43	0.7 %

Summary and Conclusions-2:

- After the injection of Regadenoson, there was a significant mean heart rate increase of 25 bpm. The mean decrease of the systolic blood pressure was also significant with approx. 6 mmHg and so was the decrease of diastolic blood pressure with approx. 5 mmHg.
- Generally, Regadenoson is well tolerated.
- The most frequent side effect was a feeling of increased breathing / shortness of breath in appr. 2/3 of all cases.
- There are various different unspecific and transient rare side effects.
- Severe / life-threatening side effects are very rare (0.17%) and easy to treat with Atropine and - as officially recommended - with Aminophylline (if regionally available) or - like in Germany - with Theophylline.

Results: Heart Rate

	Mean ± SD (Min - Max)
Rest (baseline)	70.2 ± 12.3 (33 - 140) bpm
Maximum	94.6 ± 17.3 (52 - 193) bpm* (vs. Rest)
After 10 minutes	79.4 ± 13.2 (32 - 169) bpm* (vs. Rest)

* p < 0.001 according to Student's t-Test

Severe Complications:

	Nr. of Patients	Percentage
Asystole (≥ 6 seconds) (both patients had 1 st degree AV-Block at baseline)	2	0.03 %
Intermittent 2 nd or 3 rd degree AV-Block (with a relevant pause)	2	0.03 %
Symptomatic Bradycardia (< 40 bpm)	2	0.03 %
Symptomatic Drop in Blood Pressure	2	0.03 %
Epilepsy	2	0.03 %

These severe and potentially life threatening complications could be immediately interrupted with i.v. Theophyllin and Atropine. No patient died. There was neither a history of bronchial asthma nor of COPD in the group of cases showing severe complications. There was neither any case of Regadenoson-induced bronchospasm nor any stroke. All severe complications were observed within 10 minutes after the injection of Regadenoson, none was observed afterwards.

Safety Recommendations for Regadenoson:

- Continuous monitoring of blood pressure and ECG for 10 minutes. To be on the safe side, don't remove the injection needle for at least 20 minutes.
- Be aware of the contraindications (2nd degree AV-block).
- According to our experience, increased alert for patients with preexisting 1st degree AV-Block is advisable.
- Keep the antidotes ready and available for immediate use:
 - Theophylline, 10ml = 200 mg, slowly i.v.
 - Atropine, 1 ml = 0.5 mg, 1 - 2 vials i.v.