Editorial:
Antiplatelet Therapy for Mitral Stenosis?

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IN THIS ISSUE of Circulation, Steele and Rainwater report the results of a clinical trial of sulfinpyrazone to reduce systemic thromboemboli in patients with mitral stenosis. Each patient was studied for 4 years, with careful monitoring of clinical events and repeated measurements of platelet survival. Their results indicate that sulfinpyrazone is effective in reducing the incidence of thromboemboli in a subgroup of rheumatic patients who had shortened platelet survival.

This study, if confirmed, has important ramifications for the patient and physician faced with the need to make a decision about optimal antithrombotic therapy. Before those decisions are reached, the data in this report should be carefully scrutinized because, as in most clinical trials, the variables are significant and numerous. Of particular importance is the rate of thromboembolism in the control groups, the significance of the platelet survival data, the effect of warfarin and atrial fibrillation on the results, the sex distribution of the study population, and the severity of the underlying rheumatic heart disease.

Control Groups

One question is whether the rate of thromboembolism in the control population is unusually high. Combining the placebo group with those patients having normal platelet survival, the incidence of thromboembolism is just over 15% for 4 years. Finding a comparable population in the literature is extremely difficult because most studies are poorly characterized as to rates of atrial fibrillation, anticoagulation and severity of disease. Further, most of the previous studies were carried out a number of years ago, were retrospective and considered in documentation and definition of the thromboembolic end point. And last, many reports fail to state the period of time when the data were collected.

Nonetheless, most series report an incidence of thromboembolism in mitral stenosis in the neighborhood of 20% over a 5-year period. Thus, the rate of thromboembolism in Steele's group is probably not excessive.

Platelet Survival Data

The relationship of platelet survival to thromboembolism in these patients is of great interest, but the mechanisms remain mysterious. The Denver group has previously shown that most patients with thromboembolism have reduced platelet survival, whereas the rate of embolism is very low if platelet survival is normal. In the present study, sulfinpyrazone not only halted the progressive shortening of platelet survival seen in the placebo group, but lengthened survival from 2.5 to 2.8 days (normal half-life 3.7 days) in the treated group. In their discussion, the authors mention that warfarin failed to affect platelet survival in 12 additional patients studied before and after cessation of anticoagulant therapy.

Questions abound: Why is platelet survival short in stenotic mitral valve disease? Why should so small an improvement in survival be associated with such a marked decrease in embolic events? Are the alterations in platelet survival the cause or the result of a left atrial thrombus? How does sulfinpyrazone act on platelets or vascular endothelium to affect platelet survival? In spite of these uncertainties (and the difficulties of the test), measurement of platelet survival using $^{51}$Cr serves to categorize patients into low- or high-risk groups for future thromboemboli.

Warfarin

The analysis of the sulfinpyrazone data in the preceding article is made considerably more complex because two-thirds of the patients with decreased platelet survival were concomitantly taking warfarin, and this factor was not controlled prospectively. The efficacy of warfarin in reducing systemic thromboembolism in patients with mitral valve disease has been the subject of several clinical trials that were less than optimal by today's standards. Most of these trials indicated that warfarin was effective in reducing thromboemboli, although controversy persists.

The sulfinpyrazone data suggest (but do not prove) that this antiplatelet agent is effective in reducing thromboembolism when warfarin is not given. Unfortunately, few patients were studied. For example, of 25 patients in the sulfinpyrazone group who were not taking warfarin, only one developed an embolus, an incidence similar to that of thromboembolism in the sulfinpyrazone patients who were taking warfarin (one of 26). Eight patients with thromboembolism of the 32 in the placebo group were also not taking warfarin.

Conversely, warfarin alone seemed unable to keep pace with sulfinpyrazone in reducing thromboemboli; 50% of patients (eight of 16) in the placebo group had an embolus although they were taking warfarin. It must be emphasized that these data can be viewed only as suggestive and, because of the limited number of patients, do not warrant firm conclusions.

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Atrial Fibrillation

Atrial fibrillation is strongly correlated with increased thromboembolism, as is again borne out in the sulfinpyrazone study. Two-thirds of the patients in both the placebo and sulfinpyrazone groups had constant or paroxysmal atrial fibrillation. Of those who subsequently had a thromboembolism, 80% were in atrial fibrillation. The presence of the arrhythmia, however, did not seem to reduce the effectiveness of sulfinpyrazone in reducing thromboembolism; 13 patients in the placebo group had both atrial fibrillation and embolism, whereas only one patient in the sulfinpyrazone-treated group had an embolic event.

Unfortunately, because too few were studied, we cannot draw even tentative conclusions about the patients in sinus rhythm. Of 38 patients in sinus rhythm in the placebo group, three developed thromboembolism. This figure should be compared to one patient in the sulfinpyrazone group with sinus rhythm and embolization.

Sex Distribution

Most patients in the general population who have rheumatic heart disease with mitral stenosis are women, with a ratio of females to males of 2.8:1 in most large series. In the sulfinpyrazone study, the reverse was true (1:1.6), which is most likely due to the investigators’ affiliation with a Veterans Administration Medical Center.

Some antiplatelet clinical studies, such as the Canadian TIA study and also a study of aspirin prophylaxis of venous thrombosis in hip surgery, have shown drug efficacy in males but not in females. Can the results of the present study be applied to women as well as men? Although the study group was small, sulfinpyrazone seemed to be equally effective in males and females, with a reduction of thromboembolism in both groups.

Disease Severity

The severity of the mitral stenosis in the study population may also influence the results. Disease severity was not mentioned specifically, but the placebo and sulfinpyrazone groups probably had comparable severity of disease as judged by the rate of artificial valve replacement during the study (20% in both groups). Whether increasing severity of the rheumatic heart disease leads to a higher rate of thromboembolism is controversial. Some pathologic studies suggest that more advanced heart disease is associated with an increased frequency of atrial thrombi but no increased rate of embolism.

Conclusions

Overall, the sulfinpyrazone study in mitral stenosis seems sound and the reductions in thromboembolism in the subgroup with decreased platelet survival are impressive. In this type of trial it is difficult to study enough patients at a single institution to draw conclusions about all the other relevant subgroups so that the effects of warfarin anticoagulation, atrial arrhythmias, sex, and severity of disease can be independently assessed.

Even so, from this and previous studies several patient groups may now be identified. A low-risk group would include patients without a history of thromboembolism, who have a normal platelet survival, are in sinus rhythm and perhaps have less advanced disease. A high-risk group would include patients with one or more previous thromboemboli, shortened platelet survival, an atrial arrhythmia and, possibly, more advanced disease.

The higher-risk group clearly deserves antithrombotic therapy. A 20% risk of thromboembolism within 4 years, with its often catastrophic consequences of stroke, major organ dysfunction or death, seems unacceptable. Until further studies are available to confirm the suggestion that sulfinpyrazone by itself is effective in this group of patients, combined therapy with warfarin and sulfinpyrazone seems likely to prove most effective in reducing the incidence of thromboembolism and its consequences.

Combined therapy with warfarin and sulfinpyrazone may not be without hazard. As predicted from the pharmacologic interactions of these two drugs, the addition of sulfinpyrazone to chronic warfarin therapy may lead to dramatic prolongation of the prothrombin time and possible excessive bleeding. Frequent laboratory monitoring of anticoagulant therapy must be performed and early dose reduction of warfarin instituted, if necessary. Combined therapy should probably be reserved for those patients who are well motivated, cooperative and reliable. Whether the risks of bleeding are increased in patients who have a therapeutic prothrombin time and are also taking an antiplatelet drug is unknown. The incidence of bleeding was not reported in the sulfinpyrazone study, although the medication was said to be well tolerated.

Perhaps additional studies in patients with rheumatic heart disease will be forthcoming from the Denver investigators or from other groups. Chromium platelet survival measurements are exacting, time consuming, laborious and available in relatively Few medical centers, so other platelet reactivity assays that would identify these high-risk patients would be most welcome. Perhaps study of plasma levels of platelet-derived β thromboglobulin or platelet factor 4 would be rewarding. To further define the pathogenesis of the atrial thrombus in these patients, the recent technique of 111indium platelet imaging may be helpful. Finally, additional well-controlled, carefully conducted clinical trials of antiplatelet agents in rheumatic heart disease with enough patients to allow multivariate analysis of the appropriate subgroups appear warranted. A com-
parison of sulfinpyrazone alone vs sulfinpyrazone plus warfarin would be particularly interesting. Most patients (and their physicians) would be delighted to discontinue their warfarin tablets and the all-too-frequent visits to the laboratory for prothrombin times.

References
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