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Original Article

Safety of regadenoson in patients with severe chronic obstructive pulmonary disease

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ABSTRACT

Objective: To assess the safety of regadenoson, a selective agonist of A_{2A} adenosine receptors, combined with low-level exercise in subjects with severe chronic obstructive pulmonary disease (COPD), referred for myocardial perfusion imaging (MPI).
Methods: We studied prospectively 12 male patients with severe COPD. Stress was 4 min of low-level exercise with bolus injection of regadenoson (0.4 mg) at 1.5 min, followed by ^{99m}Tc-MPI agent injection. Demographics, medical history, lung medications, adverse events, oxygen saturation ($SatO_2$), MPI findings for coronary artery disease (CAD), and changes in systolic blood pressure (SBP), and heart rate (HR) were registered.
Results: The observed adverse event profile of regadenoson was similar to that of patients with mild–moderate COPD. There was no clinical exacerbation of COPD. Adverse events were self-limiting: dyspnea (33.3%), fatigue (25.0%), chest pain, headache (16.7%, respectively), and gastrointestinal discomfort, dry mouth, flushing, feeling hot and dizziness (8.3%, respectively). 25.0% of patients did not report any symptoms. We observed significant increases in SBP and HR from baseline (142.6 mmHg ± 22.3 vs 152.5 mmHg ± 18.5, and 80 b.p.m. ± 18 vs 105 b.p.m. ± 22, respectively; $p < 0.05$).
Conclusions: Regadenoson combined with low-level exercise is safe and well tolerated in stable patients with severe COPD undergoing MPI.

Seguridad de regadenosón en pacientes con enfermedad pulmonar obstructiva crónica severa

Palabras clave:
Regadenosón
Seguridad
Efectos adversos
Enfermedad pulmonar obstructiva crónica severa
Perfusión miocárdica

RESUMEN

Objetivo: Evaluar la seguridad de regadenosón, un agonista selectivo de los receptores adenosínicos A_{2A}, combinado con ejercicio de baja intensidad, en sujetos con enfermedad pulmonar obstructiva crónica (EPOC) severa, en estudios de perfusión miocárdica.
Métodos: Se estudiaron de forma prospectiva 12 pacientes con EPOC severa (todos ellos varones). El estrés consistió en la realización de un ejercicio de baja intensidad durante 4 min junto con la administración de un bolo de regadenosón (0,4 mg) a los 1,5 min, seguido de la inyección del radiofármaco tecneciado de perfusión miocárdica. Se registraron los datos demográficos, el historial médico, la medicación para patología respiratoria, los efectos adversos, la saturación de oxígeno ($SatO_2$), los hallazgos de enfermedad coronaria en el estudio de perfusión miocárdica y los cambios en la presión arterial sistólica (PAS) y la frecuencia cardiaca (FC).
Resultados: El perfil de efectos adversos de regadenosón fue similar al de pacientes con EPOC leve-moderada. No se produjeron exacerbaciones clínicas de la EPOC. Los efectos adversos experimentados, todos autolimitados, fueron disnea (33,3%), cansancio (25%), dolor torácico, cefalea (16,7%, respectivamente), molestias gastrointestinales, boca seca, rubefacción, calor y mareos (8,3%, respectivamente). El 25% de los pacientes no informaron síntomas. Se observaron aumentos significativos desde los valores basales de la PAS y la FC (142,6 mmHg ± 22,3 vs 152,5 mmHg ± 18,5 y 80 l.p.m. ± 18 vs 105 l.p.m. ± 22, respectivamente; $p < 0,05$).
Conclusiones: Regadenosón combinado con ejercicio de baja intensidad es seguro y bien tolerado en pacientes con EPOC severa estable sometidos a estudios de perfusión miocárdica.

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Introduction

Dynamic exercise is the method of choice for producing coronary hyperaemia in myocardial perfusion imaging (MPI). Pharmacologic stress is indicated in patients unable to perform adequate exercise stress due to physical limitations or medical constraints,[1] such as chronic obstructive pulmonary disease (COPD). Adenosine and dipyridamole are non-specific agonists of all adenosine receptor subtypes (A_{1A}, A_{2A}, A_{2B} and A_3) and are contraindicated in patients with COPD, due to potential A_{2B} and A_3 receptor-mediated bronchoconstriction. Dobutamine, the classic alternative stress agent for these patients, is considered an inferior test agent with a high incidence of adverse events.[2]

Regadenoson is a selective agonist of the A_{2A} receptor, and thus the risk of bronchoconstriction in patients with COPD is much lower. Several studies[3–5] support the use of regadenoson in patients with mild to moderate COPD or asthma. However, experience with regadenoson in patients with severe COPD is limited, probably because the low prevalence of severe disease (5.2% of COPD patients[6] makes patient enrolment difficult).

In spite of the lower respiratory capacity of these patients, the combination of low-level exercise during administration of regadenoson has been shown to be safe with a significant improvement in the adverse events profile together with a higher image quality.[7]

The goal of this pilot study is to report the safety profile of regadenoson in combination with low-level exercise in patients with stable severe COPD.

Methods

Ethical approval was provided by the Regional Committee for Clinical Trials (protocol code 0030/11 EPA-SP) and all procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

We prospectively studied 12 European male patients with severe COPD recruited from January 2014 to August 2015, mean age 71.5 ± 6.2 years, who underwent clinically indicated SPECT-MPI with regadenoson combined with low-level exercise. According to the Global initiative for chronic Obstructive Lung Disease (GOLD) criteria,[9] severe COPD was considered when the post-bronchodilator forced expiratory volume in 1 s of predicted value in combination with a forced vital capacity (FEV1/FVC ratio) was <70%, and the FEV1 value was between 30% and 49% (GOLD stage III). None of the patients needed oral corticosteroid therapy and none had active wheezing.

Stress and SPECT protocol

All 12 patients underwent a 2-day pharmacologic stress combined with low-level exercise/rest protocol. Low-level exercise was walking on the treadmill at 2.7–3.5 km/h and 0° incline[7] in the six of patients. The rest of patients performed an alternative type of low-level exercise such as forcefully swinging their legs while sitting on a stretcher[8] as they were unable to walk on the treadmill due to lower extremity problems (claudication, hip or knee prosthesis). Stress was 4 min of low-level exercise with bolus injection of regadenoson (0.4 mg) at 1.5 min followed by a 5 mL saline flush and ^{99m}Tc-MPI agent injection (Fig. 1). MPI radiopharmaceutical was ^{99m}Tc-tetrofosmin ($n = 3$) or ^{99m}Tc-sestamibi ($n = 9$).

SPECT/CT studies were acquired 45–60 min after injection of the radiopharmaceutical with a hybrid camera (Infinia^{TM} Hawkeye^{TM} 4, General Electric Medical Systems); using low-energy, high-resolution collimator, 20% window at 140 KeV, 128 × 128 matrix; and 12-s dwell time per stop. Attenuation correction was performed by low dose CT. Both set of images, noncorrected and attenuation corrected were used for interpretation. Acquisitions were gated at eight frames per cycle.

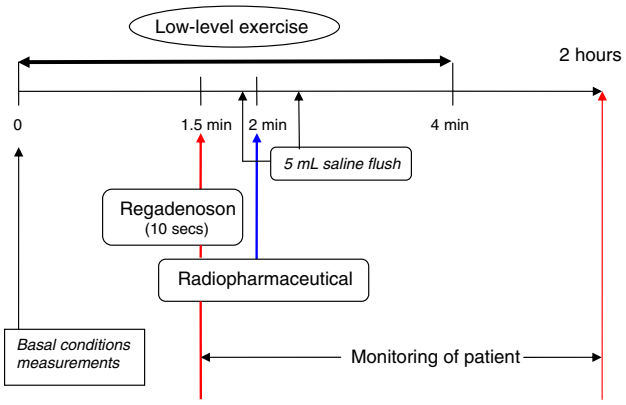

Fig. 1. Regadenoson low-level exercise protocol.

Study design

In this observational study, evaluations were carried out by monitoring the patient during the day of drug administration following the standard clinical practice of our department. Adverse events were all effects that occurred during or after the stress test (up to 2 h, because the majority of adverse events for regadenoson occur at this time[4]).

Demographics, medical history, lung medications, adverse events, oxygen saturation (pulsioxymetry measured $SatO_2$), and changes in systolic blood pressure (SBP) and heart rate (HR) were evaluated. SBP and HR were recorded as baseline (immediately before starting the test) and as maximum change (over the duration of the test) following regadenoson administration. An abnormal MPI report was also recorded (an example is shown in Fig. 2).

Demographics and clinical characteristics are shown in Table 1, whereas Table 2 shows the MPI results: type of ischemia, its location, size and intensity. The baseline respiratory medication is listed in Table 3. Nevertheless, these treatments had not been taken by the patients for at least 8 h before the test.

Data analysis

Continuous data were expressed as mean ± standard deviation (SD). Changes in SBP and HR were compared using the Wilcoxon *Z*-test for repeated measures, whereas the Friedman test was used

Table 1
Patient's characteristics.

	n	%
Patients (all male)	12	100
Age (years), mean ± SD	71.5 ± 6.2	–
BMI (kg/m^2), mean ± SD	28.6 ± 3.4	–
Hypertension	9	75.0
Dyslipidemia	8	66.7
Diabetes mellitus	6	50.0
Current smokers	1	8.3
Ex-smokers	9	75.0
Myocardial infarction	0	0
Abnormal MPI	6	50.0

n: number; SD: standard deviation; BMI: body mass index; MPI: myocardial perfusion imaging.