Serious complications associated with regadenoson administration for myocardial perfusion imaging: A commentary

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In this issue of the journal Rosenblatt et al¹ report on two cases of asystole following regadenoson administration for myocardial perfusion imaging (MPI). Recent reports have described serious complications with regadenoson including high-grade atrioventricular block/asystole, myocardial infarction (MI), and seizures.^{2–6} One of us summarized the available data on the safety of regadenoson with respect to MI and asystole from clinical trials and post-marketing surveillance and detailed the limitations posed by these sources on our understanding of risk associated with regadenoson use.⁷

Underwood et al,⁸ in a letter to the editor, describe their experience with regadenoson in Europe. During the first year of using regadenoson for MPI at their center (1,581 consecutive patients, 90% of all patients stressed) they encountered no deaths, MIs, or hospital admissions following MPI but eight patients had adverse events; one experienced bronchospasm and seven had symptomatic hypotension with inappropriate bradycardia.⁵ While one case occurred prior to regadenoson administration and was likely related to intravenous cannulation, two cases progressed to sinus arrest and asystole and required cardiopulmonary resuscitation. After the first year of

using regadenoson, Underwood et al⁸ report that they continued to experience such events (which they label as vasovagal) at very low frequency. Although they have not been able to identify patients that are at higher risk, they speculate that these events are driven by vagal stimulation and propose that atropine may be more effective at reversing these hemodynamic effects than aminophylline.

Agarwal and DePuey,⁶ who have recently reported a case of advanced degree atrioventricular block and altered mental status (unresponsiveness) after regadenoson MPI, stress the risk of seizures with regadenoson use in their editorial.⁹ Page et al² have recently reported a case series of seizures associated with regadenoson use. As Agarwal and DePuey point out,⁹ the package insert of regadenoson has been recently updated to warn of the possibility that regadenoson may lower the seizure threshold. The package insert also states that fatal and nonfatal MI, ventricular arrhythmias, and cardiac arrest have occurred following regadenoson injection and that regadenoson should be avoided in patients with symptoms or signs of acute myocardial ischemia, such as unstable angina or cardiovascular instability, since these patients may be at greater risk of serious cardiovascular reactions to regadenoson. Finally, the updated package insert indicates that new-onset or recurrent atrial fibrillation with rapid ventricular response, atrial flutter, and cerebrovascular accidents have been reported following regadenoson injection.

It has to be appreciated that the patients referred for regadenoson MPI are high-risk patients that may have similar complications with other stress modalities (exercise, dobutamine, adenosine, dipyridamole) or even during observation with no intervention. Current ASNC guidelines discuss the absolute and relative contra indications for stress testing and clearly patients with unstable symptoms should not be stressed with

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Table 1. Serious complications associated with regadenoson administration for myocardial perfusion imaging

Side effect	Occurs with exercise	Occurs with adenosine	High-risk population	Definition	Aminophylline	Other Management
Myocardial infarction	Yes	Yes	Unstable-myocardial ischemia (has been reported in stable patients)	Difficult (MI vs stress-induced ischemia) *	Should be tried, preferably at onset of ST shift	Nitroglycerin Coronary angiography Guideline-directed therapy for MI/ischemia
High-grade AV block/asystole	Rare [#]	yes	Unknown (has been reported in patients with normal MPI)	Easy	Should be tried	Atropine if no response to aminophylline
Seizures	Rare ^{\$}	Not reported	Previous history of seizures (has been reported in patients without history of seizures)	Easy	Not recommended (may increase risk of seizures) [^]	Anti-convulsants (e.g., Benzodiazepines) plus supportive care

* ST shifts (elevation or depression) could be due to ischemia rather than MI, subsequent urgent coronary intervention may lead to slight biomarker elevation. Hence not all ST elevation with biomarker elevation is due to MI.

[#]We have seen one patient with severe ischemia.¹¹

^{\$}Not clear if exercise-induced or co-incidental.

[^]Lexiscan® (regadenoson) Package Insert. Revised 07/2014.

regadenoson or any other stress modality.¹⁰ Since these serious complications are relatively rare and regadenoson is widely used, the relevant challenges are: (1) identifying patients who are at higher risk of experiencing complications, (2) recognizing the complication quickly when it occurs (increased suspicion due to awareness that regadenoson can induce these complications), and (3) intervening appropriately. Understanding the mechanism(s) by which regadenoson induces these undesirable effects may shed more light on these challenges. Until then, we propose the following table as a simple guide for these serious complications (Table 1).

Disclosures

Dr Hage has received research grants and serves on a Scientific Advisory Board for Astellas Pharma USA. Dr Iskandrian is a scientific advisor for Rapidscan pharma and has received research grants from Astellas pharma USA.

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