Variability of Serum Drug Level Following a Single Oral Dose of Dipyridamole

George M. Segall and Michael J. Davis

Nuclear Medicine Service and Cardiology Section, Veterans Administration Medical Center, Palo Alto; and Department of Radiology and Nuclear Medicine, Department of Internal Medicine, Stanford University School of Medicine, Stanford, California

Serum dipyridamole levels were measured in 27 patients undergoing planar thallium-201 myocardial perfusion scintigraphy after receiving a 300 mg oral dose. Mean serum dipyridamole level was 2.9 ± 1.6 mcg/ml (range 0.2–5.7). No correlation was found between serum level and symptoms, heart rate or blood pressure response, peak heart to lung thallium activity ratio, peak heart to liver thallium activity ratio, or peak myocardial thallium washout. Serum level following a single oral dose of dipyridamole is unpredictable and patients with low drug levels cannot be easily identified at the time of study.

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Thallium-201 (^{201}T) myocardial perfusion scintigraphy with dipyridamole in lieu of exercise is being performed with increasing frequency. The overall sensitivity and specificity of the test when performed with dipyridamole compares favorably to an exercise study (*1*). However, the sensitivity of an exercise thallium study is reduced with submaximal exercise (*2*), usually determined by failure to reach at least 85% of maximum predicted heart rate for age. Unfortunately, there are no known indicators of a "submaximal" dipyridamole study due to a suboptimal serum level. Taillefer et al. have shown that the sensitivity of the test is only 65% following a 200-mg oral dose, as opposed to 84% following a 400-mg dose (*3*). Drug levels following oral administration of dipyridamole are unpredictable due to variability of absorption (*4,5*). Moreover, laboratory measurements of drug levels are expensive, not routinely performed in most hospital laboratories, and the results are not available for several days. Since the dipyridamole-thallium technique was introduced in 1978, the symptoms and hemodynamic changes caused by this drug have been well documented. However, there has been very little published information regarding correlation of symptoms and hemodynamic changes with drug levels following dipyridamole administration (*6*). Furthermore, although thallium kinetics in normal myocardium and myocardium distal to a stenosis has been described in dogs (*7–9*), and there have been a few studies evaluating thallium washout in patients (*10–12*), relationship to drug levels has not been discussed. Therefore, we undertook this study to determine if one could correlate symptoms, hemodynamic changes, or quantitative thallium data with serum dipyridamole levels to identify suboptimal studies that might result in a higher incidence of false-negative examinations.

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For reprints contact: George M. Segall, MD, Nuclear Medicine Service (115), Veterans Administration Medical Center, 3801 Miranda Ave., Palo Alto, CA 94304.

METHODS

Patients

Twenty-seven patients were studied. Twenty patients had a coronary arteriogram within 3 ± 4 wk of the thallium study. Seventeen patients had significant coronary artery disease which was defined as 50% or greater luminal narrowing of at least one coronary artery. Three patients had triple vessel disease, nine had double vessel disease, and five had single vessel disease. Twenty patients were taking calcium channel blockers, 18 were taking nitrates, and 12 were taking beta blockers at the time of examination. No patient was taking methyl-xanthine medications and all tests were performed in the morning after an overnight fast. Caffeinated beverages were specifically proscribed.

Procedure

Three hundred milligrams of dipyridamole were administered orally. The tablets were crushed and suspended in 30 cc of raspberry syrup. Supine and standing EKG, blood pressure, and pulse were recorded every 15 min. Three mCi of thallium-201 chloride were injected intravenously 45 min later, except for one patient who had to be injected earlier for severe angina. Thallium was injected while patients were supine, but patients

were asked to stand for 2–3 min after thallium injection. Two patients were unable to stand due to neurologic disease or injury, and two were unable to stand because of orthostatic hypotension. One patient was kept supine because of severe angina. Imaging was begun 5 min after thallium injection. Ten minute planar images were acquired in the 45° LAO, anterior, 70° LAO, and 35° LAO projections. After the early images were acquired, 100 mg of aminophylline were infused intravenously. Three patients required early aminophylline infusion because of chest pain. All patients returned 3 hr after aminophylline infusion for repeat imaging.

Measurement of Drug Levels

Five cubic centimeters of blood were drawn just prior to thallium injection. A single serum sample was frozen and sent to a commercial laboratory for measurement of drug levels (National Medical Services, Willow Grove, PA). Samples were analyzed by fluorescence detection after high pressure liquid chromatography using a modification of a technique previously described (*13*). The average coefficient of variation using this method is 4.8%. Normal peak level following a single 50 mg oral dose is 0.25–0.5 mcg/ml.

Analysis of Data

All of the images were acquired in a 128 × 128 computer matrix. The calculation of heart to lung and heart to liver activity ratios was performed on the early 45° LAO view after a nine-point smooth. A region of interest representing the lung was drawn 15 pixels wide and 15 pixels from the heart in an arc extending from 0° to 90°. Similarly, a liver region of interest was drawn in an arc extending from 180° to 270°. The highest pixel activity in the myocardium was determined visually on the computer by setting the lower window of the display to zero and then decreasing the upper window until overflow of the first myocardial pixel was seen. The lower window was then raised until the last lung or liver pixel disappeared, corresponding to the maximum pixel count in those regions.

Myocardial thallium washout calculations were performed on the 45° LAO images after bilinear interpolative background subtraction. Circumferential count profiles for each image were drawn using the average pixel value along each of 60 radians. A curve representing percent washout was also drawn and the maximum value was noted.

Thallium images were independently evaluated by three nuclear medicine physicians who had no knowledge of the clinical history or angiographic findings. The majority opinion was accepted in cases of disagreement. Abnormalities in the inferior wall were ascribed to RCA disease, abnormalities in the lateral wall to LCX disease and abnormalities in the anterior wall or septum to LAD disease.

Statistical Methods

Changes in hemodynamic parameters due to dipyridamole were evaluated by calculating confidence limits. Changes were considered significant when differences compared to baseline were >0 at the 95% confidence limit. Student's t-test was used for comparison of independent sample means. Differences were considered significant when $p < 0.05$. Correlation coefficients were derived by linear regression analysis using a least squares fit. Statistical significance was determined by F-test. Correlations were considered significant when p was less than 0.05.

RESULTS

Forty-five minutes after taking dipyridamole the mean serum level was 2.9 ± 1.6 mcg/ml (range 0.2 to 5.7). During this time supine systolic blood pressure decreased 7 ± 11 mmHg, diastolic blood pressure decreased 8 ± 9 mmHg, and heart rate increased 6 ± 7 bpm. All of these changes were significant ($p < 0.01$). There was no change in mean standing systolic blood pressure following dipyridamole, but diastolic blood pressure decreased 7 ± 8 mmHg and heart rate increased 6 ± 7 bpm ($p < 0.01$). There was no significant correlation between the change in any hemodynamic parameter and serum dipyridamole level. Figure 1 shows the relationship between drug level and change in supine heart rate. Although 12 patients were taking beta blockers, there was no statistically significant difference in the heart rate response between patients who were taking beta blockers and those who were not taking them. The magnitude of the heart rate response to dipyridamole was also unaffected by calcium channel blockers.

Fifty-six percent (15/27) of patients experienced side effects. Headache or dizziness was reported by ten patients, chest pain by seven patients, and nausea by two patients. Except for three patients who required early administration of aminophylline for severe angina, side effects were mild. The mean dipyridamole level in patients with and without side effects was not significantly different (Fig. 2). In fact, the two patients with the highest levels were asymptomatic during the examination.

The peak heart to lung and peak heart to liver thallium activity ratios are shown in Figures 3–4. No significant correlation was seen with dipyridamole levels.

The correlation between thallium washout and drug

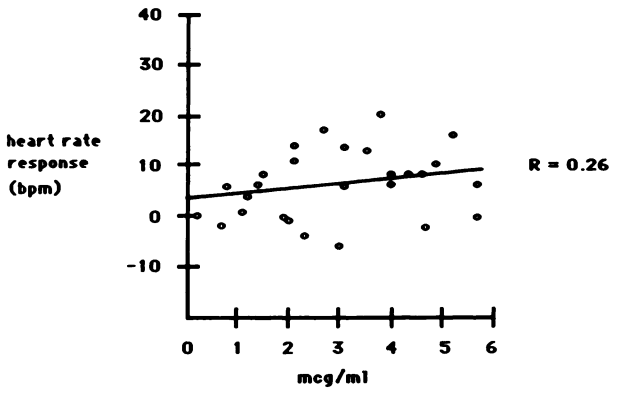

FIGURE 1
Serum dipyridamole level versus change in supine heart rate. The correlation is not significant.

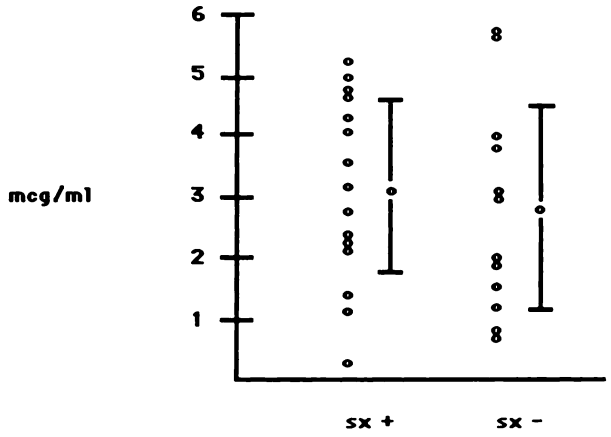

FIGURE 2
Serum dipyridamole level versus presence or absence of symptoms following a 300 mg oral dose. The bars show the mean ± 1 s.d.

level was poor (Fig. 5). Five patients showed wash-in of the radiopharmaceutical between the early and delayed images. These five patients as well as others with poor wash-out showed more lung or liver activity than patients with good wash-out.

Qualitative analysis of thallium images correctly identified 13 out of 17 patients with coronary artery disease for a sensitivity of 76%. Reversible defects were seen in 38%. Regional sensitivity and specificity was 69% (9/13) and 57% (4/7) for RCA disease, 25% (2/8) and 92% (11/12) for LCX disease, and 67% (8/12) and 100% (8/8) for LAD disease. The mean serum dipyridamole level in the 13 patients with true positive tests was 3.2 ± 1.4 mcg/ml versus 2.8 ± 1.8 mcg/ml in the four patients with false-negative tests (P = N.S.).

DISCUSSION

Dipyridamole is a potent coronary vasodilator. In patients with coronary artery disease, the differential

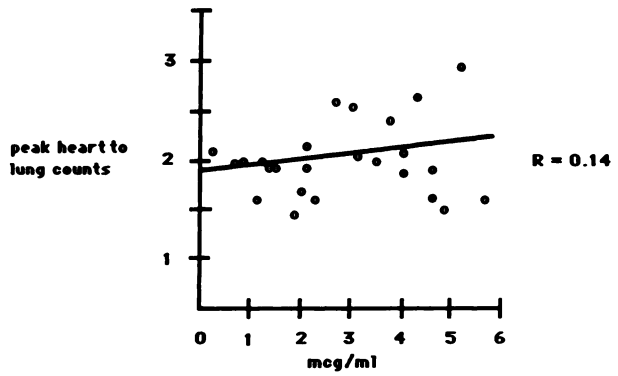

FIGURE 3
Peak heart to lung thallium activity ratio as a function of serum dipyridamole level. The correlation is not significant.

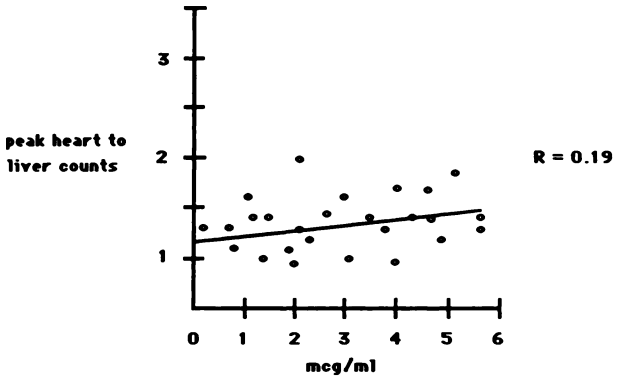

FIGURE 4
Peak heart to liver thallium activity ratio as a function of serum dipyridamole level. The correlation is not significant.

response of normal and stenosed arteries creates regional perfusion inhomogeneities which can be detected by thallium imaging. The sensitivity of the technique depends upon an adequate pharmacologic response which is dose dependent. It has been empirically determined that a dose of 0.56 mg/kg when administered intravenously or a dose of 300 mg when given orally results in good sensitivity without serious side effects (*6*, *14–17*). However, peak serum levels following an oral dose can be unpredictable due to variable absorption. We injected thallium and collected blood for drug level measurements 45 min after dipyridamole administration based on earlier studies that showed peak drug levels were achieved between 20–40 min after administration of crushed tablets (*18*) and 60 min after administration of intact tablets or capsules (*4,5*). We did not collect serial blood samples to confirm that serum dipyridamole levels had peaked at 45 min. However, there were no significant differences in hemodynamic measurements between 30–45 min after dipyridamole administration and values at both times were significantly higher than at 90 min. Furthermore, only one

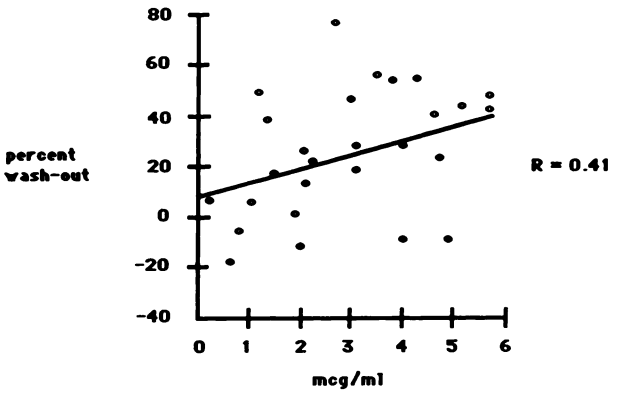

FIGURE 5
Peak thallium myocardial wash-out as a function of serum dipyridamole level. The correlation is not significant.

patient experienced side effects beginning later than 45 min. Similar observations have been made by others (*6*).

When treadmill exercise is used in conjunction with thallium imaging, the heart rate response is one of the criteria used to judge the adequacy of the stress. It has been noted that submaximal exercise results in reduced sensitivity. It has been suggested that the heart rate response can be used to titrate the optimal dose of dipyridamole in individual patients. This hypothesis has not been tested, although it has been observed that patients with larger increments in heart rate have a higher ratio of myocardial to background counts (*14*). At the present time there are no criteria by which to judge the adequacy of the pharmacologic effect.

We have shown that changes in heart rate and blood pressure, as well as presence or absence of symptoms, cannot be used to estimate drug levels. Our results are similar to those reported by Homma et al. (*6*) who found that the heart rate and blood pressure responses were similar in five patients with serum dipyridamole levels below 3 mcg/ml compared with another five patients with levels >3 mcg/ml. They also noted that two patients with angina did not have significantly different drug levels from eight patients without angina.

Although 22 patients were taking beta blockers and/or calcium channel blockers which could blunt reflex tachycardia or modify the blood pressure response secondary to dipyridamole, we did not observe this effect. Homma et al. (*6*) also reported that there was no correlation between magnitude of heart rate response or change in blood pressure and the use of beta blockers.

Gould et al. (*19*) reported that the heart to lung activity ratio increases with dipyridamole when compared to resting control values because the drug increases coronary blood flow without significant change in thallium extraction by the lungs. Although myocardial thallium uptake is not linear at high coronary blood flow, the observed lack of correlation between the heart to lung activity ratio and drug level was nevertheless disappointing. This finding was also contrary to Gould's observation that smaller doses of dipyridamole caused a smaller increase in the heart to lung activity ratio. By using the highest pixel values in calculating the ratio, we hoped to minimize the effect of coronary artery disease on myocardial thallium uptake. Although this technique may not eliminate the effect of coronary artery stenosis in patients with triple vessel disease, excluding the patients in our series with triple vessel disease, as well as those who did not have coronary arteriograms, did not change the results.

It is possible that the lack of correlation between the heart to lung activity ratio and drug level was affected by variability in thallium uptake by the lung. Gould has also noted that lung activity is higher when the patient is kept supine as opposed to standing after thallium injection (*19*). Five patients were kept supine throughout the study whereas the other patients stood up briefly after thallium injection for hemodynamic measurements. Brown et al. (*20*) reported that propranolol increased the heart to lung thallium activity ratio following treadmill exercise in patients without coronary artery disease. This effect was independent of heart rate and was due to a direct effect on thallium extraction by the lungs. This finding is opposite to our own observation that the heart to lung activity ratio was lower in patients taking beta blockers compared to patients not taking beta blockers (1.8 ± 0.4 vs. 2.1 ± 0.3, $p < 0.05$). However, there was only a moderate correlation ($r = 0.6$) between dipyridamole level and peak heart to lung thallium activity ratio in patients not taking beta blockers.

Liver thallium activity is initially high after dipyridamole administration and decreases with time, opposite to what is seen with exercise. We did not find any correlation between the peak heart to liver thallium activity ratio and drug level. None of our patients had liver disease and all had been fasting for at least 6 hr before the examination.

The correlation between peak myocardial thallium washout and dipyridamole level was poor. This finding is not unexpected since washout is dependent on many factors.

The degree of washout partly depends on the initial amount of thallium delivered to the heart, which is a function of coronary blood flow and pharmacologic effect of the drug. Thallium clearance from the myocardium is also affected by ischemia. Using a canine model, Okada et al. reported that thallium clearance is biexponential with a rapid phase during the first 20 min, followed by a slow phase (*7*). By increasing the severity of experimental coronary artery stenosis, they demonstrated a decrease in the clearance rate of thallium from the myocardium during the second phase. Using a similar model, Beller et al. also found that at subnormal myocardial blood flow, thallium efflux becomes greatly prolonged (*8,9*). To minimize the effect of coronary stenoses, we looked at peak washout from the most normally perfused myocardium. As previously mentioned, this may not avoid the problem posed by triple vessel disease, but here again, excluding the patients with triple vessels disease and the patients without arteriograms did not change the results.

Thallium washout from the myocardium is also dependent on thallium clearance from the blood, which is affected by renal function and other factors which we did not measure or control.

Bilinear interpolative background subtraction has been shown to artifactually increase washout, particularly from areas of myocardial infarction (*21*). Since nine patients had a history of myocardial infarction, and peak heart to liver thallium activity ratio for the

whole group was only 1.4 ± 0.3, significant artifact may have been introduced.

All patients received aminophylline to terminate the effect of the dipyridamole and remove any uncertainty caused by variable duration of action. In this respect, administration of aminophylline was analogous to stopping exercise. Although it is possible that the antagonistic effect of aminophylline might not outlast the pharmacologic effect of dipyridamole, this is considered unlikely since aminophylline has a serum half-life of 181-571 min (*22*) whereas dipyridamole has a half-life of 84-145 min (*4*).

A recent abstract noted that mean washout increased 2.8 times and peak washout increased 1.7 times in three patients with coronary artery disease when the dose of dipyridamole was increased from 0.56 mg/kg to 0.84 mg/kg i.v. (*23*). All three patients had false-negative examinations at the lower dose whereas one patient had a positive test at the higher dose. We did not investigate whether or not serum dipyridamole levels can be correlated with washout in individual patients by repeating the test using a higher dose. We also did not investigate whether levels could be correlated with changes in any parameter compared to a resting state in the same individual.

The reported sensitivity of oral dipyridamole thallium scintigraphy in detecting coronary artery disease varies from 48–91% (*3,6,17*). A possible explanation for this variability is unpredictable absorption of the drug as well as individual variation in responsiveness. It is intuitively obvious that there is a lower threshold of serum dipyridamole level below which the pharmacologic effect on coronary blood flow is insufficient to detect coronary artery stenosis with thallium scintigraphy. We found patients with false-negative tests to have a lower mean drug level than patients with true-positive tests, but the number of patients studied was small and the difference did not reach statistical significance.

Since routine measurement of serum dipyridamole levels is expensive and the results are usually not available for several days, it would be useful to have some means of estimating drug levels while patients are being studied. Unfortunately, it is not possible to predict serum drug levels from easily measured parameters at the time of study.

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