Regadenoson: An adenosine A2A receptor agonist for pharmacological myocardial perfusion imaging

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Myocardial flow reserve measurement is the gold standard for the 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. The 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 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 cell, 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 the bronchospasm. Half-life of adenosine is very short, less than 2 seconds 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 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 AV blocks occur 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 50-100mg 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 is observed no adverse effects in patients with serum creatinine clearance of <30 ml/min. The effect of regadenoson on coronary

circulation (rapid increase to more than 2.5-fold over baseline) is sustained for approximately 2.3 minutes and decreases to less than twice the baseline level within 10 minutes.

In the current issue of this journal, Junpaparp et al report on a rare complication of regadenoson in a 63 year-old male patient with ischemic stroke [10]. After 5 minutes of the stress test, a patient developed generalized tonic-clonic seizure that lasted for 2 minutes. It was concluded that seizure was provoked by regadenoson. Page et al reported three cases of seizures associated with regadenoson [11]. Recent clinical studies to examine the safety of regadenoson had 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 obstructive lung disease or asthma have reached to 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-hour/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 have the potential for improving stress tolerability and the reduction in the number of serious adverse event, it seems to have appearing feature for clinical use in Japan.

The safely 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 regadenoson would be superior to adenosine in the management of the 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: Nothing to report.

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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
- WPW syndrome

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