A rare complication of a common stress test

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A B S T R A C T

In 2008, regadenoson, a selective adenosine2A (A2A) receptor agonist, was approved by the US Federal and Drug Administration for use as a pharmacologic stress agent in myocardial perfusion studies. By stimulating A2A receptors in coronary smooth muscle, it can increase coronary blood flow by 2.5-fold or greater. Previous data showed non-inferiority of regadenoson in detecting reversible myocardial ischemia, compared to adenosine. Given less serious adverse effects, being better tolerated and easily administered, regadenoson has been widely used for myocardial perfusion imaging. As adenosine receptors have many sub-types and are located in multi-organ systems, regadenoson can cause various adverse effects, including bronchospasm, atrioventricular block, or hypotension. However, adverse effects on the central nervous system are rarely reported. As adenosine receptors (A1 and A2A receptors) play a major role in neuron–glial cells interaction, regadenoson can provoke seizure through A2A receptor activation. We hereby report a case of regadenoson associated-seizure and review seizure mechanism. This may raise more concern for a rare serious adverse effect of regadenoson which should be taken into consideration when selecting cardiac stress modalities.

<Learning objective: Regadenoson can provoke seizure through central A2A receptor activation. This should be taken into consideration when selecting cardiac stress test modalities, particularly in patients with known seizure disorder or history of organic brain disease.>

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Introduction

In 2008, regadenoson, selective adenosine2A (A2A) receptor agonist, was approved by the US Food and Drug Administration (FDA) for use as a pharmacologic stress agent in myocardial perfusion studies. Given less serious adverse effects, being better tolerated and easily administered, regadenoson has been widely used for myocardial perfusion imaging. Common adverse reactions of regadenoson are dyspnea, headache, flushing, chest discomfort, dizziness, nausea, and abdominal discomfort. However, regadenoson-related seizure has only been reported once.

Case report

A 63-year-old male with a history of hypertension, sick sinus syndrome with pacemaker placed in 2012, and ischemic stroke with residual right hemiparesis and expressive aphasia, presented for a stress test following multiple episodes of intermittent exertional chest pain associated with diaphoresis. Given multiple atherosclerotic risk factors, the pre-test probability was considered as moderate risk and he was arranged for regadenoson stress test. In the stress laboratory, the patient was injected intravenously with regadenoson 0.4 mg over 15 s per protocol. An estimation of 5 min later, the patient developed generalized tonic–clonic seizure which lasted for 2 min. The patient remained confused for 15 min after seizure stopped. At the time, the patient was afebrile with blood pressure of 115/70 mmHg and heart rate of 80/min. There was no bowel or bladder incontinence or new focal neurological deficit observed. The patient denied any history of seizure disorder or recent head injury. He also denied any fever, chills, or recent illness. His home medications were aspirin, metoprolol, and simvastatin. Upon admission, the patient was alert with normal orientation. Neurological examinations revealed expressive aphasia, with motor power grade 2/5 and 3/5 at right upper and lower extremities which were unchanged from baseline. The rest of the physical examination was unremarkable. The resting electrocardiography (ECG) showed electronic atrial pacing with no significant ST–T wave abnormality (Fig. 1). Blood chemistry showed...
serum sodium of 142 mmol/L, potassium of 4 mmol/L, calcium of 9.6 mg/L, and glucose of 116 mg/dL. Emergent computerized tomography of brain showed cystic encephalomalacia, compatible with chronic left middle cerebral artery territory infarct (Fig. 2). No acute intracranial abnormality was observed. Subsequent electroencephalography (EEG) study did not reveal any epileptiform activity. The patient was admitted to the observation unit for the next 24 h, during which he remained seizure free. He was subsequently discharged home. It was concluded that the seizure was provoked by regadenoson.

Discussion

Myocardial perfusion imaging (MPI) is a well-validated, non-invasive test for determining the diagnosis, severity, and prognosis of coronary artery disease. With an inability of the stenotic vessel to dilate, the discrepancy between normal and diseased myocardium can be visualized with the myocardial perfusion scan. In general, physical exercise is a preferred method of inducing stress. However, it is not suitable for all patients (e.g. musculoskeletal diseases, neurological diseases, morbid obesity, or debilitated patients). Therefore, pharmacological stress tests play a role among these groups. In the past, adenosine and dipyridamole (inhibiting the cellular uptake of adenosine) were widely used, as they both increase interstitial adenosine concentration, causing coronary vasodilation through adenosine A2A receptor. However, neither of them is specific to A2A receptor on coronary smooth muscles. With the concomitant blocking of A1, A2B, and A3, they can cause various side effects, such as flushing, chest pain, bronchospasm (A2B, A3), atrioventricular block (A1), and peripheral vasodilation (A2B) [1]. Thus, the selective A2A receptor agonist, regadenoson, came into interest after being approved by the FDA in 2008. According to ADVANCE MPI 1 and 2 trials, regadenoson was non-inferior to adenosine in detecting reversible myocardial perfusion defects, while being better tolerated and causing less serious side effects [2,3]. Moreover, regadenoson is more practical and cost-effective, as it does not require dose adjustment for renal function or body weight and can be given by a single injection of 0.4 mg intravenously. It can be safely used in chronic obstructive pulmonary disease and asthma patients, as studies showed no significant difference in pulmonary function parameters or clinical symptoms after being given regadenoson compared to placebo [4,5]. Regadenoson remains contraindicated in second- or third-degree atroventricular block and sinus node dysfunction (with an absence of pacemaker) given a low affinity toward A1 receptor. The report on safety and tolerability of regadenoson from a cross-sectional study in 753 subjects showed no significant difference in pulmonary function parameters or clinical symptoms after being given regadenoson compared to placebo [6]. Regadenoson remained contraindicated in second- or third-degree atroventricular block and sinus node dysfunction (with an absence of pacemaker) given a low affinity toward A1 receptor. The report on safety and tolerability of regadenoson from a cross-sectional study in 753 subjects showed no significant difference in pulmonary function parameters or clinical symptoms after being given regadenoson compared to placebo [6]. Regadenoson remains contraindicated in second- or third-degree atroventricular block and sinus node dysfunction (with an absence of pacemaker) given a low affinity toward A1 receptor. The report on safety and tolerability of regadenoson from a cross-sectional study in 753 subjects showed no significant difference in pulmonary function parameters or clinical symptoms after being given regadenoson compared to placebo [6]. Regadenoson remains contraindicated in second- or third-degree atroventricular block and sinus node dysfunction (with an absence of pacemaker) given a low affinity toward A1 receptor. The report on safety and tolerability of regadenoson from a cross-sectional study in 753 subjects showed no significant difference in pulmonary function parameters or clinical symptoms after being given regadenoson compared to placebo [6]. Regadenoson remains contraindicated in second- or third-degree atroventricular block and sinus node dysfunction (with an absence of pacemaker) given a low affinity toward A1 receptor. The report on safety and tolerability of regadenoson from a cross-sectional study in 753 subjects showed no significant difference in pulmonary function parameters or clinical symptoms after being given regadenoson compared to placebo [6]. Regadenoson remains contraindicated in second- or third-degree atroventricular block and sinus node dysfunction (with an absence of pacemaker) given a low affinity toward A1 receptor. The report on safety and tolerability of regadenoson from a cross-sectional study in 753 subjects showed no significant difference in pulmonary function parameters or clinical symptoms after being given regadenoson compared to placebo [6]. Regadenoson remains contraindicated in second- or third-degree atroventricular block and sinus node dysfunction (with an absence of pacemaker) given a low affinity toward A1 receptor. The report on safety and tolerability of regadenoson from a cross-sectional study in 753 subjects showed no significant difference in pulmonary function parameters or clinical symptoms after being given regadenoson compared to placebo [6].

In 1972, Burnstock et al. were the first to discover purinergic neurotransmission, involving release of adenosine tri-phosphate (ATP) as an efferent neurotransmitter [10]. Later, multiple studies confirmed that adenosine plays a key role in seizure regulation by controlling neuron–glial cell interactions, which made adenosine augmentation a new target of antiepileptic therapy [11]. Adenosine exerts central neuromodulation mainly through A1 and A2A receptors, given significantly lower affinity of A2B and A3 receptors. A1 receptor activation can decrease neuronal transmission
through inhibition of pre-synaptic neurotransmitter release and stabilization of post-synaptic membrane potential, which leads to seizure termination. In contrast, $A_{2A}$ receptor activation has both proconvulsant and anticonvulsant activities, depending on the brain location. In animal models, $A_{2A}$ receptor activation at cerebral cortex can enhance glutamatergic excitatory, and inhibit the neuroprotective activity of the $A_1$ receptor thereby causing cortex and limbic seizures, whereas activation at brainstem inhibits seizure. Based on this mechanism, the use of a selective adenosine $A_{2A}$ receptor agonist can potentially cause seizure [12,13]. In contrast, adenosine and dipyridamole have never been reported to cause seizure as they also activate $A_1$ receptor which is neuroprotective. By excluding other potential causes of seizure, such as metabolic causes and acute intracerebral pathology, we believe that regadenoson caused seizure in our patient. In 2012, Page et al. reported a case series of regadenoson-associated seizure, in which most of the patients had known epilepsy. The seizure evolved from partial to secondary generalized seizure. Although aminophylline is used to treat other reactions, its role in treating seizure remains inconclusive as it was found to prolong seizure in one case [9]. We therefore suggest having access to seizure termination medications (e.g. benzodiazepines) in the area of stress laboratories.

In conclusion, we hereby report a rare complication of a common cardiac stress test, which may raise more concern on stress test selection, particularly in patients with known seizure disorder or history of organic brain disease.

Conflict of interest

The authors declare no conflict of interest.

References