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.

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.
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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 μg/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].

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

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

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Affinity for A2A receptor (Ki)*</th>
<th>Duration of action, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>2700–5000</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td>Regadenoson</td>
<td>1095</td>
<td>3.4 ± 0.5</td>
</tr>
<tr>
<td>CGS21680</td>
<td>157</td>
<td>14.5 ± 0.5</td>
</tr>
<tr>
<td>Binodenoson</td>
<td>21</td>
<td>21.9 ± 0.9</td>
</tr>
</tbody>
</table>

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