Effect of Platelet Suppressant Treatment with Dipyridamole and Aspirin on Exercise Performance and Platelet Survival Time in Coronary Disease*

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Platelets may contribute to the pathogenesis of atherosclerotic coronary artery disease (CAD), and platelet reactivity may be activated by exercise. Fourteen men with CAD participated in a double-blind, crossover study of aspirin (ASA), dipyridamole (DPY), ASA-DPY, and placebo. The ASA therapy increased platelet survival time (autologous labelling with $^{51}$Cr), but had no effect on either the duration of angina-limited treadmill exercise or the heart rate-systolic blood pressure product ($\times 10^{-2}$) at peak exercise. The combination DPY-ASA had a greater effect on platelet survival, but did not substantially increase the duration of exercise. Administration of DPY alone at a higher dosage increased the exercise duration and had a similar effect on platelet survival. At the time that control exercise was completed with the higher dosage of DPY, the rate-pressure product was decreased. The results suggest that DPY and ASA favorably alter the platelet survival in men with CAD, and that DPY, but not ASA, favorably alters exercise performance. Although ASA and ASA-DPY may alter platelet response to exercise, the effect is not shown in hemodynamic measurements during exercise. In higher dosages, DPY may be an effective coronary vasodilator for men with CAD.

Interaction of blood platelets with vascular endothelium probably contributes to the pathogenesis of atherosclerosis and its complications. Most patients with atherosclerotic coronary disease have shortened platelet survival time.1 Several drugs have been shown to lengthen platelet survival time in men with coronary disease, and one of these drugs, sulfinpyrazone, has been shown to alter favorably the natural history of patients with coronary disease and myocardial infarction.2

In patients with coronary artery disease, exercise and rapid atrial pacing induce myocardial ischemia. During exercise and pacing stress, platelet-specific proteins3,4 are released by platelets and vasoactive prostaglandins are released by either platelets or myocardial cells.5,6 Platelet suppressant drugs might inhibit the platelet release reaction during exercise, which might benefit patients with coronary disease. The present study was undertaken to determine if platelet suppressant therapy with aspirin and dipyridamole improves exercise performance in men with coronary disease.

Materials and Methods

Thirty-three men with clinically stable, arteriographically defined coronary disease were studied. To establish the effect on platelet reactivity of aspirin, dipyridamole, and these drugs in combination, platelet survival time was measured on four occasions with two to three weeks between measurements, as control; following seven days of treatment with aspirin, 330 mg three times a day; a week of treatment with dipyridamole, 75 mg three times a day in combination with aspirin, 330 mg three times a day; and after a week of placebos. All drugs were administered orally. These measurements were carried out in a double-blind fashion, with random assignment of the drugs. All men had abnormal control platelet survival time.

Fourteen of these men subsequently were enrolled in a second study, which consisted of three months of treatment with aspirin, 330 mg three times a day, or three months of dipyridamole, 75 mg three times a day combined with aspirin, 330 mg three times a day. This portion of the study did not include placebo, but was double-blind, with random treatment assignment. Subsequently, two additional treatment periods of three months each were undertaken with dipyridamole, 100 mg four times a day, and placebo, one dose four times a day. This pair of treatments also was double-blind, with random assignment. Platelet survival time and treadmill exercise were undertaken as control and during the last week of each treatment period. All men had at least 1 mm of ST segment depression on their ECGs (modified V_{6} lead) during control treadmill exercise, and all had angina during this exercise test.

Platelet survival time was measured by labelling the patient's platelets with about 150 $\mu$Ci of $^{51}$Cr. Following re-infusion of labelled platelets, platelet count rate was ob-
tained daily for seven days. A single exponent was fitted to the platelet count-rate data by computer to obtain the platelet survival half-time. Citrated blood was used for platelet labelling. Normal platelet survival half-time averages 3.7 days, with an SE of 0.03 days (N=28) and a normal range of 3.3 to 4.2 days.

Maximal, angina-limited exercise was performed with a motor-driven treadmill using a graded exercise protocol. During and at completion of exercise, arterial blood pressure was obtained by cuff for calculation of the heart rate-systolic blood pressure product. All exercise tests were undertaken by one of the authors (P.S.), so that a consistent recognition of symptom-limited endpoints would occur.

Statistical significance of changes in the averages was assessed with the paired Student's t-test. All men understood the experimental nature of treatment with dipyridamole and aspirin, its potential risks, and the risks of measurement of platelet survival time and of treadmill exercise testing.

**RESULTS**

The combination of dipyridamole and aspirin increased platelet survival time. Control platelet survival averaged 2.4 ± 0.05 days (±SEM; N=33) and was 2.7 ± 0.07 days (P<0.001) following seven days of treatment. Aspirin treatment alone resulted in a smaller, but statistically significant, increase in platelet survival (2.4 ± 0.05 to 2.5 ± 0.06 days; P<0.05). Placebo did not result in a change in platelet survival in any patient by more than 0.1 day. Treatment with dipyridamole in combination with aspirin resulted in an increase in platelet survival of at least 0.2 days in 28 of these 33 men (85 percent). Aspirin alone resulted in an increase in platelet survival time of at least 0.2 days in 18 of 33 men (54 percent).

Similar results were observed in the 14 men who received therapy for three months and had exercise testing. The control average platelet survival time for these 14 men was 2.3 ± 0.09 days, after three months of aspirin was 2.5 ± 0.11 days (P < 0.05), and after three months of aspirin combined with dipyridamole was 2.9 ± 0.11 days (P < 0.01; Fig 1).

Treatment with aspirin alone did not alter the duration of exercise, control exercise was terminated at an average of 5.1 ± 0.8 min, and treatment with aspirin resulted in duration of exercise of 5.9 ± 0.9 min (NS). Aspirin did not alter heart rate, systolic blood pressure, or the heart rate-blood pressure product at rest, at submaximal (one half of control exercise duration) exercise, or at peak exercise (Fig 2).

Combined treatment with aspirin and dipyridamole resulted in a small, statistically significant, but biologically unimportant, improvement in exercise time (5.1 ± 0.8 to 6.0 ± 0.8 min; P < 0.05).
Treatment with aspirin-dipyridamole also did not result in alteration of either resting, submaximal or peak exercise heart rate × systolic blood pressure product (HR × BP). Resting average values for HR × BP (×10²) were as follows: control, 94 ± 4; aspirin, 102 ± 10 (NS); and aspirin-dipyridamole, 93 ± 6 (NS). The HR × BP at completion of exercise was 182 ± 15 for control, 189 ± 16 for aspirin (NS), and 182 ± 15 for aspirin-dipyridamole (NS; Fig 2). All men had ST segment depression and angina during control exercise and during exercise with aspirin and with aspirin-dipyridamole.

The small changes in exercise performance observed with aspirin-dipyridamole in a modest dose, suggested that an increase in dose might result in a more substantial effect. In addition, dipyridamole in a dose of 400 mg/day has been shown to lengthen platelet survival time.¹ These 14 men subsequently were given dipyridamole, 100 mg orally four times a day for three months and placebo given orally four times a day, for three months using a double-blind, crossover design. This higher dosage of dipyridamole had no greater effect on platelet survival time (2.9 ± 0.12 days) than the lower dose of dipyridamole (75 mg three times/day) in combination with aspirin (2.9 ± 0.11 days; NS; Fig 1).

The higher dose of dipyridamole did result in an increase in exercise performance. Exercise duration averaged 8.3 ± 1 min for the higher dose compared with placebo (5.0 ± 0.9 min; P < 0.05). The higher dosage of dipyridamole did not result in a change in either the resting HR × BP (97 ± 4) or HR × BP at peak exercise (171 ± 14) compared with control (rest HR × BP 95 ± 5; peak exercise 188 ± 15; Fig 3). Favorable effects of the higher dose of dipyridamole during exercise were apparent when the duration of exercise was controlled. Average HR×BP during treatment with dipyridamole, at the time during control exercise that exercise was terminated was 148 ± 10 (P < 0.05; Fig 3). During treatment with dipyridamole, eight men continued to have ST segment depression at the exercise time of control. The placebo did not result in a change in exercise hemodynamics or ST segment changes when compared with control (Fig 3). Thus, the higher dosage of dipyridamole is associated with a decreased heart rate × blood pressure product during submaximal exercise and with an increase in duration of exercise in men with coronary disease.

**DISCUSSION**

This study suggests that the combination of aspirin and dipyridamole increases platelet survival time in men with coronary disease. Treatment with aspirin results in a less marked increase in platelet survival in these men. Neither aspirin nor aspirin-dipyridamole altered exercise performance. Dipyridamole in a higher dosage of 400 mg/day effects similar to those of aspirin combined with a lower dose of dipyridamole on platelet survival time, and this higher dose of dipyridamole increased exercise performance. These results fail to support any relationship between alteration of exercise performance and alteration of platelet survival time. Dipyridamole appears to have two effects—alteration of platelet survival and improvement in exercise performance—and these two effects do not appear to be related.

Other investigators have been unable to alter exercise performance with aspirin in patients with coronary disease. Frishman and associates⁴ gave 11 patients with coronary disease and angina aspirin, 2,400 mg/day, and demonstrated inhibition of epinephrine-induced platelet aggregation, but no change in bicycle exercise performance. Davis and associates⁵ gave 13 men with angina a single oral dose of aspirin, 650 mg, and observed no alteration in treadmill exercise performance.

In this study aspirin had the expected inhibitory effect on collagen-induced platelet aggregation.⁸

**Figure 3.** Average heart rate-blood pressure product (± SEM) for rest, submaximal, and peak exercise (EXER) (closed circles) for 14 men with coronary disease (CAD) during treatment with placebo and dipyridamole (DPY) (400 mg/day). Peak and submaximal exercise measurements during dipyridamole treatment but for shorter exercise duration of control plotted as open circles. Values are significantly less than corresponding control values (P<0.05).
The dose of aspirin used in these studies was between 650 mg and 2,400 mg/day, and we used 990 mg/day. These doses of aspirin may be excessive relative to inhibition of the platelet release reaction and conceivably could create an unfavorable relationship between platelet release of thromboxane and endothelial synthesis of prostacyclin. Inhibition of both platelet and endothelial prostaglandin synthetic activity by aspirin could result in no change in exercise performance if a balance between these substances is important during exercise in patients with coronary disease. Our results suggest that this dose of aspirin increases shortened platelet survival time and aspirin in a dose of 1,000 to 1,200 mg/day appears to decrease thromboembolism in patients with prosthetic aortic valves and in patients with cerebrovascular disease and transient ischemic attacks.

A number of drugs have been shown to alter platelet survival time in patients with coronary disease. We have suggested that clofibrate and sulfinpyrazone increase shortened platelet survival, and Ritchie and Harker have shown that the combination of aspirin and dipyridamole, in the doses used in the current study, improved platelet survival time in patients with coronary disease. Of interest in the study of Richie and Harker is the relationship between the frequency and intensity of angina and shortened platelet survival, suggesting that myocardial ischemia and platelet reactivity may be related.

Platelet activation occurs during exercise. Men with coronary disease appear to have an exaggerated release of platelet β-thromboglobulin and platelet factor 4 during exercise. Treatment with sulfinpyrazone decreased both resting and exercise levels of β-thromboglobulin. Sulfinpyrazone has effects on platelet survival and on platelet release that are similar to those of aspirin-dipyridamole. Green and associates observed an enhanced release of platelet factor 4 during exercise in patients with coronary disease, and their data suggest a relationship between angina and ST segment during exercise and the magnitude of platelet release. Kumpuris and associates measured platelet aggregates in the venous blood of patients with coronary disease and in normals. Platelet aggregates were observed at completion of exercise in patients with coronary disease, and aspirin treatment inhibited aggregate formation. These results suggest that platelet activation occurs during dynamic exercise in patients with coronary disease, but the relationship between platelet activation and myocardial ischemia is unclear.

The major difficulty with many of these studies is that myocardial blood flow was not measured. In the men included in our study, it is likely that myocardial ischemia occurred during exercise, since they experienced angina and had ST segment depression. Improvement in myocardial blood flow, particularly if the improvement is only modest, may not be apparent if duration of exercise and ST segment changes are used as indicators. That is, aspirin and dipyridamole in combination with aspirin may be improving myocardial blood flow during exercise, and available methods as were used in this study, are not sufficiently sensitive to detect these differences. The results of this study neither refute nor confirm the possibility that platelet-platelet and platelet-endothelial interaction contribute to the development of myocardial ischemia in patients with coronary atherosclerosis.

Our results support a favorable effect of dipyridamole on exercise performance in men with coronary disease. A dose of 400 mg/day appears to be required to achieve this effect as an alteration of exercise performance was not observed at a dose of 222 mg/day (in combination with aspirin). The mechanism of alteration of exercise performance by dipyridamole is unclear, but is most likely to be a result of its coronary arterial vasodilating action. Dipyridamole is established as a vasodilator of small precapillary resistance coronary arteries. In acute experiments in open-chest dogs, Becker observed that intravenously (IV) administered dipyridamole increased myocardial blood flow to nonischemic regions while preserving flow to ischemic areas. In animals and in humans with an area of coronary stenosis, dipyridamole administered IV resulted in differences in myocardial blood flow with increased flow in arteries without stenosis. It is possible that coronary vasodilation induced by dipyridamole could result in a marked decrease in poststenotic coronary pressure and an absolute decrease in endocardial flow. We have not been able to show differences in flow distribution in men with coronary disease after orally administered dipyridamole, and there were no "paradoxical" responses to dipyridamole treatment in the men in our study in that clinical worsening occurred either in anginal frequency or exercise performance.

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