Oral vs Intravenous Dipyridamole Echocardiography for Detecting Coronary Artery Disease*

Fabio Lattanzi, M.D.; Eugenio Picano, M.D.; Ansano Frugoli, M.D.; Leonardo Bolognese, M.D.; Lidia Rossi, M.D.; Cristina Piccinino, M.D.; Gabriella Lencioni, M.D.; and Alessandro Distante, M.D.

The usefulness of the intravenous dipyridamole-echocardiography test (12-lead and two-dimensional [2-D] echo monitoring during dipyridamole infusion) in the diagnosis of coronary artery disease recently has been suggested. However, the intravenous form of dipyridamole is not available for clinical use in some countries and therefore the administration of oral dipyridamole has been employed in combination with echocardiography. In order to evaluate the relative usefulness of the oral (300 mg of pulverized tablets) vs the intravenous (up to 0.54 mg/kg in 10 min) dipyridamole-echocardiography test, we performed the two tests, on different days and in random order, in 28 in-hospital patients: 21 had coronary artery disease (seven had one-vessel disease, eight had two-vessel disease, and six had three-vessel disease); seven patients had no significant coronary artery disease. For both tests, the diagnostic end-point was the development of a transient dyssynergy of contraction. Sensitivity was 95 percent for the intravenous and 52 percent for the oral dipyridamole-echocardiography test (p<0.01); in positive cases, the dyssynergy after the dipyridamole administration appeared at 6.5±2.5 min for the intravenous and at 27.8±12.4 min for the oral test (p<0.01). Specificity was 100 percent for both the intravenous and oral dipyridamole-echocardiography test. One or more extracardiac side effects (headache, gastrointestinal upset, flushing, etc) occurred in 61 percent of the intravenous and 68 percent of the oral tests (p=ns). Nine patients with a positive intravenous and oral dipyridamole-echocardiography test also had a positive exercise-electrocardiography test. A significant correlation between exercise time (ie, the time from onset of exercise and 0.1 mV of ST segment shift) and dipyridamole time (ie, the time from onset of dipyridamole administration and the development of frank dyssynergy) was present for the intravenous (r = 0.6, p<0.05) but not for the oral test. We conclude that the oral dipyridamole-echocardiography test, in comparison with the intravenous dipyridamole-echocardiography test, has a lower sensitivity and requires a substantially longer imaging time. The dipyridamole time is related to exercise time for intravenous but not for the oral dipyridamole-echocardiography test.

(Chest 1992; 102:1189-92)

In patients unable to exercise, intravenous dipyridamole has been used successfully in conjunction with two-dimensional echocardiography for detecting coronary artery disease (CAD). However, the intravenous form of dipyridamole is not available for clinical use in some countries, including the United States. Some authors use oral administration dipyridamole in lieu of an intravenous preparation for thallium 201 myocardial imaging with a good diagnostic accuracy for CAD. More recently, the usefulness of the oral dipyridamole echocardiography test for detecting CAD has been shown. The present investigation assesses the relative feasibility and diagnostic accuracy of the oral vs the intravenous dipyridamole-echocardiography test for detecting CAD in the same cohort of patients with a chest pain syndrome.

From the Institute of Clinical Physiology, CNR, Pisa (Drs. Lattanzi, Picano, and Distante); Divisione di Cardiologia, Ospedale, Lucce (Drs. Frugoli and Lencioni); and Divisione di Cardiologia, Ospedale Maggiore (Drs. Bolognese, Rossi, and Piccinino), Novara, Italy.

Manuscript received April 4, 1991; revision accepted March 6, 1992.

Reprint requests: Dr. Lattanzi, CNR Institute of Clinical Physiology, Via Trieste N. 41, Pisa, Italy 56100

Materials and Methods

Twenty-eight patients (25 men and three women; mean age, 54 ± 7 years) presenting for coronary angiography for the evaluation of chest pain were prospectively studied after informed consent was obtained. A history of myocardial infarction was present in eight patients. All were in-hospital patients and not receiving antianginal therapy since at least three days at the time of testing.

Patients with recent myocardial infarction (within three months), unstable angina, valvular or congenital disease, congestive heart failure, need to use xanthines for obstructive pulmonary disease, and significant gastric disease were excluded from the study.

All patients underwent an oral and intravenous dipyridamole-echocardiography test on different days and in random order. During the test, the patients were explicitly questioned regarding the occurrence of any side effect and this information was recorded. For both tests, patients were instructed to fast for at least 6 h before the study, and, particularly, to avoid tea, coffee, and cola drinks for at least 24 h.

All patients also performed a maximal multistage exercise electrocardiography test.

Intravenous Dipyridamole-Echocardiography Test

Two-dimensional echocardiographic monitoring was performed in combination with dipyridamole infusion: 0.56 mg/kg during 4 min, no dose for 4 min, and then, if the test remains negative, 0.25 mg/kg during 2 min. The cumulative dose was therefore 0.84 mg/kg during 10 min. During each minute of the procedure, blood
pressure and the 12-lead electrocardiogram was recorded. Two-dimensional echocardiograms were continuously monitored and intermittently recorded during and up to 10 min after dipyridamole administration. A commercially available wide-angle phased-array imaging system (model 77020, with 2.5- and 3.5-MHz transducers, Hewlett Packard, Andover, Mass) was used. The test was terminated if new wall motion dyssynergy was detected by two-dimensional echocardiography or if symptoms were judged to be unacceptable by the cardiologist performing the test.

Aminophylline was readily at hand and administered (80 to 240 mg intravenously) as soon as dyssynergy was demonstrated. Also in negative cases, patients received intravenous aminophylline (40 to 70 mg over 1 min) at the end of the test, in order to reverse or prevent side effects.

**Oral Dipyridamole-Echocardiography Test**

Based on a previously used dose, 300 mg of dipyridamole (four pulverized 75-mg tablets) was administered orally. With the patient remaining in a supine position, two-dimensional echocardiograms were repeated every 5 min, starting from 5 and ending at 90 min. Electrocardiographic monitoring and notation of symptoms were done throughout, with 12-lead electrocardiograms recorded every 5 min. If chest pain developed, the two-dimensional echocardiogram was recorded at that time. The test was terminated if new wall motion dyssynergy was detected by two-dimensional echocardiography or if symptoms were judged to be unacceptable by the supervising cardiologist. Aminophylline, 40 to 140 mg over 1 to 2 min, was given intravenously if dyssynergy appeared or symptoms were considered severe. In order to prevent possible delayed effects of dipyridamole, all patients received intravenous aminophylline (70 mg over 1 min) at the end of the procedure.

**Regional Wall Motion Analysis**

Positivity of both intravenous and oral test was linked to the detection of a new transient ventricular dyssynergy of contraction absent or of a lesser degree at the baseline. Wall motion was qualitatively graded as normal, hypokinetic, akinetic, or dyskinetic in conventionally defined wall segments. Any region that was already dyskinetic or akinetic in resting conditions was excluded from the analysis. Two independent observers (blind to the results of coronary angiography and of the other dipyridamole-echocardiography test) separately reviewed the intravenous and the oral test.

**Coronary Angiography**

Left-sided heart catheterization and coronary angiography were performed in a standard manner by the Judkins or Sones technique. Significant coronary artery stenosis was defined as >70 percent reduction in the luminal diameter of any of the three coronary arteries or their primary branches or >50 percent reduction of the luminal diameter of the left main coronary artery. Angiograms were reviewed by two angiographers who were unaware of the results of the dipyridamole-echocardiography test.

**Statistical Analysis**

Sensitivity, specificity, and diagnostic accuracy were calculated according to standard definitions. Where appropriate, 95 percent confidence intervals (CI) are given. Data are reported as mean ± standard deviation. Differences between values are tested for significance by means of chi 2 and unpaired Student's t test. Linear regression analysis was employed to correlate the dipyridamole-echocardiography test and exercise-electrocardiography findings. A p value <0.05 was considered statistically significant.

**Results**

Normal or noncritical CAD was detected in seven patients. Significant coronary artery disease was found in 21 patients: seven had one-vessel, eight had two-vessel, and six had three-vessel disease.

All patients completed the oral or intravenous dipyridamole-echocardiography test without major adverse effects. Seventeen patients (61 percent) experienced minor side effects during the intravenous dipyridamole-echocardiography test; ten of them had a positive test. Nineteen patients (68 percent; p = ns vs intravenous findings) experienced minor side effects during the oral dipyridamole-echocardiography test; seven of them had a positive test. Headache was found in ten (36 percent) patients with the intravenous and in ten (36 percent) patients with the oral tests; gastrointestinal upset and nausea in eight (29 percent) patients with the oral tests and in none with the intravenous tests; other minor side effects (flushing, dizziness, dyspnea, etc.) occurred in eight (29 percent) patients with the intravenous and in three (11 percent) patients with the oral dipyridamole tests.

Interpretable echo images were obtained in all patients for both the intravenous and oral dipyridamole-echocardiography test. Sensitivity for CAD was 20/21 for intravenous and 11/21 for the oral test (95 percent CI, 76 to 100 vs 52 percent; CI 30 to 74, p<0.01). Specificity was 100 percent (CI, 59 to 100) in both tests. Diagnostic accuracy was 96 percent for the intravenous and 64 percent for the oral dipyridamole-echocardiography test (p<0.01). All patients with positive oral dipyridamole-echocardiography tests also had a positive intravenous test. The transient dyssynergy involved the same region in the ten patients with both tests positive: interventricular septum in three, apex in two, anterior wall in one, lateral in one, and inferoposterior in three. In every case, the dyssynergic region was fed by a stenotic vessel. In positive cases, the transient dyssynergy appeared 6.5 ± 2.5 min after intravenous and 27.8 ± 12.4 min after oral dipyridamole administration. The histogram of the time course of the positive tests after both the intravenous and the oral test is displayed in Figure 1. Of the 20 patients with positive intravenous dipyridamole-echocardiography tests, 12 (60 percent) also had diagnostic (>0.1 mV) ST segment shift and 11 (55 percent) had chest pain during the procedure. Of the 11 patients with positive oral dipyridamole-echocardiography tests, seven (64 percent) also had diagnostic ST segment shift and four (36 percent) had chest pain. When compared with patients with single-vessel disease, those with multivessel disease had a shorter intravenous dipyridamole time (5.6 ± 2.1 vs 8.0 ± 2.5 min, p<0.01), but a similar oral dipyridamole time (25 ± 7 vs 35 ± 22 min, p = ns). Of the ten patients with positive intravenous and oral dipyridamole-echocardiography tests, nine also had a positive exercise-electrocardiography test. A significant correlation between exercise time (ie, the time from onset of exercise...
and 0.1 mV of ST segment shift) and dipyridamole time (ie, the time from onset of dipyridamole administration and the development of frank dyssynergy) was present for the intravenous \((r = 0.6, p < 0.05)\) but not for the oral \((r = -0.2, p = ns)\) dipyridamole-echo-cardiography test.

**Discussion**

Oral and intravenous dipyridamole-echocardiography tests were equally feasible since no limiting side effects occurred and interpretable echo images could be obtained in all patients. However, the intravenous test was significantly more sensitive than the oral test for detection of CAD and required a substantially shorter imaging time. A similar incidence of side effects occurred for both the intravenous and oral test. Furthermore, the intravenous dipyridamole-echocardiography test not only gives a binary (positive or negative) result, but the positivity can be usefully stratified according to the timing of the dyssynergy. The "dipyridamole time" has important anatomic, physiologic, and prognostic implications since a shorter dipyridamole time is associated with a more severe anatomic coronary disease,\(^a\) lower exercise tolerance,\(^a\) and worse prognosis.\(^b\) This temporal stratification was tested in the present work only in comparison with the exercise tolerance and angiographically assessed coronary disease. Consistent with the results of a previous study,\(^a\) there was a significant positive correlation between intravenous dipyridamole time and exercise time, and an inverse correlation between intravenous dipyridamole time and the extent of coronary disease. This relation did not exist with oral dipyridamole. A possible explanation might be that the time and dose coronary vasodilator response is very likely more homogeneous with intravenous than with oral dipyridamole.\(^c\) Because of variable absorption of the dipyridamole tablets, neither time of onset nor time to peak blood levels of the medication can be predicted. It is apparent that the lack of correlation with exercise time further severely limits the diagnostic appeal of the oral dipyridamole-echo-cardiography test. In fact, as pointed out by Demer et al.,\(^d\) any diagnostic test for CAD should not give only a dichotomous response. Coronary disease is not an all-or-none condition, but, in actuality, it is a continuous spectrum of severity.\(^e\) The timing of the positive response is crucial, as we have seen above, for allocating the patient in one point or another of this spectrum of severity. The data derived from the simple population of this work, although limited in size, do not support the possibility that a similar stratification might be operated by an oral dipyridamole-echocardiography test. Although the relatively small sample size determines wide confidence intervals of sensitivity and values, the purpose of the study was to compare the relative usefulness of the two tests, rather than to assess their absolute diagnostic accuracy.

It is also known that visual inspection of coronary arteriograms is a less than ideal gold standard.\(^f\) Nevertheless, although subjective visual estimate of "percent stenosis" lacks accuracy and repeatability
and provides no accurate insight into the hemodynamic impact of a lesion, the simplicity of the percentage of stenosis estimate and the force of tradition favor its continued use. The recorded large difference in sensitivity between the intravenous and oral test might appear surprising. With the combination of thallium scintigraphy and a higher dose of oral dipyridamole (400 mg), a sensitivity of 84 percent was found, comparable to the sensitivity of 79 percent of intravenous dipyridamole. However, in respect to that study, we employed higher doses of intravenous dipyridamole (0.84 mg/kg over 10 min), which determines a sharp step up in sensitivity when the transient dysynchrony of contraction, and therefore ischemia, is the diagnostic criterion of positivity. In addition, again with a higher dose of dipyridamole (400 mg), a sensitivity of 81 percent was found in a recent study with oral dipyridamole echocardiography. This may suggest that the oral dose we employed, which was the one employed by thallium imaging at the time the study was designed, was too low to reach the full ischemic potential of the oral formulation.

We conclude that the intravenous (0.84 mg/kg over 10') dipyridamole-echocardiography test, in comparison with the oral (300 mg) dipyridamole-echocardiography test, has a higher sensitivity and requires a substantially lower imaging time. The time to dyssynchrony is related to exercise time and angiographic severity of CAD for the intravenous but not for the oral dipyridamole-echocardiography test. Minor side effects are equally frequent with the oral and the intravenous test. When dipyridamole ampoules for intravenous use are commercially available, the intravenous dipyridamole-echocardiography test should be preferred to the oral dipyridamole-echocardiography test.

ACKNOWLEDGMENTS: We are grateful to Ms. Claudia Taddei for secretarial assistance.

REFERENCES