Effects of Clofibrate and Sulfinpyrazone on Platelet Survival Time in Coronary Artery Disease

By Peter Steele, M.D., Dennis Battock, M.D., and Edward Genton, M.D.

SUMMARY
Platelet survival time was measured (autologous labelling with \(^{51}\)chromium) in 68 men with coronary artery disease (CAD). Survival was shortened slightly (3.2 ± 0.04 days; mean ± SEM) as compared to normal (3.7 ± 0.04 days; \(N = 18; P < 0.001\)), and 60% had shortened survival (< 3.3 days). Thirty-seven had hyperlipoproteinemia (36 with Type IV and one with Type III) and platelet survival was shortened (3.1 ± 0.10 days) and significantly different from survival of men with normal lipoproteins (3.3 ± 0.12 days; \(P < 0.05\)). Twenty-two with shortened platelet survival and CAD received either clofibrate or sulfinpyrazone. Clofibrate prolonged platelet survival (2.6 ± 0.09 to 3.4 ± 0.14 days; \(P < 0.001\)) and ten of 12 had prolongation of survival. Sulfinpyrazone increased survival (2.8 ± 0.12 to 3.6 ± 0.21; \(P < 0.001\)) and nine of ten had prolongation of platelet survival. Clofibrate lowered serum cholesterol and tryglyceride but alteration in lipids did not correlate with alteration of survival. Sulfinpyrazone did not alter lipids. Data suggest that survival is shortened in CAD and that clofibrate and sulfinpyrazone alter survival. Platelet suppressant agents may prove beneficial in reducing the extent and complications of atherosclerotic arterial injury.

THE RELATIONSHIP between thrombosis and atherosclerosis has been investigated for many years.\(^{1-8}\) Recently, consideration that the interaction between the blood platelet and the arterial endothelium contributes to the pathogenesis of the vascular damage has led to proposals that therapeutic trials of agents which interfere with this interaction might show that the extent and impact of vascular damage could be reduced.\(^{6,7}\)

In an earlier study we suggested that platelet survival time was frequently shortened in patients with coronary artery disease.\(^8\) Eleven of 21 patients (52%) with angiographically confirmed coronary disease had shortened platelet survival.

Recently, data has been presented which suggests that clofibrate, a lipid-lowering drug, favorably alters mortality in patients with coronary disease,\(^8-11\) although some of the conclusions of these studies have been questioned on statistical grounds\(^12\) and very recently, the Coronary Drug Project Research Group reported that clofibrate failed to alter mortality in men with coronary disease.\(^13\) Of particular interest in these clinical trials was the finding that the alteration of mortality by clofibrate was not associated with the lowering of serum lipids. This suggested another mechanism for the drug’s favorable effect. Gilbert and Mustard have shown that clofibrate prolonged platelet survival time in ten of 11 patients, six of whom probably had coronary disease,\(^14\) and recently, Carvalho and associates have demonstrated that clofibrate normalized abnormal platelet sensitivity to aggregating agents in vitro in patients with familial hyperbetalipoproteinemia.\(^15\)

The present study was undertaken to determine the frequency of occurrence of shortened platelet survival time in coronary disease and to assess the effect of clofibrate and sulfinpyrazone on shortened platelet survival in these patients.

Patients
Platelet survival time was measured in 68 men (age 29–61 years, average age, 47 years). Coronary arteriography established that each patient had at least one area of at least 50% obstruction in at least one major coronary artery. Patients gave their informed consent to undergo measurement of platelet survival. Coronary arteriography was undertaken for the usual diagnostic reasons and not solely for this study. Medications known to alter platelet behavior were prohibited. These 68 men include the 21 men previously reported.\(^8\)

Methods
Platelet survival time was measured by labelling the platelets from about 450 ml of the patients’ venous blood with \(^{51}\)chromium.\(^{16}\) By computer-assisted least-squares analysis a single exponent was fitted to seven days of platelet count-rate data obtained at two to three hours following
reinfusion of labelled platelets and daily for the next six days. Normal platelet survival half-time was 3.7 ± 0.04 days (mean ± SEM; N = 18) with a normal range of 3.3-4.2 days. Platelet survival time was measured either just before or several weeks after coronary arteriography to avoid possible effects of the procedure or of contrast media.

Serum cholesterol, triglyceride, and lipoprotein electrophoresis on paper was measured during performance of platelet survival and patients typed as to lipoprotein class. Prior to obtaining blood for these analyses the patient had been on a standard American diet and fasting for at least 14 hours. Student’s t-test was used to statistically compare the means.

Results

Average platelet survival half-time for the 68 men with coronary disease was only slightly shortened at 3.2 ± 0.04 days, but significantly different (P < 0.001) from the normal average of 3.7 days (fig. 1). Forty-one of the 68 (60%) had shortened platelet survival (<3.3 days) and 27 (40%) had normal platelet survival. As noted previously, platelet survival did not correlate with the extent of coronary disease as assessed by angiography, a history of myocardial infarction, or the presence or absence of angina or its severity.

Thirty-seven of the 68 men had hyperlipoproteinemia with 36 having Frederickson Type IV and one having Type III hyperlipoproteinemia. Average platelet survival time for the patients with hyperlipoproteinemia was shortened at 3.1 ± 0.10 days (fig. 2). Twenty-seven of the 37 (73%) had shortened platelet survival. Of the men with normal lipoproteins, 16 of 31 (52%) had shortened platelet survival and the average value was normal at 3.3 ± 0.12 days (fig. 2). The average value for patients with hyperlipoproteinemia was significantly different (t = 2.10; 0.05) from the average of those with normal lipoproteins.

Table 1

<table>
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<tr>
<th>Pt</th>
<th>Type</th>
<th>Control Surv (1/2g. days)</th>
<th>Control Chol (mg %)</th>
<th>Control Trig (mg %)</th>
<th>Clofibrate Surv (1/2g. days)</th>
<th>Clofibrate Chol (mg %)</th>
<th>Clofibrate Trig (mg %)</th>
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<td>±0.14</td>
<td>±0.17</td>
<td>±0.48</td>
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Abbreviations: Pt = patient; Type = Lipoprotein type; Surv = platelet survival; Chol = serum cholesterol; Trig = serum triglyceride; Norm = normal; SEM = standard error of the mean.

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CLOFIBRATE & SULFINPYRAZONE IN CAD

Effect of clofibrate on mean platelet survival time in 12 men with coronary disease.

Twenty-two of these men with shortened platelet survival were treated with either clofibrate (2 g/day) or sulfinpyrazone (800 mg/day) for three months and measurement of platelet survival, lipids, and lipoproteins repeated.

Twelve men received clofibrate which significantly ($P < 0.001$) prolonged average platelet survival time from $2.6 \pm 0.09$ to $3.4 \pm 0.14$ days (table 1, fig. 3). Ten had prolongation of platelet survival by more than 0.2 days half-time and six became normal ($> 3.3$ days). Clofibrate had the expected lipid-lowering effect (table 1), but alteration of platelet survival did not correlate with either the initial lipid level or the alteration of lipids.

Ten patients received sulfinpyrazone which significantly ($P < 0.001$) prolonged average platelet survival time from $2.8 \pm 0.12$ to $3.6 \pm 0.21$ days (table 2, fig. 4). Sulfinpyrazone prolonged shortened platelet survival by at least 0.2 days in nine and normalized survival in eight men ($> 3.3$ days). Sulfinpyrazone did not alter serum lipids.

Discussion

These results provide further support for earlier reports that platelet survival time is shortened in coronary artery disease. Platelet survival time theoretically measures the interaction of platelets with the arterial luminal surface. Thus, in coronary atherosclerotic disease decreased platelet survival time could reflect increased platelet–surface interaction due to plaque rupture with release of thrombogenic material into the arterial lumen due to platelet adherence to exposed subendothelium consequent to endothelial injury as a response to excessive circulating catecholamines or due to turbulence induced by the irregular surface. Platelet adherence and aggregation induced by these mechanisms, or other mechanisms, is likely to be harmful through formation of macro- or microthrombi on the vascular surface.

Sulfinpyrazone has been shown to prolong shortened platelet survival time in patients with valvular heart disease and arterial thrombosis.

Table 2

<table>
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<tr>
<td>± SEM</td>
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<td>±0.12</td>
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</table>

See table 1 for abbreviations.
NS = not significant.

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Harker and Slichter have shown that diprydamole prolongs shortened platelet survival in patients with prosthetic heart valves54 and arterial thrombosis.55

In this report sulfipyrazone has been demonstrated to alter shortened platelet survival time in coronary artery disease. Clofibrate also prolongs shortened platelet survival, which is of particular interest in regard to evidence from clinical trials that clofibrate reduced mortality in patients with coronary disease.9-11 In the clinical trials the favorable effect of clofibrate did not correlate with the alteration of lipids. In our study the alteration of platelet survival by clofibrate did not correlate with either the alteration of lipids or the pretreatment lipid levels. This suggests that the effect of clofibrate on platelet survival is not mediated through the drug’s effect on lipids. This point is further supported by similar alteration of platelet survival time by sulfipyrazone, as this drug did not alter lipids. Carvalho and associates15 have shown that clofibrate normalized platelet hypersensitivity to aggregating agents in patients with hyperbetalipoproteinemia and that clofibrate had no effect on lipids in these patients.

The effects of clofibrate on platelets and on platelet-surface interaction as measured by platelet survival time might explain the drug’s apparent beneficial effect in coronary artery disease.9-11

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