Editorial Comment

Dipyridamole and Adenosine Vasodilator Stress for Myocardial Imaging: Vive la Différence!*

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The development and clinical validation of nonexercise pharmacologic stress modalities have proceeded at a dizzying pace over the past decade. Reports indicate that the vasodilators dipyridamole and adenosine (and the beta-agonist dobutamine) yield excellent results in the diagnosis of coronary artery disease and stress-induced ischemia, and provide prognostic information after myocardial infarction and perioperatively. Although Food and Drug Administration approval of both intravenous dipyridamole and adenosine for cardiac imaging has progressed cautiously, it is clear that large multicenter safety studies such as those described in the current report by Cerqueira et al. (1) are extremely valuable to this approval process. These data, and previous multicenter reports regarding the side effect profile of dipyridamole (2,3), represent a significant advance over previously reported institutional experiences with either agent. It is now safe to conclude that both agents offer a low risk alternative to exercise stress in appropriately selected patients.

Although no direct comparison of these agents has been published, the power provided by the statistical analysis of large patient populations permits the detection of subtle but clinically significant differences between dipyridamole and adenosine. Specifically, the Adenoscan Multicenter Trial Registry study (1) has identified patients ≥70 years of age as having a significantly increased risk of atrioventricular (AV) block, which frequently (28%) necessitated a reduction or premature termination of the adenosine infusion. Whereas previous studies have demonstrated the safety (4) and prognostic value (5) of dipyridamole thallium-201 myocardial imaging in elderly persons, it appears that this side effect may limit the application of adenosine stress imaging in this age group. Although adenosine stress imaging can be prognostically (6) and diagnostically (7–9) useful, elderly patients may require careful screening for preexisting sick sinus syndrome and conduction defects and extra vigilance during adenosine stress testing.

Cerqueira et al. (1) have conclusively demonstrated that severe reactions to adenosine such as myocardial infarction (0.0001%), serious bronchospasm (0.1%) and cardiac death (0%) are rare, although moderate to severe adverse reactions did occur in 15% of patients being evaluated by these experienced investigators. As shown in Table 1, these test-related morbidity and mortality rates are comparable to those observed with dipyridamole infusion. Rates of serious side effects of dipyridamole (2% vs. 2.5%) and aminophylline reversal (15% vs. 15%) do not differ between patients ≥70 versus <70 years old (4). It is also important to note that both dipyridamole and adenosine have the potential to provoke and sustain serious bronchospasm in patients with extrinsic or intrinsic asthmatic conditions. After the exclusion of vasodilator side effects, dyspnea and nonspecific chest discomfort, which each occurred in more than one third of adenosine-tested patients, other less common adenosine-induced adverse reactions were relatively rare and unpredictable in nature.

It is of some concern that cessation of "short-acting" adenosine infusion did not universally abort adverse reactions in all patients (1). Seventy-one Adenoscan Registry patients required additional aminophylline, suggesting that some adverse reactions may outlast the ultrashort serum half-life of this agent. Events that are serious enough to warrant aminophylline reversal can occur even in the hands of the most experienced stress imaging investigators. Preliminary intracoronary Doppler flow velocity data from our medical center suggests that the rate of dipyridamole (0.56 mg/kg body weight) reversal by 125 mg of aminophylline is slightly slower but comparable to that of cessation of adenosine infusion (10).

The relatively high rate (23%) of "delayed or recurrent" adenosine-related adverse events reported in this study is somewhat disturbing. Physicians performing dipyridamole studies have worried about the potential for late vasodilator side effects after the use of this longer-acting agent, and to prevent this possibility, they have frequently administered aminophylline or given caffeine-containing beverages to patients who are leaving the stress laboratory after dipyridamole testing. The Adenoscan Registry substudy of >10,000 patients at five medical centers suggests that a similar cautious approach might also be warranted after adenosine stress testing.

Having raised these concerns, we must reemphasize that adenosine and dipyridamole are both highly effective coronary and systemic vasodilators that exhibit more similarities than differences. Side effect profiles for both agents are largely extensions of these vasodilator actions. Their pharmacologic interactions are complex and immutable (Fig. 1). Although much has been written about the significant biokinetic and AV node receptor differences between these...
agents (11,12), it is interesting that age, gender and body
habitut remain nonmodifiable patient variables that deter-
mine the frequency of adverse events for both adenosine and
dipyridamole studies (1,13,14).

Multicenter safety data, now available for both adenosine
(1) and dipyridamole (2), have significantly enhanced our
understanding of the relative value of these agents among the
growing list of pharmacologic stress modalities. In the vast
majority of clinical subsets with known or suspected coro-
nary artery disease, adenosine and dipyridamole are valu-
able pharmacologic vasodilator stress alternatives. A grow-
ing number of stress laboratories, including our own, keep
both these agents "on the shelf." However, to suggest that
they are interchangeable would be incorrect, in view of their
different effects on the AV node, particularly in elderly
patients. Therefore, clinical judgment is still required in the
process of patient selection for these studies. A more casual
approach could result in unwanted and potentially serious
side effects and frequent premature discontinuation of diag-
nostic studies.

Finally, one would be remiss in not including dobutamine
in any discussion of pharmacologic stress testing. The use of
this agent with echocardiographic and myocardial perfusion
imaging continues to grow at a rapid pace. Although no large
multicenter study has yet examined the safety and side effect
profile in a fashion similar to studies of dipyridamole and
adenosine, recent reports indicate a safety profile similar to
the profile of these coronary vasodilators. Mertes et al. (15)
reported noncardiac side effects in 26% of 1,118 patients
undergoing dobutamine echocardiographic stress testing,
with chest pain, arrhythmia and AV block occurring in
12.7%, 3.5% and 0.6%, respectively, of patients studied.

In pharmacologic stress imaging (as in parenting), the
issue of whether one agent (or child) is preferred or better
than its sibling seems moot. As the guardians of pharma-
cologic cardiac stress imaging, noninvasive cardiologists must
be prepared to acknowledge and accept la difference be-
tween these related agents.

**Table 1. Reported Side Effects of Intravenous Adenosine and
Dipyridamole Imaging Multicenter Studies**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Adenosine (present study)</th>
<th>Dipyridamole (ref 2)</th>
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<tbody>
<tr>
<td>Noncardiac</td>
<td></td>
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<tr>
<td>Flushing</td>
<td>36.5</td>
<td>3.4</td>
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<tr>
<td>Dyspnea</td>
<td>35.2</td>
<td>2.6</td>
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<tr>
<td>Chest pain</td>
<td>34.6</td>
<td>19.7</td>
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<tr>
<td>Gastrointestinal distress</td>
<td>14.6</td>
<td>5.6</td>
</tr>
<tr>
<td>Headache</td>
<td>14.2</td>
<td>12.2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8.5</td>
<td>11.8</td>
</tr>
<tr>
<td>Cardiorespiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV block</td>
<td>7.6</td>
<td>0</td>
</tr>
<tr>
<td>ST-T wave changes</td>
<td>5.7</td>
<td>7.5</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>3.3</td>
<td>5.2*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>0.1</td>
<td>0.15</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.0001</td>
<td>0.05</td>
</tr>
<tr>
<td>Death</td>
<td>0*</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Ventricular arrhythmias. †One subsequent death reported. All data are reported as percent of patients.

**Figure 1. Pharmacologic interactions of dipyrida-
mole and adenosine at the level of the vascular
smooth muscle cell membrane (upper portion) and
intracellular messenger (lower portion). AMP = ada-
носine monophosphate; ATP = adenosine triphos-
phate; cAMP = cyclic adenosine monophosphate.
References


