

Effects of adenosine A_{2A} receptor low affinity agonist Regadenoson in patients with obstructive pulmonary disease, at risk for adenosine-induced bronchoconstriction mediated via A_{2B} and/or A₃ adenosine receptors.

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Citation

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Abstract

The pharmaceutical Regadenoson (Lexiscan[™]) Produced by Astellas Inc. Is currently in use as a pharmacological stress agent for myocardial perfusion imaging within the field of Nuclear Cardiology. Regadenoson is a selective A_{2A} adenosine receptor agonist, and also has a low affinity for adenosine receptors which cause bronchoconstriction in patients with reactive airways mediated via A_{2B} and A₃ adenosine receptors. In a study of 42 patients with mild to moderate asthma and/or moderate to severe COPD who had a positive adenosine monophosphate test, Regadenoson proved to be relatively safe and well tolerated by most patients (90%).

INTRODUCTION

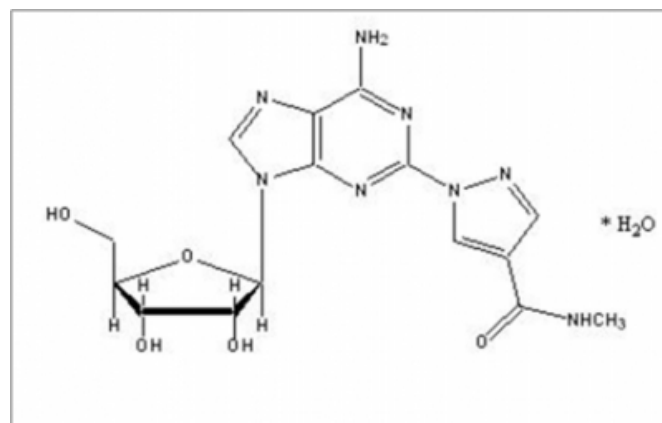
Regadenoson is a selective A_{2A} A-adenosine receptor agonist currently in use as a pharmacologic stress agent in myocardial perfusion imaging studies within Nuclear Medicine. It was approved by the United States Food and Drug Administration on April 10, 2008.⁸ Regadenoson is a low affinity agonist ($K_i \approx 1.3 \mu\text{M}$) for the A_{2A} adenosine receptor, with at least 10-fold lower affinity for the A₁ adenosine receptor ($K_i > 16.5 \mu\text{M}$), and weak, if any, affinity for the A_{2B} and A₃ adenosine receptors.^{2,9} Activation of the A_{2A} adenosine receptor by regadenoson produces coronary vasodilation⁸ and increases coronary blood flow (CBF). It produces maximal hyperemia quickly and maintains it for an optimal duration that is practical for radionuclide myocardial perfusion imaging.^{1,7} Regadenoson is delivered as a rapid bolus intravenously with no dose adjustment required by weight.⁴

REVIEW

Regadenoson is chemically described as adenosine, 2-[4-[(methylamino) carbonyl]-1H-pyrazol-1-yl]-, monohydrate. The molecular formula for regadenoson is $\text{C}_{15}\text{H}_{18}\text{N}_8\text{O}_5 \cdot \text{H}_2\text{O}$ and its molecular weight is 408.37.^{4,5}

Its structural formula is:

Figure 1



The solution is clear and colorless. Each 1 mL in the 5-mL vial or pre-filled syringe contains 0.084 mg of regadenoson monohydrate, corresponding to 0.08 mg regadenoson on an anhydrous basis, 10.9 mg dibasic sodium phosphate dihydrate or 8.7 mg dibasic sodium phosphate anhydrous, 5.4 mg monobasic sodium phosphate monohydrate, 150 mg propylene glycol, 1 mg edetate disodium dihydrate, and Water for Injection, with pH between 6.3 and 7.7.⁵ The recommended intravenous dose of Regadenoson is 5 mL (0.4 mg regadenoson).⁵

Regadenoson has a 2-3 minute biological half-life, as

compared with adenosine (predecessor's) 30 second half life.^{4,5} Regadenoson stress tests are not affected by the presence of beta blockers, as regadenoson acts as a vasodilator but does not stimulate beta adrenergic receptors.^{4,9} Oral ingestion of caffeine, a nonselective competitive A_{2A} receptor antagonist, is usually contraindicated before vasodilator MPI^{9,8} because it attenuates the coronary hyperemia caused by the nonselective adenosine receptor agonists adenosine and dipyridamole in a dose-dependent manner.³ It has this effect on regadenoson, and was withheld in this clinical trial.

Patients with reactive airways are at risk for adenosine-induced bronchoconstriction, mediated via A(2B) and/or A(3) adenosine receptors.^{7,3} Since patients who have these conditions are being treated and tested with MPI (Myocardial Perfusion Imaging) using Regadenoson currently post-FDA approval, it is significant to note which precautions should be used with patients with prior lung conditions, and outcomes post MPI stress testing using Regadenoson. Benefits include statistical data on the safety and optimal use of the new pharmaceutical Regadenoson in populations of patients who have clinically stable COPD, asthma, or emphysema, in which the predecessor vasodilator Adenosine could not be used effectively without inducing bronchospasm.⁴ Effectiveness and ability to use Regadenoson in this population of patients, reduces patients further risk by potentially eliminating the need for cardiac catheterization in the event that a non-invasive cardiac stress test may be performed for analysis of coronary stenosis.

To examine the effects of regadenoson on airway resistance, a randomized, double-blind, placebo-controlled crossover trial was conducted with asthmatic and/or COPD patients with a positive adenosine monophosphate challenge test. Subject population comprised of patients with moderate to severe, yet clinically stable chronic obstructive pulmonary disease (COPD), and known asthmatics. Patients receiving glucocorticoids or oxygen and those with pretreatment wheezing were included². Short-acting bronchodilators were withheld for approximately 4 hours before treatment, with the exception of patients who presented with pre-test wheezing, who were administered a nebulized albuterol solution. A forced expiratory volume test was conducted as a baseline for each patient, with a mean forced expiratory volume in 1 second (FEV₁) of 1.67 +/- 0.50 L. Approximately 40% of the patient population in the study complained of dyspnea during daily activities. A forced

expiration volume test was conducted approximately 5 mins and 45 mins post Regadenoson administration. The mean ratio of the forced expiratory volume in 1 second (FEV₁) at each tested time point relative to the baseline FEV₁ gives an inclination the level of bronchoconstriction in these patients post administration of the pharmaceutical Regadenoson⁹. This was compared with placebo from 5 to 45 minutes after treatment.

No differences emerged between regadenoson and placebo on multiple lung function parameters, including repeated FEV₁ and forced vital capacity, respiratory rate and oxygen saturation¹. The most common adverse events with regadenoson were hypotension and tachycardia (58%), dizziness (53%), headache (44%), and dyspnea (26%). The mean heart rate increased with regadenoson (maximum of +10.4 beats/min) compared to placebo. The mean maximum decline in FEV₁ was 0.11 +/- 0.02 L with Regadenoson. On placebo the mean maximum decline was 0.12 +/- 0.02 L. Wheezing post Regadenoson was observed in 19% of the assessed patients. Wheezing post placebo was observed to be 9%. No patients required acute treatment with oxygen post Regadenoson, however 14% of patients actively wheezing pre-Regadenoson were administered a bronchodilator consisting of 2.5 mg nebulized albuterol. Out of the 14% of patients which developed acute wheezing, half of those patients were administered aminophylline intravenously, which alleviated bronchoconstrictive symptoms². The other half were administered a nebulizer treatment similar to treatment pre regadenoson, post FEV analysis. The aminophylline vs. albuterol challenge post onset of acute wheezing showed aminophylline to cause a reduction in acute symptomology an average of 4.8 minutes faster than albuterol. The mean ratio of the forced expiratory volume in 1 second (FEV₁) at each tested time point relative to the baseline FEV₁ was shown to be significantly higher after treatment with regadenoson as compared with placebo from 5 to 45 minutes after treatment. Three patients had a significant but asymptomatic FEV₁ reduction (-39.6%) after regadenoson that reversed spontaneously.

CONCLUSIONS

In a study of 42 patients with mild to moderate asthma and/or moderate to severe COPD who had a positive adenosine monophosphate test, Regadenoson proved to be relatively safe and well tolerated by most patients (90%). Its bronchoconstrictive effects were minimal, and although it

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reduced expiratory volume in most patients, it caused no significant effects more than a short term reduction in FEV.

TRADEMARKS

1. Marketed by: Astellas Pharma US, Inc. Deerfield, IL 60015. Vials Manufactured by: Baxter Pharmaceutical Solutions LLC, Bloomington, IN 47403. Syringes Manufactured by: Hospira, Inc. Lake Forest, IL 60045 USA. FDA Rev date: 4/10/2008 .

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