The Role of Sulfinpyrazone in the Prevention of Arterio-venous Shunt Thrombosis


SUMMARY
The effect of sulfinpyrazone on the incidence of thrombosis of arterio-venous shunts was investigated in a double-blind crossover study in 45 patients on chronic hemodialysis over a period of 12 months. The incidence of thrombosis was reduced from 0.64 thrombi per patient month when on placebo to 0.21 thrombi per patient month when on sulfinpyrazone (P < 0.001). The therapeutic effect was more striking in men than in women and became evident within a week of starting the drug. The side effects were minimal, requiring withdrawal from the study of only one patient. This crossover study strengthens the findings in the previous report that sulfinpyrazone is of value in the prevention of thrombosis.

We have previously reported that sulfinpyrazone reduces the incidence of arteriovenous shunt thrombosis in patients undergoing chronic hemodialysis.1 The original study was planned as a double-blind crossover study but it was decided to carry out an interim analysis at the time when every patient had completed the first part of the crossover design, mainly because of the potential hazard of platelet suppressive drugs in patients with renal failure. The results of this interim analysis showed that not only was the drug safe but that there was a significant benefit of sulfinpyrazone compared to placebo in terms of a reduced incidence of arterio-venous shunt thrombosis. Because of their general interest, these results were reported as a between-patient study.

However, most of the patients by the time had been crossed over and had been receiving the alternative therapy for about three months and since the drug appeared to be safe, it was decided to complete the crossover study as originally planned. This completed study provided additional information about the time of onset of the antithrombotic effect of sulfinpyrazone and a more sensitive evaluation of the benefits of the drug including a differential effect between males and females.

The interim analysis was carried out without disclosing the code for particular patients to the nephrologists responsible for making the diagnostic assessment of shunt thrombosis so that the blind nature of the study was maintained.

Patients and Methods

Patients
All patients were in the Regional Hemodialysis Programme at St. Joseph's Hospital, Hamilton, Ontario. They were selected after the purpose and design of the study had been fully explained and they had given informed consent.

All patients had straight arterio-venous shunts,2 and malalignment between shunt cannulas and attached vessels had been excluded by shunt angiography. Although the arterio-venous fistula is now used as the primary method of access to the circulation, during these studies the arterio-venous shunts that functioned well were retained.

Experimental Design
This was a double-blind crossover study, the allocation of the patients to treatment being made according to a prescribed randomized arrangement. Some patients received sulfinpyrazone, 200 mg three times daily, and the others an identical placebo.* At the end of a six month period the patients were crossed over to the alternative therapy for a further six months. Oral anticoagulants (Coumadin) were used in some of the patients as previously described.1

The hematology team supervised the medications, and the nephrology team documented shunt thrombosis. Shunt thrombosis was suspected when there was cessation of flow in the shunt and was documented by direct observation at the time of its removal from the shunt by means of a coiled extractor. Thrombi usually started in the vein close to its junction with the teflon cannula and often extended back

*Sulfinpyrazone and placebo kindly provided by Ciba-Geigy Pharmaceuticals.
into the shunt and forward up the vein. If thrombosis occurred secondarily to clotting in the dialysis apparatus it was not included in the assessment. All patients kept a daily drug record and were interviewed monthly to assess compliance and side effects.

Results

Sixty-two patients entered the study and 45 patients completed the 12 month trial. The reasons for withdrawal of the 17 patients are summarized in table 1. The 45 patients included 29 males and 16 females ranging in age from 24 to 65 with an average age of 43 years. Other relevant clinical descriptions were given in the previous report.1 There was no difference in the duration of dialysis or any other change in therapy while the patients were on sulfinpyrazone as compared to while they were on the placebo.

Twenty-one patients were on oral anticoagulants throughout the study; ten were started on anticoagulants because of the development of three or more thrombi in one month and two had anticoagulants discontinued. Of the ten who were started on anticoagulants, eight were started prior to the crossover: seven while on placebo and one while on sulfinpyrazone. Following crossover, two were started on anticoagulants while on placebo and none while on sulfinpyrazone. Two patients had anticoagulants discontinued prior to the crossover: one while on placebo because of pericarditis following a myocardial infarction and the other while on sulfinpyrazone because of dyspepsia. In all, anticoagulants were used for a total of 168 patient months concomitant with placebo and 163 patient months with sulfinpyrazone. It is unlikely, therefore, that the effects of anticoagulants could have biased the interpretation of the results.

A summary of the data relating to shunt thrombosis is shown in table 2. It can be seen that the over-all rate of thrombi per patient month was 0.64 during the placebo period, which is three times the corresponding rate during the sulfinpyrazone treatment period. The corresponding ratio was about 4 to 1 for males which was statistically significant, and slightly less than 2 to 1 for females. This apparent difference between the sexes can be examined more critically by looking at the relative benefit of the drug in individual patients. The mean reduction in the number of thrombi per patient month was 0.55 for males and this reduction is statistically highly significant (paired t-test: one-sided test: $t_{15} = 4.98; P < 0.001$). The mean reduction for females favors sulfinpyrazone but is not statistically significant ($t_{15} = 1.48; 0.10 > P > 0.05$) but the over-all mean reduction of 0.43 thrombi per patient month for all patients is statistically highly significant ($t_{4} = 4.88; P < 0.001$).

Comparison of the number of thrombi in each treatment group for individual patients showed that 22 males did better on sulfinpyrazone compared with three who did better on placebo; four males had equal numbers of thrombi in the two treatment periods. Correspondingly seven females did better on sulfinpyrazone, four did better on placebo and five had similar outcomes on the two treatments. It therefore appears that sulfinpyrazone had a greater therapeutic effect in males than in females.

The total number of thrombi for each of the 12 months of study are shown separately in figure 1, for the groups who had sulfinpyrazone initially or placebo initially. There was a marked difference in the number of thrombi in the sulfinpyrazone and placebo treatment period within each of these groups. To determine how quickly a therapeutic effect was achieved and how quickly the effect was lost, the weekly incidence of thrombosis was compared in the month immediately preceding and following crossover. These are shown in figure 2. It is clear that the therapeutic effect of the drug became evident within a week of treatment and that the protection was lost within a week or so after medication was withdrawn.

Few side effects were encountered in either group. Over the 12 month period of study, two patients complained of dyspepsia, one on sulfinpyrazone and one on placebo. A diabetic patient on insulin and sulfinpyrazone had a brief episode of hypoglycemia but he recovered spontaneously. Three patients had gas-

Table 1

<table>
<thead>
<tr>
<th>Reasons for Withdrawal from Study</th>
<th>P</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncompliance</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Renal transplantation</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Deaths</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Construction of A-V fistulae</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Gastro-intestinal bleeding</td>
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<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: P = placebo; S = Sulfinpyrazone.

Table 2

<table>
<thead>
<tr>
<th>Pt</th>
<th>Treatment</th>
<th>Total thrombi</th>
<th>Rates thrombi/patient month</th>
<th>Difference in rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>S</td>
<td>32</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>P</td>
<td>127</td>
<td>0.73</td>
<td>0.55*</td>
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<tr>
<td>F</td>
<td>S</td>
<td>26</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>P</td>
<td>47</td>
<td>0.49</td>
<td>0.22</td>
</tr>
<tr>
<td>All</td>
<td>S</td>
<td>58</td>
<td>0.21</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>P</td>
<td>174</td>
<td>0.64</td>
<td>0.43*</td>
</tr>
</tbody>
</table>

*Statistically highly significant ($P < 0.001$).

Abbreviations: sed = standard error of the difference; Pt = patients; S = sulfinpyrazone; P = placebo.

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trointestinal bleeding, two on sulfinpyrazone and one on placebo. The patient on placebo was also taking oral anticoagulants and had a duodenal ulcer. One of the patients on sulfinpyrazone was not being treated with oral anticoagulants and suffered a brief episode of melena but was able to continue on the trial.

Discussion

This 12 month crossover study has confirmed our previous findings that sulfinpyrazone reduces the incidence of arterio-venous shunt thrombosis and this effect was more apparent in males than in females. The reason for this sex difference is not evident.

The mechanism of the antithrombotic effect of sulfinpyrazone is unknown. The drug has been shown to prolong the reduced platelet survival reported in patients with chronic rheumatic heart disease and prosthetic valve replacements, recurrent venous thrombosis, and gout. The time required to achieve an effect on platelet function in these studies is uncertain. This was because the drug did not have a demonstrable effect on other tests of platelet function and since the platelet survival studies were usually performed at least three months after sulfinpyrazone had been started. Our findings indicate that the antithrombotic effect of sulfinpyrazone is apparent within a week of commencing therapy. The drug was well tolerated even when used in combination with anticoagulants and therefore appears to have considerable potential as an antithrombotic agent in man.

Acknowledgments

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References

The role of sulfinpyrazone in the prevention of arterio-venous shunt thrombosis.
A Kaegi, G F Pineo, A Shimizu, H Trivedi, J Hirsh and M Gent

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