Asystole following regadenoson injection for myocardial perfusion imaging

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Abstract

We present a patient who developed asystole immediately after intravenous injection of regadenoson. After cardiopulmonary resuscitation, she recovered without clinical sequelae. Subsequent myocardial perfusion imaging with dobutamine showed normal perfusion, wall motion and ejection fraction. Regadenoson has a low incidence of second- or third-degree AV-block and only a few isolated cases of systole have been published. The exact mechanism by which regadenoson might cause asystole is unclear. Postulated mechanisms include vagal stimulation caused by central A_{2A} receptor activation or by activation of A_{2A} receptors in sympathetic afferent nerves, and increased production of endogenous adenosine.

Case

An 80-year old female was referred for myocardial perfusion imaging because of progressive shortness of breath. Her medical history included hypertension, hypercholesterolemia, diabetes mellitus, chronic obstructive pulmonary disease and resection of a myxoma from the left atrium. Prior to stress testing, a baseline ECG was recorded (figure 1), which demonstrated a normal sinus rhythm. Approximately 15 seconds after intravenous injection of 400 µg regadenoson, she suddenly became unresponsive, while the ECG showed asystole (figure 2). Cardiopulmonary resuscitation was started and after approximately 20 seconds she regained consciousness and was alert and oriented. Blood pressure was 176/81 mmHg at baseline and 140/75 mmHg immediately after the asystole. She did not experience any (worsening of) shortness of breath, chest pain, nausea, vomiting or other symptoms. Clinical monitoring at the coronary care unit and Holter ECG examination did not show any further signs of arrhythmia. Subsequently, myocardial perfusion imaging was performed with dobutamine as pharmacological stressor, without any complications. The perfusion images showed a normally sized left ventricle with normal perfusion, normal wall motion and normal ejection fraction.

Discussion

Regadenoson is a selective adenosine A_{2A} receptor agonist that increases coronary blood flow by >2.5-fold for a duration of 2-3 minutes and exhibits a tri-exponential decline in plasma concentration with a t½ of the initial phase of ±2-4 minutes, followed by an intermediate phase with a t½ of ±30 minutes (which coincides with loss of pharmacodynamic effect) and a terminal elimination phase with a t½ of ±2 hours (1,2). The selectivity of regadenoson for adenosine A_{2A} receptors suggests a low incidence of side effects such as flushing, shortness of breath, chest pain and transient AV block and arrhythmia, which are caused by effects at adenosine A_1 receptors (negative dromotropic, inotropic and chronotropic effects), A_{2B} receptors (bronchoconstriction and peripheral vasodilatation) and A_3 receptors (bronchoconstriction) (3,4). Phase II and III trials demonstrated that regadenoson is comparable (i.e. non-inferior) to adenosine in detecting perfusion defects, but better tolerated (5-7). Regadenoson received marketing authorization from the U.S. Food & Drug Administration (FDA) and European Medicines Agency (EMA) in 2008 and 2010, respectively.

In the phase III trials of regadenoson, no asystole or third-degree AV block was seen and second-degree AV block only occurred once. However, by study design, all patients were evaluated with an initial myocardial perfusion study with adenosine prior to randomization for a second imaging study with either regadenoson or adenosine and patients who developed high-degree atrioventricular block during the initial adenosine study were not eligible to be randomized, thereby introducing selection bias (6,7). Postmarketing evaluation of several large cohorts confirmed that regadenoson is safe and well tolerated (8,9), but a small number of isolated cases of severe bradycardia (10), advanced heart block (11,12) and asystole (13-18) have since been reported. A meta-analysis showed that the incidence of second- or third-degree AV-block after regadenoson

injection was 0.05%, significantly lower than adenosine at 5.21% (19). No cases of asystole after regadenoson injection were reported in any of the included studies, but case reports were excluded from the analysis. The exact mechanism by which regadenoson might cause asystole is unclear. Regadenoson has only weak action at A_1 receptors (>13-fold lower affinity than for A_{2A} receptors) and animal studies have shown that regadenoson does not prolong AV nodal conduction time (20). Postulated mechanisms include vagal stimulation caused by A_{2A} receptor activation in the hypothalamus, nucleus tractus solitarius or area postrema (Bezold-Jarisch reflex) or by activation of A_{2A} receptors in sympathetic afferent nerves, and increased production of endogenous adenosine (9,10,15,16,18,19,21). Administration of the nonselective adenosine receptor antagonist aminophylline may be administered to counteract adverse effects of regadenoson, similar to adenosine (21).

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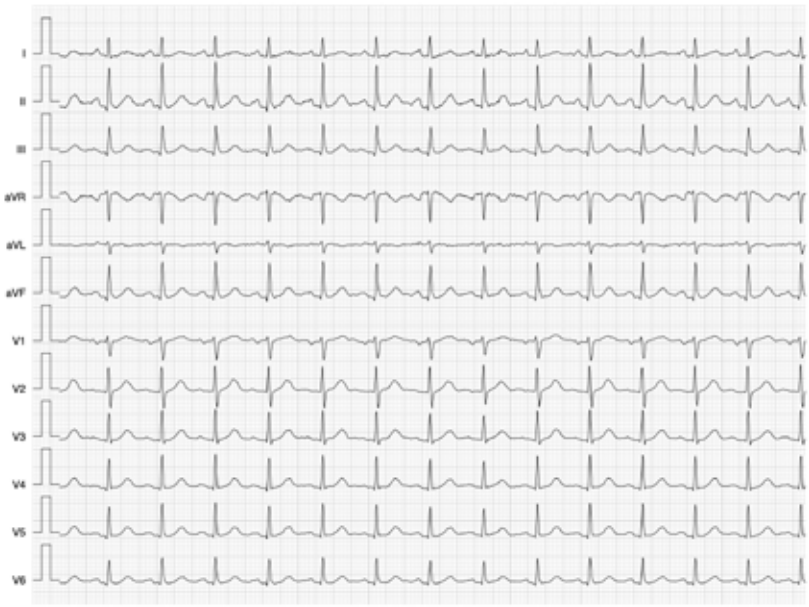

Figure 1. Baseline ECG.

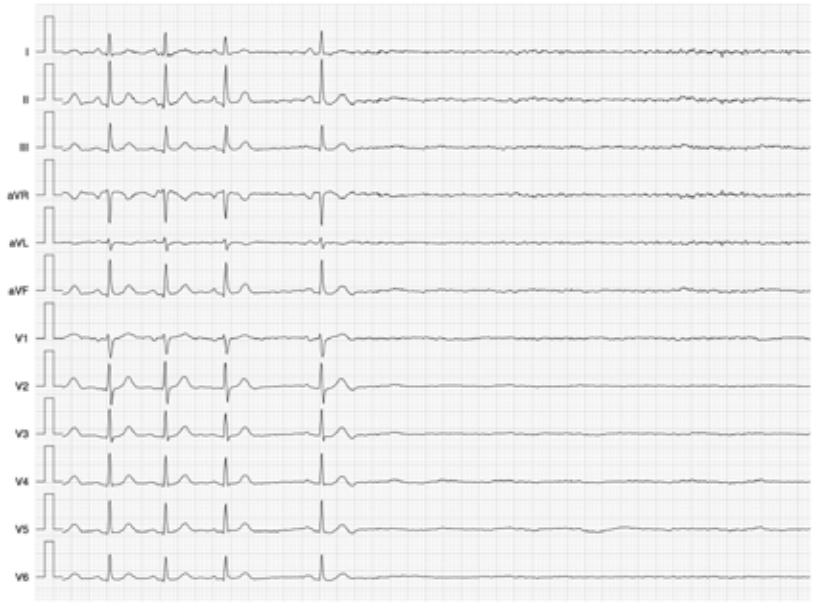

Figure 2. Asystole approximately 15 seconds after regadenoson injection.

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