Altered Platelet Function in Patients with Prosthetic Mitral Valves

Effects of Sulfinpyrazone Therapy

By HUGH S. WEILY, M.D., AND EDWARD GENTON, M.D.

SUMMARY
Platelet survival time and platelet adhesiveness and aggregation were examined in 16 patients with prosthetic mitral valves. Subsequently, nine patients were treated with sulfinpyrazone in doses of 400 mg and 800 mg/day, and the studies were repeated after a treatment period of 5 to 8 weeks. $^{51}$Chromium survival time was shortened in 15 of 16 patients, and the mean value for the entire group was 5.49 ± 0.23 days (normal, 6.73 ± 0.21 days; $P < 0.001$). Mean platelet adhesiveness in glass bead columns was 53 ± 5% (normal, 30 to 60%). Platelet aggregation (turbidometric technic of Born) was normal. Treatment with 400 mg of sulfinpyrazone daily reduced platelet adhesiveness to 40 ± 5% ($P < 0.05$), but effected no change in platelet survival time or platelet aggregation. Therapy with 800 mg of sulfinpyrazone daily corrected platelet survival time to normal, 6.68 ± 0.57 days ($P < 0.01$), but it produced no further decrease in adhesiveness and no change in aggregation. It is concluded that platelet abnormalities regularly occur in patients with prosthetic mitral valves and may contribute to thromboembolism in this group. Platelet survival time is a more sensitive measure of altered platelet kinetics than platelet adhesiveness or platelet aggregation. Therapy with 800 mg of sulfinpyrazone per day corrects demonstrated abnormalities and may be useful for prevention of thromboembolism in patients with prosthetic mitral valves.

Additional Indexing Words:
Platelet survival time
Platelet adhesiveness
Platelet aggregation

SYSTEMIC emboli remain the major cause of late morbidity and mortality in patients with prosthetic cardiac valves.1–13 Newer designs and modifications of previously employed valves appear to be associated with a lower risk of thromboembolism,14–19 but they have not eliminated this complication. Although anticoagulants have reduced the incidence of embolic episodes in patients with aortic valve prostheses, they have provided, at best, only partial protection in patients with prosthetic mitral valves.1,2 This failure suggests that factors involved in thrombosis, which are unaffected by conventional anticoagulant therapy, may be important. Demonstration that platelets play a key role in initiating thrombosis20 and that they are not affected by inhibition of the coagulation mechanism21 has led to much recent interest in evaluating platelet function in patients with thromboembolism or with conditions predisposing to thromboembolic disease. Studies of this nature have demonstrated that postoperative patients and patients with recurrent venous thrombosis or pulmonary embolism have increased platelet adhesiveness22, 23 and suggest that platelets are important in thrombogenesis in many clinical situations.

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That the platelet may be important in the pathogenesis of thromboembolism in patients with cardiac valve prostheses is suggested by the demonstration of decreased platelet survival time in this group. Several compounds are known to alter platelet activity, and there is evidence to suggest that they may be useful in the prevention of emboli in patients with prosthetic cardiac valves. Sullivan and associates have shown a decrease in the number of embolic episodes in such patients treated with dipyridamole in addition to warfarin, when compared to a control group treated with warfarin alone. Recently, Harker demonstrated that shortened platelet survival time in patients with heart valve prostheses can be partially corrected with acetylsalicylic acid and completely corrected with dipyridamole.

Sulfinpyrazone alters platelet reactivity and has been shown capable of decreasing platelet adhesiveness, decreasing the response of platelets exposed to collagen when large doses are given acutely and increasing platelet survival time with several weeks of therapy. Studies of its effect on platelet activity in patients with prosthetic cardiac valves, however, are lacking. It was the purpose of this study to examine platelet survival and platelet adhesiveness and aggregation in a group of patients with prosthetic mitral valves and to determine the response of these parameters to treatment with sulfinpyrazone.

Methods

Platelet Survival Time

Platelet survival time was determined by using autologous chromium-labeled platelets according to the technic of Aster and Jandl.

Platelet Adhesiveness

Platelet adhesiveness in glass bead columns was determined by employing a modification of the technic of Salzman. Using a two-syringe technic, 2 ml of blood was drawn into a plastic heparinized syringe and immediately passed through a standardized glass bead column in exactly 1 min.

Platelet Aggregation

Platelet aggregation was determined by using a modification of the turbidometric technic of Born. An Aminco fluoromicrophotometer was adapted to measure light transmission through platelet-rich plasma maintained at 37°C, with constant agitation provided by a magnetic stir bar. Adenosine diphosphate (ADP) in a final concentration of 2 to 20 μg/ml of plasma or twofold dilutions of a collagen suspension* were added and the resulting aggregation observed.

Sulfinpyrazone Levels

Plasma levels of sulfinpyrazone were determined by a method previously described. In most cases, the samples were drawn at random. In two patients, levels were determined serially 1, 2, 4, and 6 hours following the usual oral dose of 200 mg.

Analysis of Data

For testing of platelet survival data, the Wilcoxon matched pair, signed-rank test, and the rank-sum test were employed. In addition, the slope of the regression line, from which the half-life of chromium was determined, and a pooled F-value for change in slope were calculated. Platelet adhesiveness data were tested using the Wilcoxon matched pairs, signed-rank test.

Subjects

Studies of platelet adhesiveness, aggregation, and survival time were performed in 16 patients with prosthetic mitral valves. The patient group included 11 men and five women, aged 33 to 63 years, who had mitral valve prostheses placed 6 mo to 6 years prior to entry into the study. Of these, 13 had Starr-Edwards ball valves, and three had Kay-Shiley disc prostheses. With the exception of one patient who had valve replacement as a result of severe papillary muscle dysfunction, all had underlying rheumatic heart disease. Following completion of initial studies, nine of these patients, eight with Starr-Edwards prostheses and one with a Kay-Shiley valve, were treated with sulfinpyrazone. Therapy was initiated with 400 mg per day in six and with 800 mg per day in three patients. After 5 to 8 weeks of treatment, platelet survival studies were repeated. During therapy, measurements of platelet adhesiveness and aggregation and sulfinpyrazone plasma levels were made weekly when possible or at the time of repeat platelet survival study. Following the second study, the dose, for those patients initially given 400 mg/day, was increased to 800 mg/day, and after an additional treatment period of 5 to 8 weeks, studies were repeated as described above.

*Sigma C-9879—Collagen from bovine Achilles tendon.
Results of Platelet Survival Studies in Patients with Prosthetic Mitral Valves Prior to and Following Sulfinpyrazone Therapy

<table>
<thead>
<tr>
<th>Prosthetic valve patient</th>
<th>Platelet survival time (days)</th>
<th>Sulfinpyrazone 400 mg/day</th>
<th>Sulfinpyrazone 800 mg/day</th>
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<tr>
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<td>P.J.</td>
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<td>R.K.</td>
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<td>M.K.</td>
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<td>7.60</td>
<td>6.10</td>
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<td>E.B.</td>
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<tr>
<td>Mean</td>
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<td>5.47</td>
<td>6.08</td>
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</table>

*Kay-Shiley prosthesis.

Results

Platelet Survival Time (Table 1)

Mean platelet survival time in seven normal controls was $6.73 \pm 0.21$ days (standard error of the mean). Platelet survival time was shortened in 15 of 16 patients with prosthetic mitral valves, and the mean for the entire group, $5.49 \pm 0.23$ days, was significantly shorter than normal ($P < 0.001$; fig. 1). In the two patients on whom two control studies were performed, results varied by 6% and 11%. Platelet survival time averaged $5.51 \pm 0.27$ days in patients with Starr-Edwards prostheses and $5.44 \pm 0.06$ days in those with Kay-Shiley valves. The difference in these values is not statistically significant ($P > 0.50$). The mean platelet survival time before treatment was $5.58 \pm 0.27$ days in those patients subsequently treated with sulfinpyrazone. There was no significant difference between this value and that found in the patients with prosthetic valves who were not treated ($P > 0.50$). Treatment with 400 mg of sulfinpyrazone per day resulted in no significant change in platelet survival time. However, treatment with 800 mg of sulfinpyrazone was associated with an increase in platelet survival time in seven of nine patients, to a mean survival time of $6.68 \pm 0.57$ days (fig. 2). This was a statistically significant increase ($P < 0.01$), but the resulting mean survival time did not differ significantly from that of the normal group ($P > 0.50$).

Platelet Adhesiveness (Table 2)

The normal range for platelet adhesiveness in this laboratory is 30% to 60%. In the nine patients subsequently treated with sulfinpyrazone, pretreatment platelet adhesiveness averaged 53 ± 5%. Following therapy with 400 mg

<table>
<thead>
<tr>
<th>Prosthetic valve patient</th>
<th>Av. platelet adhesiveness (%)</th>
<th>Sulfinpyrazone 400 mg/day</th>
<th>Sulfinpyrazone 800 mg/day</th>
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</tr>
<tr>
<td>B.M.</td>
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<td>25</td>
<td>41</td>
</tr>
<tr>
<td>Mean</td>
<td>53</td>
<td>40</td>
<td>38</td>
</tr>
</tbody>
</table>

*Figure 1

Platelet survival time in normal controls and in patients with prosthetic mitral valves (mean ± SEM).

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Platelet survival time: Effect of sulfinpyrazone therapy (mean ± SEM).

of sulfinpyrazone per day, this decreased to 40 ± 5% (P < 0.05; fig. 3). When the dose of sulfinpyrazone was increased to 800 mg/day, mean platelet adhesiveness decreased further to 38 ± 2.5%, but this was not significantly different from that found with the lower dose.

Platelet Aggregation

In this group of patients, values for collagen and ADP-induced aggregation closely paralleled each other, and when compared with normal, no abnormalities were demonstrated in terms of the amount of aggregation produced by a given concentration of ADP or collagen, the slope of the dose-response curve, or the degree of maximal aggregation. No change in these parameters occurred following treatment with sulfinpyrazone.

Sulfinpyrazone Levels

During chronic therapy, plasma levels of sulfinpyrazone ranged between 10 and 25 mg/L in all subjects. In two patients, determination of levels 1, 2, 4, and 6 hours after oral administration of 200 mg revealed that the sulfinpyrazone plasma concentration remained relatively constant, that is, between 15 and 20 mg/L.

Discussion

The results of this study confirm the observation that platelet survival is shortened in patients with prosthetic cardiac valves. The cause for this remains unclear, but it may result from mechanical trauma to the platelet similar to that which produces chronic red cell damage in these patients. Alternatively, chronic red cell destruction with concomitant ADP release may result in concentrations of ADP in the area of the valve sufficient to produce formation of platelet aggregates on the prosthesis. Finally, it is possible that the shortened survival time is a result of continued formation of platelet aggregates in response to the presence of a large foreign object, the prosthetic valve. Whatever the cause, the fact that platelet survival time is shortened in patients with prosthetic heart valves supports the view that platelets are important in the pathogenesis of thromboemboli in this group.

Although a significant decrease in mean platelet adhesiveness occurred with sulfinpyrazone therapy, only three of nine patients had abnormally high initial values, and mean adhesiveness before treatment was within normal limits. Similarly, no abnormalities in collagen or ADP-induced aggregation were demonstrated prior to therapy. These results suggest that platelet survival time may be a more sensitive indicator of altered platelet function than studies of either platelet adhesiveness or platelet aggregation.

With regard to platelet aggregation, it has previously been shown that in rabbits, intravenous infusion of sulfinpyrazone in doses.
ranging from 25 to 150 mg/kg blocks the aggregating action of collagen on platelets.\textsuperscript{35}

In those studies, suppression of aggregation was noted with a dose of 50 mg/kg and a corresponding plasma level of 200 mg/L. No change in collagen-induced aggregation was noted in the present study, but much smaller doses of sulfinpyrazone, given orally, were used, and plasma levels ranged from 10 to 25 mg/L.

This group of patients was not large enough nor the observation period long enough to allow conclusions regarding (1) the effectiveness of sulfinpyrazone in preventing thromboembolism, or (2) the usefulness of the platelet survival time in predicting the likelihood of systemic emboli. However, four of the patients studied had embolic episodes following placement of the prosthetic valve and prior to entry into the study. All of these patients had shortened platelet survival times. While on therapy, one patient continued to have cerebral emboli associated with evidence of severe valvular dysfunction requiring additional surgery. This patient (C.S.) had a very short platelet survival time and an incomplete response to therapy. At surgery, thrombus formation on the valve was found to be extensive. No other patients had evidence of systemic emboli while being treated with sulfinpyrazone. These observations are in agreement with the promising results of others who have used drugs which alter platelet function in the treatment of patients with prosthetic heart valves.\textsuperscript{24, 36} Further investigations in this area, including a controlled study employing the methods used in our study, seem indicated.

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