Advances in Pharmacologic Agents in Imaging: New A2A Receptor Agonists

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Pharmacologic stress myocardial perfusion imaging is being performed with increasing frequency over exercise stress. Dipyridamole and adenosine have a high side-effect profile, provide higher than needed coronary artery flow rates, and use a relatively complicated method of administration. Based on preclinical animal work, three selective adenosine A2A receptor agonists, regadenoson (CVT3146), binodenoson (MRE0470 or WRC0470), and apadenoson (BMS068645 or ATL146e), may overcome these limitations and are now in Phase III studies as pharmacologic stress agents. For single-photon emission CT imaging, binodenoson and regadenoson were concordant with adenosine images for detection and quantitation of ischemia. Despite the high A2A selectivity of binodenoson and regadenoson in preclinical studies, subjective side effects attributable to other adenosine receptor subtypes were still observed in human studies and are similar to or slightly lower than adenosine. There have been no reports of atrioventricular block or bronchospasm with either regadenoson or binodenoson in published trials.

Introduction

Adenosine and dipyridamole are the most commonly used agents to induce coronary arterial vasodilation for myocardial perfusion imaging, most commonly in conjunction with single-photon emission CT (SPECT), but also with echocardiography, positron emission computed tomography (PET), and MRI. Both are given as a continuous infusion and act by a final common pathway: stimulating adenosine A2A receptors on arteriolar vascular smooth muscle cells. Unfortunately this effect is nonselective and there is activation of adenosine A1, A2B, and A3 receptors, which results in frequent undesirable side effects, and less frequent but serious side effects such as bronchospasm and high-grade atrioventricular (AV) block [1,2]. In addition, there are concerns regarding the extent of hyperemia produced with adenosine and dipyridamole as both agents produce a 4- to 4.5-fold increase in coronary blood flow (CBF) [3–5]. Because all the available radiotracers have nonlinear uptake at higher flow rates, so called plateau or drop-off effect, a lower extent of hyperemia is desirable. Given the side-effect profile, higher than needed flow rates and a complicated method of administration for adenosine and dipyridamole, there is a need for a more selective agonist of the A2A receptor subtype that is easier to administer and is capable of producing controlled hyperemia in terms of magnitude and duration.

Currently, three selective adenosine A2A receptor agonists have begun Phase III studies as pharmacologic stress agents, regadenoson (CVT3146), binodenoson (MRE0470 or WRC0470), and apadenoson (BMS068645 or ATL146e). Much of the preliminary animal and early human work has not been published as sponsors want to assure adequate patent documentation prior to public disclosure. The features of these agents are reviewed in detail in terms of how they meet the characteristics of the ideal agent, followed by the published clinical trial data.

Ideal Features of a Novel Pharmacologic Stress Agent

The ideal pharmacologic stress agent should be a selective A2A adenosine receptor agonist, provide selective coronary vasodilatation, have rapid onset and termination of action, and should be administered as a bolus [6]. It should reduce the total occurrence of undesirable side effects and specifically reduce the more serious side effects such as AV block and bronchospasm in patients with reactive airway disease. Selective coronary vasodilation should produce minimal or no effect on blood pressure. Rapid onset and offset would allow the vasodilatory effect to be available only when needed, 2 to 4 minutes to allow extraction of the radiotracer and increase blood flow two to three times above the baseline. Bolus administration, especially using a fixed dose, would obviate the need for an infusion pump and dose calculation.

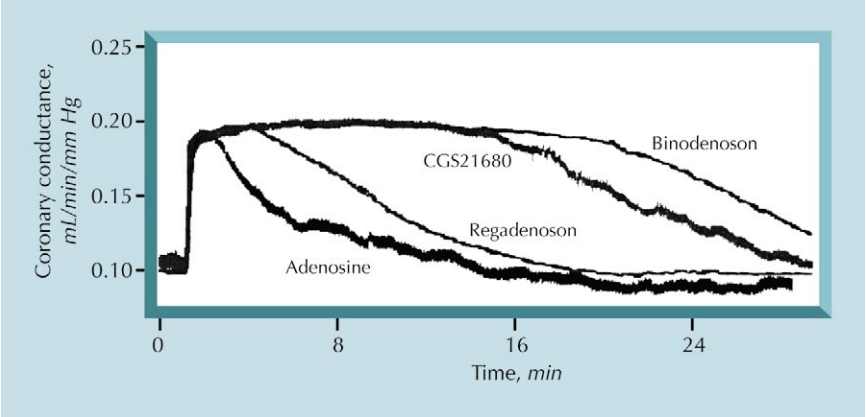

Figure 1. Time course of changes in coronary conductance caused by regadenoson, binodenoson, CGS21680, and adenosine. (*Data from* Gao et al. [9].)

Table 1. Affinity and duration of action of adenosine, regadenoson, CGS21680, and binodenoson

Agonist	Affinity for A2A receptor (Ki)*	Duration of action, *min*
Adenosine	2700–5000	1.6 ± 0.1
Regadenoson	1095	3.4 ± 0.5
CGS21680	157	14.5 ± 0.5
Binodenoson	21	21.9 ± 0.9

*The higher the Ki value, the lower the affinity for the A2A receptor. (*Data from* Cerqueira [6] and Gao et al. [9].)

Preclinical Studies

Selectivity, affinity, and clinical implications

The potency of an A2A agonist to induce coronary vasodilation depends primarily on four factors: 1) the affinity of the agonist for the target receptor (ie, agonist binding); 2) the density of the receptors at the targeted location; 3) the intrinsic efficacy of the bound agonist to activate the target receptor; and 4) the efficacy of coupling of the receptor activation to the response [7].

Increase in CBF

The ideal agent should give a rapid increase in CBF and maintain it for a sufficiently long duration to allow for maximal radiotracer extraction. In an experimental conscious dog study comparing bolus administration of adenosine and regadenoson at varying doses, it was shown that both agents produced a dose-dependent increase in flow that had a variable duration [8]. Overall, adenosine was less potent at comparable concentrations. After a 10-second injection of regadenoson (2.5 μg/kg), the increase in CBF remained at least twofold above baseline for 97 seconds, whereas for adenosine (267 μ/kg), the twofold increase in CBF lasted only 24 seconds ($P < 0.01$). A 30-second injection of 2.5 μg/kg of regadenoson prolonged the twofold increase in CBF up to 221 seconds. No AV block was observed.

Duration of effect

Gao et al. [9] reported the selectivity, affinity, and duration of action of A2A agonists including adenosine, regadenoson, binodenoson, and CGS21680. All of the agents tested achieved comparable and maximal increases in coronary vasodilation as shown in Figure 1. However, there was a difference observed in the duration of the coronary conductance. Adenosine had the fastest drop-off in conductance or flow followed by regadenoson and binodenoson. This can be explained by the inverse relationship between affinity for the A2A receptor and duration of action as shown in Table 1 [6]. Gao et al. [9] reported that low-affinity agonists, such as adenosine and regadenoson, can produce a response that is of equivalent magnitude, but more rapid in termination, than that caused by a high-affinity agonist such as binodenoson or CGS21680. Thus, an agonist with a relatively low affinity for the A2A receptor can cause maximal coronary vasodilation that is rapid both in onset and in termination. This may provide the clinical benefit of enhanced control and may prove to be superior to a high-affinity, longer-acting agonist as a coronary vasodilator for myocardial perfusion SPECT [6].

Selectivity for A2A

Another desirable feature is A2A selectivity and the duration of effect. In a study of conscious dogs, Zhao et al. [10] measured the magnitude of vasodilation by regadenoson and adenosine in different vascular beds. The maximal increase in CBF response to the two drugs was similar, but the potency of regadenoson and adenosine was markedly different. The highest dose of regadenoson caused a longer duration of coronary vasodilation than the highest dose of adenosine. This may be of clinical benefit in radionuclide SPECT by allowing maximal extraction of the radiotracer during heterogeneous blood flow induced by bolus injection rather than continuous infusion. The higher doses of regadenoson and adenosine induced comparable cardiac output and regadenoson induced smaller decreases in total peripheral resistance and smaller increases in lower body flow versus adenosine. Regadenoson has also been demonstrated to be functionally selective for the A2A receptor versus the A1 in isolated rat hearts, thus suggesting that regadenoson will not be likely to induce A1-mediated AV block in humans [9].

Selectivity and clinical implications

The preclinical studies reviewed above demonstrate that regadenoson is a highly subtype-selective, potent, low-affinity A2A agonist that can achieve a magnitude of maximal hyperemia equivalent to adenosine and, importantly, maintain maximal hyperemia for a short time period that is practical for radionuclide imaging. In the published studies for binodenoson, infusion has either been performed as a continuous infusion or as a bolus over 30 seconds [11,12,13•]. In addition to these beneficial characteristics, a novel A2A agonist for pharmacologic stress should also have minimal effect on peripheral vasodilation, avoid AV nodal block, and allow for rapid reversibility of drug effect.

Clinical Studies

Clinical studies for all agents are currently in Phase III trials to determine whether the promising characteristics demonstrated in animal models and isolated cells will translate to clinical benefit in human subjects. Kerensky et al. [14] investigated the magnitude and duration of the effect of regadenoson (10–500 μg) on CBF velocity in humans. Results demonstrated that regadenoson at a fixed dose administered by a 10-second bolus injection produced a dose-dependent increase in duration of CBF velocity augmentation. At all dose levels, regadenoson caused a rapid increase in CBF velocity that was near peak within 30 seconds of the bolus delivery. At regadenoson doses greater than or equal to 100 μg, peak effects on CBF velocity were equivalent to 18 μg of intracoronary adenosine. Regadenoson produced no major changes in heart rate or blood pressure. At the 400-μg dose, the maximum increase in heart rate at 1 minute was 18 ± 8 beats per minute. Also at 1 minute following regadenoson administration, the maximum decreases in systolic and diastolic blood pressures were 20 ± 8 mm Hg and 10 ± 5 mm Hg. Regadenoson was generally well tolerated and side effects at all doses were infrequent, mild, and self limited. For all patients (n = 36) at all doses, the most common side effects were chest discomfort (n = 3), increased heart rate (n = 3), flushing (n = 2), hypotension (n = 2), and shortness of breath (n = 2). No AV block or bronchospasm was reported.

On the basis of the above results, the fixed 400-μg dose of regadenoson allows bolus injection as a push and achieves at least a 2.5-fold increase in CBF velocity for duration of 2.5 minutes or longer [14,15•]. With binodenoson, the clinical trials have relied on 30-second infusion at weight-adjusted doses of 0.5 to 1.5 μg/kg and the radionuclide was injected 3.5 minutes after starting the bolus. One group also received a continuous infusion of 0.5 μg/kg over 3 minutes with radionuclide administration at the end of the 3-minute infusion [13•]. In ongoing clinical trials, apadenoson is administered as a weight-adjusted bolus at 1.0 μg/kg and the radionuclide is given 2 minutes after the bolus.

In a pilot crossover clinical study comparing the ability of regadenoson at 400 (n = 18) and 500 μg (n = 17) bolus injection to adenosine for the detection of myocardial perfusion defects on SPECT imaging, Hendel et al. [15•] demonstrated that overall agreement for the presence of reversible hypoperfusion was 86%. No dose-dependent effect of regadenoson on ischemia detection was noted. Regadenoson was generally well tolerated and side effects were mild and self limited. As expected, the 500-μg group reported a higher incidence of side effects than the 400-μg group, with dose-dependent changes in hemodynamics, flushing, dyspnea, and dizziness. Some form of adverse event occurred in 61% of the 400-μg group and 83% of the 500-μg group. There were no occurrences of AV block or bronchospasm.

In a trial involving 240 patients, four dosing methods with binodenoson were compared with standard adenosine infusion. There was good concordance, range of 79% to 87%, between the two stress agents with regard to exact categorical agreement in the extent and severity of reversible perfusion defects [13•]. With regard to any objective or subjective adverse event, the occurrence was 33% in the 0.5-μg/kg, 73% in the 1.0-μg/kg, and 72% in the 1.5-μg/kg bolus groups, and 80% in the 1.5-μg/kg continuous-infusion group. With adenosine, 92% (207 of 226) of patients reported adverse events [13•].

Regadenoson, Binodenoson, and Adenosine

Based on preclinical and early clinical studies reported in the literature, regadenoson at the 400-μg dose using a rapid (≤ 10-sec) bolus delivery, produces a magnitude of maximal hyperemia comparable with adenosine that is rapid in onset (30 sec) and short in duration (2.8 min) [14]. This provides a favorable time frame to facilitate radionuclide imaging. In comparison, maximal hyperemia induced by binodenoson has been reported to be slower in onset (3.3–5.5 min) and more prolonged in duration (3.0–9.4 min) [12]. In contrast to the rapid bolus injection of regadenoson, binodenoson is delivered by slow bolus over 30 seconds. Regarding hemodynamic variables, early clinical studies suggest that regadenoson and binodenoson produce similar effects, with both A2A agonists inducing minimal changes in heart rate and mild decreases in mean arterial pressure. Clinical information has not been reported for apadenoson.

For SPECT imaging, regadenoson images were concordant with adenosine images for detection and quantitation of ischemia, and in a much larger number of patients' binodenoson SPECT images are comparable with adenosine SPECT images in the extent and severity of reversible perfusion defects. Despite the high A2A selectivity of binodenoson and regadenoson in preclinical studies, subjective side effects attributable to other adenosine receptor subtypes were still observed in human studies and are similar to or slightly lower than those of

adenosine. There have been no reports of AV block with either regadenoson or binodenoson in published trials to date, signifying a lack of affinity of these agents for the A1 receptor subtype.

Conclusions

Based on available results from experimental and clinical trials of selective A2A receptor agonists, regadenoson and binodenoson hold significant potential as pharmacologic stress agents. There is insufficient information on apadenoson in humans to know the efficacy or side-effect profile, but the animal work suggests that it has comparable potential as the other two agents. Ongoing trials will further elucidate the potential benefits of all three agents with regard to 1) improved safety, tolerability, and hemodynamic effects; 2) lack of AV block and bronchospasm; and 3) image quality and ischemia detection comparable with adenosine SPECT. In the future, clinical applications for regadenoson pharmacologic stress may extend beyond myocardial perfusion SPECT to other cardiac imaging modalities, including cardiac perfusion PET, cardiac MRI, and myocardial contrast echocardiography.

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- •• Of major importance

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First trial on A2A-selective agents given as a rapid bolus at a fixed dose. Showed preliminary safety and efficacy in a small trial.