EDITORIAL

Dipyridamole/Thallium-201 Imaging: How Safe Is It? When Should It Be Used?

Induction of myocardial ischemia is not a prerequisite for a positive test during myocardial perfusion imaging. All that is required is the establishment of flow mismatch between different myocardial beds. One way to achieve this mismatch is to exercise a patient on a treadmill or a bicycle to increase cardiac output, which increases myocardial oxygen demand, which in turn augments coronary blood flow. Regions of the myocardium subtended by normal coronary vessels experience a several-fold increase in flow, while regions subtended by diseased vessels do not experience as great an increase. This variability in coronary flow reserve in different vessels results in variability in flow to myocardial regions *without necessarily* inducing ischemia in regions not receiving maximal flow. Techniques used to image myocardial perfusion can, therefore, detect mismatch in myocardial flow *prior to* the occurrence of ischemia.

If the same patient is exercised longer, the oxygen demand in the region supplied by the diseased vessel will outstrip the blood supply, resulting in myocardial ischemia. This ischemia will become manifest as regional dysfunction, followed by ST-segment depression on the electrocardiogram, followed by angina (*1*). Not all patients who are exercised will reach these endpoints. Because of this temporal sequence of events during exercise, myocardial perfusion imaging is more sensitive than the electrocardiogram, which in turn is more sensitive than the occurrence of angina for the detection of coronary artery disease (CAD) (*2*).

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MECHANISM OF ACTION OF DIPYRIDAMOLE

Another way to achieve mismatch in myocardial blood flow is to induce it pharmacologically by giving a coronary vasodilator such as dipyridamole or papavarine. Unlike papavarine, dipyridamole can be given intravenously without major hemodynamic changes. Dipyridamole is a phosphodiesterase inhibitor that causes an increase in cyclic 3′,5′ adenosine monophosphate levels, leading to smooth muscle dilation (*3*). The peak vasodilatory effect of intravenously administered dipyridamole is noted 4–5 min after infusion and lasts for as long as 15–30 min (*3*). The advantage of pharmacologic-induced compared to exercise-induced increase in coronary flow is that it is reproducible and can be standardized. The disadvantage is that, unlike exercise, it does not provide additional clinically useful information such as exercise capacity and functional status of a patient. Were it not for this limitation, a strong argument could be made for pharmacologic stress in lieu of exercise-stress in *all* patients undergoing evaluation for known or suspected CAD.

WHEN SHOULD DIPYRIDAMOLE/^{201}Tl IMAGING BE USED?

As would be expected from the above discussion, the sensitivity of dipyridamole/^{201}Tl imaging is similar to that for exercise ^{201}Tl imaging in unselected patients (*4*). Nevertheless, the patients in whom this technique is most commonly used are those who cannot exercise due either to physical limitations or to their medical condition.

The former group mostly consists of patients who are to undergo major vascular surgery. In this population, dipyridamole/^{201}Tl imaging is highly effective in identifying patients at increased risk for cardiac events either in the operating room or shortly thereafter (*5–8*). The presence of redistribution is particularly useful in this regard and, when combined with other clinical variables, offers a high degree of certainty in identifying high-risk patients (*8*). Increased lung/heart ^{201}Tl ratio during dipyridamole/^{201}Tl imaging also correlates with markers of ischemia such as ST-segment depression suggesting that, apart from producing flow mismatch, dipyridamole can also induce ischemia in high-risk patients with multivessel disease, probably by coronary steal (*9*).

The other set of patients in whom this test can be used are those with acute myocardial infarction (*10–13*). In this subset, high-risk patients can be identified prior to hospital discharge using this test, which can be performed in lieu of pre-discharge low-level exercise testing. An initial study reported very good results in patients who underwent this test 10–16 days after their infarction (*10*). A more recent study has suggested that this test can be performed safely 1–4 days after acute infarction and still provide useful prognostic information (*13*). The practical utility of such an approach is that low-risk patients could be identified early after infarction and discharged from the hospital, while high-risk patients could undergo early aggressive evaluation. The impact of this approach on reducing hospital costs could be significant.

HOW SAFE IS DIPYRIDAMOLE?

The most comprehensive review of the safety of intravenous dipyridamole comes from the Boehringer Ingelheim data registry, encompassing 3,911 patients from 70 centers, who underwent dipyridamole/^{201}Tl imaging between 1978 and 1985 (*14*). In

this series, 47% of the patients experienced side effects, mostly limited to headache, dizziness, chest pain, and ST changes on the electrocardiogram. Serious life-threatening complications included acute myocardial infarction, which occurred in four patients (0.10%), two of which were fatal. Three of these four patients had recent histories of unstable angina. Six patients (0.15%) also experienced acute bronchospasm, of whom four had asthma or wheezing prior to testing. Despite the common occurrence of side effects, of the 454 patients receiving intravenous aminophylline, 97% had resolution of symptoms.

These compiled data, however, do not include specific demographic and clinical characteristics of the populations studied, which might allow identification of patient subgroups at high-risk for severe dipyridamole-induced complications. The study by Perper and Segall in this issue of the *Journal* attempts to determine whether specific patient subsets are at particularly high risk for significant complications (*15*). Like others, this study found a high incidence of minor side effects (69%) despite routine administration of aminophylline. Unlike others, however, this study specifically excluded patients with recent unstable ischemic syndromes, and no episodes of myocardial infarction or death were recorded.

In their report, Perper and Segall have painstakingly related all pertinent variables, such as patient age, presence of pulmonary disease, extent of CAD, and presence of left ventricular dysfunction, to the incidence of significant dipyridamole-induced side effects (*15*). They have found that patients greater than 70 yr of age were not more likely to have severe chest pain or hypotension than younger patients. Theophylline-requiring patients with chronic obstructive pulmonary disease were more likely to develop dyspnea, while those with left ventricular dysfunction were more likely to develop chest pain or hypotension. In contradistinction to a previous report (*16*), these authors found that patients with more extensive angiographic CAD were more likely to have severe chest pain after dipyridamole and patients with severe chest pain were more likely to have redistribution.

Some caution should be exercised before extending the observations of Perper and Segall to the general population. As the authors point out, this study probably involved a select population, since patients who were deemed unsuitable for dipyridamole testing were excluded. The protocol used routine aminophylline administration after acquisition of the initial images. Although severe dyspnea occurred in only 3% of patients with chronic obstructive pulmonary disease after administration of dipyridamole, those most likely to experience this side effect were those who were theophylline-dependent. Finally, Perper and Segall have also found that dipyridamole can produce clinically apparent ischemia, particularly in patients with multi-vessel disease or recent unstable angina.

INTRAVENOUS VERSUS ORAL DIPYRIDAMOLE

Until recently, intravenous dipyridamole has been an investigational drug. In order to use it clinically for ^{201}Tl imaging, several investigators have used the oral form (*15,17*). The paper by Perper and Segall focuses on the safety of oral dipyridamole. As noted in their present paper (*15*) and a previous report (*17*), this form of the drug is as safe as the intravenous form, although the gastrointestinal side effects tend to be higher with the oral preparation (*17*). There are several reasons, however, to prefer the intravenous form. First, the onset of action is sooner and more predictable. Second, the blood levels of the drug are not influenced by factors that might affect its absorption from the gastrointestinal tract. Third, one dose of intravenous aminophylline is adequate to reverse the side effects of the intravenous form, whereas, theoretically, the duration of action of aminophylline may be shorter than the period of gastrointestinal absorption of dipyridamole. Earlier this year, the Food and Drug Administration approved the use of intravenous dipyridamole and it is likely that this form of the drug will be used routinely for dipyridamole/^{201}Tl imaging.

CONCLUSIONS

Dipyridamole (intravenous or oral), in doses sufficient to produce maximal coronary vasodilation, is safe in humans. Commonly occurring side effects are minor and nearly always promptly reversed with aminophylline. Life-threatening cardiorespiratory complications occur infrequently, and mortality is extremely rare. With careful pre-test review of each individual patient's clinical status, particularly for conditions such as recent unstable angina or bronchospastic disease, such complications can be minimized.

Dipyridamole/^{201}Tl imaging has a definite role in the evaluation of patients with suspected or known CAD who are unable to exercise. It will most likely also play a greater role in the risk-stratification of patients with recent infarction who are otherwise stable. Although the level of exercise (as long as some increase in cardiac output occurs) is not as crucial for exercise ^{201}Tl imaging as it is for exercise electrocardiography (*18*), by inducing maximal flow mismatch, dipyridamole may also be preferable to exercise in patients unable to exercise to a reasonable level. At what level of exercise dipyridamole may provide greater diagnostic and prognostic information than treadmill or bicycle exercise is a clinically relevant question that still needs to be answered.

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