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Editorial

Editorial: Regadenoson: An adenosine A_{2A} receptor agonist for pharmacological myocardial perfusion imaging

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Myocardial flow reserve measurement is the gold standard for risk stratification in patients with suspected coronary artery disease [1]. Vasodilator pharmacological stress myocardial perfusion imaging is based on the heterogeneity of radioisotope uptake in the myocardium being supplied by significantly diseased versus non-diseased coronary artery. Indications for pharmacological stress test are listed in Table 1. Pharmacologic stress perfusion imaging is an excellent adjunctive method for identifying high- and low-risk patients from an intermediate-clinical risk pool [2,3].

Regadenoson, a selective adenosine A_{2A} receptor agonist, is a novel pharmacologic stress agent under clinical development for myocardial perfusion imaging [4]. Regadenoson was approved by the US Food and Drug Administration (FDA) in 2008 in myocardial perfusion studies. In Japan, dipyridamole and adenosine triphosphate as well as adenosine had been used. The action of dipyridamole is mediated by increasing endogenous adenosine at the receptor site [5,6]. In 2006, adenosine was approved by the Ministry of Health, Labour and Welfare in Japan for the use of stress perfusion imaging. It enters the extracellular space by a carrier-mediated mechanism after the injection of adenosine. It also enters the intracellular space of endothelial, smooth muscle by facilitated transport. Several types of adenosine receptors are known. The adenosine A2 receptor is located on vascular cells, which are divided into A_{2A} and A_{2B}. Coronary vasodilation is mediated by the adenosine A_{2A} receptor. The A_{2B} and A3 receptors are responsible for bronchospasm. The half-life of adenosine is short, less than 2 s and adenosine has a rapid onset of action. Adenosine can increase coronary blood flow by 2.5-fold or greater. Therefore adenosine is used for the noninvasive evaluation of myocardial flow reserve in the clinical setting. The most common reported side effects of adenosine are flushing, shortness of breath, and chest pain, which usually disappear after the cessation of the infusion [7]. First- and second-degree of atrioventricular (AV) blocks occur in less than 10% of patients, and advanced AV block occurs in less than 1% of patients [8]. The most severe side effect, that is, bronchospasm can be treated rapidly with 50–100 mg of intravenous theophylline, which competitively blocks the adenosine receptor.

Like adenosine, regadenoson causes coronary vasodilation through its action on the adenosine A_{2A} receptor subtype [9]. A_{2A} receptor stimulation seems to be a desired way to cause significantly higher myocardial blood flow with more sustained hyperemia compared to adenosine. Regadenoson can be administered by a single bolus injection of 0.4 mg through peripheral vein without weight-adjustment. There is no need to adjust the dose in patients with renal failure as no adverse effects in patients with serum creatinine clearance of <30 ml/min have been observed. The effect of regadenoson on coronary circulation (rapid increase to more than 2.5-fold over baseline) is sustained for approximately 2.3 min and decreases to less than twice the baseline level within 10 min.

In the current issue of this journal, Junpaparp et al. [10] report on a rare complication of regadenoson in a 63-year-old male patient with ischemic stroke. After 5 min of the stress test, a patient developed generalized tonic–clonic seizure that lasted for 2 min. It was concluded that seizure was provoked by regadenoson. Page et al. [11] reported three cases of seizures associated with regadenoson. Recent clinical studies to examine the safety of regadenoson have been reported. The drug could be used safely in patients with chronic kidney disease [12]. Similarly, regadenoson could be given with end-stage liver disease patients waiting for liver transplantation [13]. Studies on patients with chronic

Table 1
Indications for pharmacological myocardial perfusion imaging.

Inability to exercise
- Physical limitations (elderly people, etc.)
- Recent operation
- Peripheral artery disease
Limited exercise capacity
- Medication such as beta-blocker
- Poor motivation for exercise
- Limited physical conditions
Contraindications to exercise
- Aortic aneurysm
- Acute coronary syndrome
- Severe aortic stenosis
False positive results may occur
- Left bundle branch block
- Ventricular pacing
- Wolff–Parkinson–White syndrome

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obstructive lung disease or asthma have reached the consensus that regadenoson can be used in patients with mild or moderate reactive airway disease [14]. However, regadenoson should be used with caution in chronic obstructive lung disease patients with a 24-h/day home oxygen requirement, prior intubation for respiratory failure, or recent exacerbation. ADVANCE MPI trials showed that regadenoson achieved non-inferiority to adenosine for pharmacologic stress test [15]. The agreement rates between the initial adenosine procedure and the second randomized procedure with either adenosine or regadenoson were almost identical. Since regadenoson has the potential for improving stress tolerability and a reduction in the number of serious adverse events, it appears to have appealing features for clinical use in Japan.

The safety of the drug is not completely assured for Japanese, under the circumstances that regadenoson is not yet approved in Japan. Care should be taken in performing regadenoson stress especially in patients with ischemic stroke or known seizure disorder, considering that the true incidence of seizures induced by regadenoson in these subjects is not known. Furthermore there is no good reason to suspect that regadenoson would be superior to adenosine in the management of patients with coronary artery disease. It would need further investigations in a larger clinical trial to grasp the nature of this medicine.

Conflict of interest

None.

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