Favorable Effect of Sulfinpyrazone on Thromboembolism in Patients with Rheumatic Heart Disease

PETER STEELE, M.D., AND JOSEPH RAINWATER, M.D.

SUMMARY Thromboembolism complicates the course of patients with rheumatic heart disease (mitral stenosis) and platelet survival time has been shown to be shortened in patients with a history of thromboembolism; sulfinpyrazone has been shown to increase platelet survival in these patients. A prospective, blinded trial of sulfinpyrazone therapy in patients with rheumatic heart disease has been completed. One hundred fifty-four of 186 patients had shortened platelet survival (chromium-51 labeling of autologous platelets) on enrollment and were randomized to treatment with either sulfinpyrazone or placebo. Thirty-two patients with initially normal platelet survival were neither randomized nor treated. New thromboembolism occurred in 19 patients during 4 years of observation; two received sulfinpyrazone, 16 received placebo ($x^2 = 12.75, p < 0.01$) and one had normal initial platelet survival time. Sulfinpyrazone increased platelet survival time (control $2.5 \pm 0.04$ days [average $\pm$ SEM]; normal half life $3.7 \pm 0.03$ days; 1 year $2.8 \pm 0.04$ days; $n = 78$) relative to placebo (control $2.6 \pm 0.04$ days; 1 year $2.5 \pm 0.05$ days; $n = 76, p < 0.01$). The results of this trial confirm earlier work suggesting that platelet survival time is frequently shortened in patients with rheumatic heart disease, and that sulfinpyrazone increases platelet survival. Sulfinpyrazone appears to decrease thromboembolism in patients with rheumatic mitral stenosis.

THROMBOEMBOLISM frequently occurs in patients with rheumatic heart disease. Although anticoagulants appear to be effective in preventing embolism in these patients, these drugs are associated with a definite risk of bleeding and are inconvenient for the patient to take. A role for platelets in the pathogenesis of thromboembolism in these patients was suggested by the frequent occurrence of shortened platelet survival time, particularly in patients with a history of thromboembolism. The platelet-suppressant drug sulfinpyrazone increases platelet survival time in patients with rheumatic heart disease. We undertook a prospective clinical trial to determine the value of treating rheumatic heart disease patients with sulfinpyrazone and measuring platelet survival time.

Patients

Patients with clinical evidence of rheumatic heart disease (mitral stenosis) underwent measurement of platelet survival time and those with shortened platelet survival were randomized to treatment (double blind) with either sulfinpyrazone (200 mg orally four times daily) or placebo. Patients whose initial platelet survival time was normal were not randomized and were not treated. All patients had the characteristic auscultatory findings of mitral stenosis and most had undergone cardiac catheterization and echocardiography.

All patients with rheumatic heart disease encountered by the authors were asked to participate in this study, except those certain to undergo mitral or aortic valve replacement surgery within the next year or patients with another serious illness. Patients were excluded if they had clinical evidence of coronary, cerebral or peripheral vascular disease or arterial hypertension. Patients enrolled in the study would be asked to come to Denver for study once a year for 4 years. Twenty-three patients (14 men) declined to participate after discussing the study with the authors. Eight declined because they planned to move from the Rocky Mountain region and another five thought it would be difficult for them to come to Denver for study. Three patients were advised by their physician not to participate and six could not accept randomization. One patient may have had an allergic reaction to sulfinpyrazone. Of the 23 who did not participate, one had a history of embolism (the patient with the allergic reaction).

Diagnostic and therapeutic decisions (e.g., cardiac catheterization, warfarin administration, mitral valve surgery) regarding rheumatic heart disease were not made by the physicians directly involved in the trial. The risks, benefits and design of the trial were explained to all patients and their consent to participate was obtained.

Methods

Platelet survival time was measured on enrollment and yearly for the next 4 years by modification of the method of Aster. Citrated, platelet-rich plasma was obtained by centrifugation of approximately 350 ml of the patient's venous blood and the platelets were labeled with 100–150 $\mu$Ci of chromium-51. After reinfusion, samples were obtained daily for 7 days; a
A single exponent was fitted to the count-rate data by computer-assisted, least-squares analysis and the halftime was computed. The platelet survival halftime in 26 normal subjects was 3.7 ± 0.03 days (±SEM) (normal range 3.3–4.2 days). Patients with shortened platelet survival on entry (less than 3.3 days) were randomized to receive either sulfinpyrazone or placebo in identical capsules. Patients with an initial platelet survival time of 3.3 or more days were not randomized and did not receive platelet-suppressant therapy or placebo. All patients understood that sulfinpyrazone was being tested as a platelet-suppressant drug and that aspirin may also be a platelet suppressant. Patients were asked not to use aspirin (acetaminophen was allowed) or other nonsteroidal antiinflammatory drugs during the trial. The trial was undertaken to determine whether sulfinpyrazone prevents systemic embolism in patients with rheumatic heart disease. Patients participated in the trial for 4 years or until an embolic episode occurred. Other events that ended participation by a patient were mitral valve replacement (patients with commissurotomy were continued), adverse reaction to sulfinpyrazone (or placebo) and death.

Recognizing systemic embolism is difficult in respect to both specificity and sensitivity. When a patient experienced an event that was considered embolic (sudden loss of organ function on a vascular basis), the patient and his or her physicians were interviewed as soon after the event as possible and the clinical evidence for and against embolism was reviewed. These data were reviewed without knowing whether the patient was being treated with sulfinpyrazone or placebo. The circumstances of a patient’s death were similarly reviewed.

**Results**

One hundred eighty-six patients (115 men) were enrolled and 154 with shortened platelet survival time were randomized to receive sulfinpyrazone (78 patients) or placebo (76 patients). Risk factors for thromboembolism were comparable for patients randomized to sulfinpyrazone and placebo (table 1). New systemic embolism occurred in 19 patients. Sixteen patients with new thromboembolism had been randomized to receive placebo, two patients were in the sulfinpyrazone group and one patient had a normal platelet survival on entry. Using two-by-two chi-square analysis there was a significant difference in thromboembolism between the sulfinpyrazone and placebo groups (fig. 1).

Thromboembolism occurred before enrollment in this trial in 49 patients and two of these patients (both taking placebo) had a second embolic episode during the trial. Embolism occurred during the trial in 16 of 76 placebo patients (21%), in two of 76 sulfinpyrazone patients (3%), and in one of 32 untreated patients (normal initial platelet survival) (3%). Three deaths resulted from embolism, all in the placebo group. Autopsy showed embolic occlusion of the left main coronary artery in one patient, embolic occlusion of the superior mesenteric artery in another and embolic occlusion of the basilar artery in the third. Embolism was manifested as stroke in 12 patients. Embolism occurred 8–42 months after randomization in the placebo-treated patients, 29–37 months after randomization in sulfinpyrazone-treated patients and at 30 months in the untreated patient (fig. 2). Seven women and 12 men had embolic episodes. One of the two patients with embolism who received sulfinpyrazone and 11 of the 16 patients with embolic episodes in the placebo group were men.

There may be a relationship between atrial fibrillation and thromboembolism in these patients. Atrial fibrillation was present at the time of new embolism in 15 of 19 patients, and normal sinus rhythm was pres-

**Table 1. Sulfinpyrazone in Rheumatic Heart Disease**

<table>
<thead>
<tr>
<th>Risk factors for new TE entry</th>
<th>Randomized to placebo (n)</th>
<th>Randomized to SFP (n)</th>
<th>Normal platelet survival (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior thromboembolism</td>
<td>25 (33%)</td>
<td>23 (29%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Age &gt; 35 years</td>
<td>55 (72%)</td>
<td>61 (78%)</td>
<td>29 (91%)</td>
</tr>
<tr>
<td>Fixed atrial fibrillation</td>
<td>26 (34%)</td>
<td>42 (54%)</td>
<td>15 (47%)</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>12 (16%)</td>
<td>11 (14%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Prior mitral commissurotomy</td>
<td>14 (18%)</td>
<td>7 (9%)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Shortened platelet survival time</td>
<td>76 (100%)</td>
<td>78 (100%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Abbreviations: SFP = sulfinpyrazone; TE = thromboembolism.

**Figure 1. Frequency of new thromboembolism (TE) in patients randomized to placebo and sulfinpyrazone (SFP).**
ent in the other four ($\chi^2 = \text{NS})$. Of two patients with embolism in the sulfinpyrazone group, one had atrial fibrillation and one was in sinus rhythm. Thirteen of 16 patients with thromboembolism in the placebo group and the single patient with embolism in the untreated group had atrial fibrillation.

Anticoagulation with warfarin was frequently undertaken in these patients during the trial (table 2). The decision to use warfarin anticoagulation was made by the patient's primary physician. Warfarin did not appear to decrease the risk of new embolism in these patients. Nine of the 19 patients with new embolism had been treated with warfarin for at least 6 months before embolism and 10 had not been treated. In the sulfinpyrazone-treated patients one (of two) was receiving warfarin and the single patient with initially normal platelet survival was not anticoagulated. Eight of the placebo patients who had thromboembolism were anticoagulated with warfarin. Prothrombin times were at least twice control in all anticoagulated patients with embolism. Prothrombin times were repetitively measured between 3 and 6 weeks in all anticoagulated patients.

**Table 2. Anticoagulation with Warfarin**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n)</th>
<th>SFP (n)</th>
<th>Normal platelet survival (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin on entry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 108)</td>
<td>38 (50%)</td>
<td>49 (63%)</td>
<td>21 (60%)</td>
</tr>
<tr>
<td>Warfarin begun</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>during study (n = 11)</td>
<td>6 (8%)</td>
<td>3 (4%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Continued on</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>warfarin during</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>study (n = 93)</td>
<td>35 (45%)</td>
<td>41 (53%)</td>
<td>17 (53%)</td>
</tr>
<tr>
<td>Total patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treated with</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>warfarin for at</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>least 6 months of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>study (n = 119)</td>
<td>44 (58%)</td>
<td>52 (67%)</td>
<td>23 (72%)</td>
</tr>
</tbody>
</table>

Abbreviation: SFP = sulfinpyrazone.

During the trial 33 patients underwent mitral valve replacement and were carried in the study up to the point of valve replacement surgery. Mitral replacement was undertaken in 15 placebo-treated patients, 16 sulfinpyrazone patients, and two patients with normal platelet survival. Mitral valve replacement was performed 14–47 months after entry in the trial.

During the trial 15 patients died. Three died of thromboembolism, five died within 10 days of mitral valve replacement, five died of cardiorespiratory causes, one died of a self-inflicted injury and one patient died suddenly.

Medication had to be discontinued in five patients. Three patients were taking placebo (headache, epigastric pain and arthralgia) and two sulfinpyrazone (allergic rash, thyroid nodule). None of these five patients had a new embolism.

Sulfinpyrazone increased platelet survival time (fig. 3). There was no difference in control platelet survival

**Figure 2.** Percent of patients free from new thromboembolism at 12-month intervals for the three patient groups — normal platelet survival on entry (normal Surv), short platelet survival randomized to sulfinpyrazone (SFP) and short platelet survival randomized to placebo. RHD = rheumatic heart disease.

**Figure 3.** Effect of sulfinpyrazone (SFP) and placebo on platelet survival time in 154 patients with rheumatic heart disease (RHD). Average values (±SEM) are compared. The normal range (3.3–4.2 days) is indicated at the left.
between patients randomized to sulfinpyrazone (average 2.5 ± 0.04 days [± SEM], n = 78) and those randomized to placebo (2.6 ± 0.04 days, n = 76). At each yearly measurement, platelet survival time was significantly increased by sulfinpyrazone compared with placebo (12 months: 2.8 ± 0.04 days [n = 76] vs 2.5 ± 0.04 days [n = 74], p < 0.01; 24 months: 2.8 ± 0.05 days [n = 72] vs 2.4 ± 0.04 days [n = 66], p < 0.01; 36 months: 2.8 ± 0.05 days [n = 63] vs 2.4 ± 0.04 days [n = 57], p < 0.01; 48 months: 2.9 ± 0.06 days [n = 48] vs 2.3 ± 0.05 days [n = 36], p < 0.01) (fig. 3).

During the 4 years of the study, platelet survival time decreased significantly both in the placebo group (control 2.6 ± 0.04 days [n = 76]; 48 months: 2.3 ± 0.05 days [n = 36], p < 0.01) and in the group with normal initial platelet survival time (control 3.5 ± 0.03 days [n = 32]; 48 months: 3.3 ± 0.05 days [n = 20], p < 0.05). The sulfinpyrazone-treated patients did not show this decrease with time (12 months: 2.8 ± 0.04 days [n = 76]; 48 months: 2.9 ± 0.06 days [n = 48], NS).

Medication compliance was monitored by supplying each patient with a 3-month supply of medication and by counting capsules. In addition, serum uric acid was measured yearly during measurement of platelet survival time.

Discussion

The results of this study suggest that sulfinpyrazone decreases the frequency of occurrence of systemic embolism in patients with rheumatic heart disease. In the present study embolism occurred in two of 78 patients treated with sulfinpyrazone and in 16 of 76 patients treated with placebo during 4 years of observation. Sulfinpyrazone was well tolerated in these patients and did not appear to alter the natural history of rheumatic heart disease unfavorably.

The results further suggest that platelets contribute to the pathogenesis of thromboembolism in patients with rheumatic heart disease. Platelet survival time appears to be a sensitive index of past systemic embolism in patients with rheumatic heart disease. Shortened platelet survival time was observed in 47 of 48 patients (98%) who had a history of systemic embolism before entry in this trial. Platelet survival time appears to predict embolism, as 18 of 19 patients (95%) who developed embolism during the study had shortened platelet survival time. Sulfinpyrazone increased platelet survival time in these patients and has also been shown to decrease thromboembolism in uremic patients with external arteriovenous shunts and in patients with recurrent venous thrombosis.

The cause of shortened platelet survival in patients with rheumatic heart disease is unclear but may be due to increased interaction of platelets with the damaged left atrial endothelial surface. Histologic study of the left atria of patients with rheumatic heart disease has revealed thrombi containing platelets in association with scar-like hyaline connective tissue. Fibrinogen survival studies were not performed in the patients in this study, and thus, quantitative data regarding the rate of fibrin deposition are lacking. Selective consumption of platelets is suggested, however, by the effect of sulfinpyrazone and the lack of effect of warfarin on shortened platelet survival. Twelve patients with rheumatic heart disease and shortened platelet survival time were studied after completion of 4 years in this trial while taking warfarin and again 3 months after discontinuing warfarin. The average platelet survival time did not change, and no patient had a change of greater than 0.2 days. In patients with active venous thrombosis, Harker and Slichter observed decreased survival of both platelets and fibrinogen. In these patients heparin increased both platelet and fibrinogen survival but the platelet-suppressant drug dipyrindamole had no effect. The results in rheumatic heart disease suggest selective consumption of platelets similar to results obtained in patients with arterial thrombosis and prosthetic cardiac valves.

Although platelet survival time is shortened in patients with rheumatic heart disease who have a history of embolism and who develop embolism, this measurement is not specific for thromboembolism. On entry in the present study, 138 patients did not have a history of thromboembolism and 107 (78%) had shortened platelet survival time. During 4 years of observation, two patients with prior embolism had recurrence and 17 patients had their first embolic episode. The two with recurrence had shortened platelet survival and 16 of 17 with their first embolic episode had shortened platelet survival. Thus, the risk of embolism is associated with shortened platelet survival, but this abnormality is very commonly observed in patients with rheumatic heart disease.

Acknowledgment

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