Platelet Function in Coronary Artery Disease: Effects of Coronary Surgery and Sulfinpyrazone

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Summary Platelet survival and plasma concentrations of β-thromboglobulin and platelet factor 4 were measured in 44 patients before and 6 months after coronary artery bypass grafting. Postoperatively, patients were randomized to receive sulfinpyrazone, 800 mg/day, or placebo. Preoperatively, platelet survival was significantly shorter than normal, and plasma concentrations of both platelet-specific proteins were significantly elevated. Postoperatively, all three indexes of platelet function tended to become normal, but these changes were statistically significant only in patients treated with sulfinpyrazone. Postoperative exercise testing correlated significantly with plasma concentrations of β-thromboglobulin and platelet factor 4 measured preoperatively and postoperatively. These results are consistent with reports of the effects of sulfinpyrazone on platelet involvement in other conditions, and suggest that the drug reduces platelet activation and inhibits actual destruction. The results also show a relationship between abnormalities of platelet function and an index of postoperative myocardial ischemia.

ABNORMALITIES of platelet function have been well documented in patients with coronary artery disease,1-4 supporting the proposition that anti-platelet drugs might modify the natural history of this condition. This proposition has been tested recently in large, multicenter trials of antiplatelet drugs in the secondary prevention of myocardial infarction.5,6 The most positive finding from these trials has been a significant reduction in sudden death in patients treated with sulfinpyrazone in the first 6 months after acute myocardial infarction.5,8

In patients undergoing coronary artery bypass surgery, Steele et al.9 correlated shortened platelet survival with graft occlusion, raising the possibility that antiplatelet drugs might also be of value after coronary artery surgery. In the present study, platelet survival and release were measured in patients with angiographically documented coronary artery disease before and 6 months after coronary artery bypass surgery, and the effect of sulfinpyrazone on the postoperative measurements was assessed in a randomized, double-blind, placebo-controlled trial.

Methods

Patients

All patients had disabling angina and were placed on the waiting list for coronary bypass grafting after angiographic demonstration of operable coronary artery disease. Selection criteria included freedom from symptoms of peptic ulcer, absence of the need for other drugs that might alter platelet function (especially aspirin-containing preparations) and ability to undergo postoperative evaluation. Normal values were obtained during the course of the study from 15 subjects of comparable age who were free from clinical cardiovascular disease.10

Platelet Function

Platelet survival was determined by standard methods.10 The packed cells were returned to the patient after the infusion of the 51Cr-labeled, platelet-rich plasma. Blood samples were then collected twice daily for 5 days. Criteria for acceptance of platelet survival data were established before the study and included platelet label greater than 85%, red cell label less than 10%, plasma label less than 10% and recovery 12 hours after infusion greater than 40%. Radioactivity was measured in duplicate on heparinized and saponified whole blood samples. Platelet life span was calculated using the multiple-hit model, which gave results that correlated most strongly with plasma concentrations of platelet-specific proteins.10 Beta-thromboglobulin (BTG) and platelet factor 4 (PF4) concentrations in plasma were measured by radioimmunoassay.11

Sulfinpyrazone

Sulfinpyrazone (Anturane, Ciba-Geigy) was given in a dose of one 200-mg tablet four times daily. A placebo tablet of identical appearance was given four times daily to control patients.

Procedure

All preoperative tests were performed during the week before surgery and at least 1 week after the most recent cardiac catheterization. Postoperative platelet function measurements were made approximately 6 months after surgery. Patients were randomized to receive sulfinpyrazone or placebo postoperatively. Treatment was given on a double-blind basis commencing 5 days after surgery and continuing until the postoperative tests were completed. Compliance was checked by tablet counts at monthly visits.

Indexes of Myocardial Ischemia

Angina was graded preoperatively and postoperatively according to a slightly modified New York Heart Association classification.12 Exercise testing was per-
formed preoperatively and postoperatively on a bicycle ergometer. The development of ST depression was recorded\textsuperscript{13} and the maximal work load was expressed as a percentage of the predicted maximum.\textsuperscript{13, 14} Coronary angiography was performed preoperatively and postoperatively,\textsuperscript{15} and vessel patency was graded as described by Jenkins et al.\textsuperscript{16}

### Psychological Testing

The Eysenck Personality Questionnaire was administered to 14 patients postoperatively and a score derived on the neuroticism scale.\textsuperscript{17}

### Analyses

For statistical purposes, the two null hypotheses were that there were no differences in platelet function before and 6 months after surgery and that there were no differences in platelet function between patients receiving treatment (sulfinpyrazone) or placebo. Three independent indexes of platelet function were used in each analysis: platelet survival and plasma concentrations of $\beta$T$G$ and PF$4$. The former hypothesis was tested in the placebo group by paired $t$ test comparing preoperative and postoperative values in the same patient. The latter hypothesis was tested by paired $t$ test comparing, in the treatment group, preoperative and postoperative values in the same patient, and by unpaired $t$ test comparing, between the treatment and placebo groups, the changes in platelet function (postoperative minus preoperative value) in each patient. Comparability of the treatment and placebo groups preoperatively was assessed by unpaired $t$ test. Preoperatively, the entire group of patients was compared with normal subjects by unpaired $t$ test.

### Results

Forty-four patients entered the study and 39 completed it. There were five withdrawals: three (one sulfinpyrazone and two placebo) because of failure to take tablets and two (both sulfinpyrazone) because of gastrointestinal side effects.

### Platelet Function

Preoperatively, all three indexes of platelet function were significantly different from normal. Platelet life span was $143 \pm 46$ hours (mean $\pm$ sd) (normal $179 \pm 31$ hours, $p < 0.01$), plasma $\beta$T$G$ was $54 \pm 20$ ng/ml (normal $32 \pm 13$ ng/ml, $p < 0.01$) and plasma PF$4$ was $12 \pm 7$ ng/ml (normal $4 \pm 3$ ng/ml, $p < 0.001$).\textsuperscript{10} For platelet survival, 32% of patients were outside the normal range (mean $\pm 2$ sd), for $\beta$T$G$ 32% and for PF$4$ 53%.

Preoperatively, the treatment and placebo groups were not significantly different from each other with respect to plasma $\beta$T$G$ and PF$4$ concentrations, but platelet life span was significantly shorter in the treatment group than in the placebo group ($p < 0.05$) (table 1).

In the placebo group, the preoperative abnormalities in all three indexes of platelet function tended to become normal postoperatively, but these changes were not significant (table 1). In the treatment group, the preoperative abnormalities in all three indexes of platelet function were significantly improved postoperatively (table 1). The changes in each index of platelet function were also greater after treatment than after placebo, but these changes were significant only for platelet survival ($p < 0.05$).

We previously showed that plasma concentrations of $\beta$T$G$ and PF$4$ and indexes of platelet survival were significantly correlated in patients with coronary artery disease.\textsuperscript{10} In the present study, we showed that the preoperative-to-postoperative changes in these indexes are also significantly correlated. Thus, for $\beta$T$G$ and PF$4$, $r = 0.52$ ($p < 0.01$); for $\beta$T$G$ and platelet life span, $r = 0.27$ (NS) for the multiple-hit model, $r = 0.31$ ($p < 0.05$) for the linear model and $r = 0.36$ ($p < 0.05$) for the exponential model; for PF$4$ and platelet life span, $r = 0.54$, 0.67 and 0.60 (all $p < 0.01$) for the three models, respectively.

### Platelet Function and Postoperative Myocardial Ischemia

Postoperative angina did not correlate with any index of platelet function measured either preoperatively or postoperatively. However, postoperative angina was significantly related to preoperative angina ($F = 3.62$, $p < 0.05$), although not to preoperative exercise testing or coronary angiography score.

Postoperative exercise testing was significantly correlated with plasma concentrations of $\beta$T$G$ and PF$4$ measured both preoperatively and postoperatively (table 2), but not with platelet survival. Postoperative exercise testing (percent predicted) was also related to preoperative angina ($F = 4.42$, $p < 0.01$), although not to preoperative exercise testing or coronary angiography score.

Postoperative coronary angiography (graft patency) was not correlated with any of the indexes of platelet function, measured either preoperatively or postoperatively. However, graft patency was significantly related to preoperative coronary angiography score ($F = 8.57$, $p < 0.05$), although not to preoperative angina or exercise testing.

### Platelet Function and Psychological Testing

Abnormal platelet function tended to be associated with lower neuroticism scores, but these changes were not statistically significant.
TABLE 2. Relation of Platelet Release and Exercise Testing

<table>
<thead>
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<th>Platelet release</th>
<th>Exercise testing</th>
<th>% predicted</th>
<th>Postop</th>
<th>Change</th>
<th>Postop</th>
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<td>ST depression</td>
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Values are correlation coefficient (r).
*p < 0.05.
†p < 0.001.
Abbreviations: See table 1.

Discussion

In this study, patients with coronary artery disease had significant abnormalities in platelet survival and plasma concentrations of βTG and PF4. Between one-third and one-half of the patients had values outside the normal range. After coronary artery surgery, all three indexes of platelet function returned toward normal. These changes were statistically significant only in patients treated with sulfipyrazone.

Preoperatively, platelet survival was fortuitously shorter in patients randomized to the treatment group, so that the postoperative effects of sulfipyrazone on platelet survival are difficult to assess. Since the lack of preoperative comparability of the treatment and control groups did not apply to the plasma concentrations of βTG and PF4, the significant decrease in these levels postoperatively in the treatment group, but not in the placebo group, suggests that sulfipyrazone did, in fact, tend to normalize the platelet changes in patients with coronary artery disease undergoing coronary artery bypass grafting.

The effect of sulfipyrazone in normalizing platelet function after coronary artery surgery is consistent with reports in which the shortened platelet survival in patients with gout,18 prosthetic heart valves,19, 20 recurrent venous thromboembolism21 and coronary artery disease3 has been prolonged after treatment with sulfipyrazone. In the present study, release of platelet-specific proteins, as well as platelet survival, were normalized after drug treatment, which indicates that sulfipyrazone reduced platelet activation as well as inhibited destruction.

Coronary artery bypass grafting reduces angina postoperatively, but improvement in objective indexes has been harder to document.4, 22 All three indexes of platelet function showed a trend toward normalization postoperatively, even in the placebo group (NS). This finding could have interesting implications for determining the site of production in the circulation of the platelet changes in patients with coronary artery disease.4 The usual presumption is that such platelet changes are generated diffusely and are associated with the generalized arterial disease that such patients are prone to have. If these changes resolve after coronary artery surgery alone, it would imply that even small segments of diseased arteries can give rise to platelet activation detectable systemically. However, other possible explanations for platelet activation preoperatively are circulating catecholamines generated by pain, fear, or stress, although in a limited survey we could not show any relation between psychological testing and platelet function.

The clinical effects, if any, of the normalization of platelet function after coronary artery surgery and sulfipyrazone cannot be determined from the present study. Preliminary reports indicate that other antiplatelet agents, aspirin with and without dipryridamole, for example, do not increase graft patency.23, 24 However, it is possible that an improved clinical outcome could accompany the normalization of platelet function in such patients, because abnormalities of platelet function are postulated to be associated with clinical thromboembolic disease. This therapeutically encouraging postulate is supported by the present study, in which one index of postoperative myocardial ischemia (exercise testing) was significantly correlated with plasma concentrations of βTG and PF4 measured both postoperatively and preoperatively. The correlation with postoperative βTG levels supports a pathogenetic relationship between platelet activation and myocardial ischemia. The correlation with preoperative βTG and PF4 levels suggests that these tests might have predictive clinical value.

References

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