A Randomized Trial of Aspirin and Sulfinpyrazone in Patients with TIA

L. Candelise, M.D.,* G. Landi, M.D.,* P. Perrone, M.D.,* M. Bracchi, M.D.,* and G. Brambilla, M.D.†

SUMMARY In a double-blind multicenter study, 124 patients with transient ischemic attacks were randomly allocated to one of two groups treated with aspirin (ASA) or sulfinpyrazone respectively. Patients were followed up to assess the relative efficacy of the two treatments in the prevention of the outcomes of stroke, myocardial infarction, vascular death, and worsening or no improvement of TIAs.

No significant difference was observed between the two treatments at the end of the follow-up period. Statistical analysis revealed a significant interaction of sex, treatment, and occurrence of events. Analysis of the results according to sex showed that male patients treated with ASA had a highly significant benefit (p < 0.001) with a 53% risk reduction for further events. In female patients, sulfinpyrazone showed a favorable trend which was not statistically significant.

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THE ANTURANE TIA ITALIAN STUDY (ATIAIS) was started in June 1976 when it was already widely accepted that the majority of transient ischemic attacks (TIA) and strokes have a thromboembolic pathogenesis and that drugs inhibiting platelet activity might reduce their incidence. In this context, two drugs had raised particular interest: acetylsalicylic acid (ASA) and sulfinpyrazone. Because previous studies had already indicated the potential usefulness of these drugs in TIA patients, it was decided not to include a placebo-treated group in ATIAIS. Moreover, two large studies were already being performed at that time: Aspirin in Transient Ischemic Attacks (AITIA), and the trial organized by the Canadian Cooperative Study Group (CCSG).

The aim of our study was to evaluate the relative efficacy of ASA and sulfinpyrazone in reducing the recurrence of TIAs (minor events) and in preventing fatal and nonfatal vascular complications such as stroke and myocardial infarction (major events) in a population with TIA.

Patients and Methods

This was a multicenter, randomized, double-blind, clinical trial carried out on a consecutive series of patients of both sexes, aged ≤ 70 yr, who in the preceding three months had had one or more episodes of amaurosis fugax or of TIA in the carotid and/or vertebrobasilar territory. A diagnosis of TIA was made only when the focal symptoms regressed completely within 24 hr. Patients with isolated symptoms that could not be clearly diagnosed as TIA (vertigo, diplopia, dysarthria, dysphagia) were not included in the study.

Patients who had neurologic signs at entry, those with active or previous peptic ulcer, marked renal or hepatic insufficiency, or other life-limiting diseases were excluded from the study. Also excluded were patients with TIA due to cardiac or hemodynamic causes because they did not require antiaggregant treatment. Lastly, patients who did not give sufficient guarantee that they would continue the treatment for the entire scheduled period were excluded, as were those who for other reasons had to take drugs with antiaggregant or anticoagulant action. Since surgical treatment was not used at that time in any of the participating centers, no patient had to be excluded for this reason.

At entry into the study, a detailed medical history of the patients was taken including risk factors and characteristics of the episodes. The patients underwent a complete neurologic examination; they were examined by a cardiologist, an ECG and a series of laboratory and other tests were performed. CT scan and angiography were encouraged but were not necessary for entry into the study.

After the baseline evaluation, the patients admitted to the study were randomly allocated to one of two therapeutic schedules: sulfinpyrazone (400 mg twice a day) or ASA (500 mg twice a day). In view of sulfinpyrazone's uricosuric action, treatment was started at halfdose for the first week so as to avoid renal colic. Randomization was performed separately in each
center in blocks of 6 patients. The blind condition was maintained by giving the patients, at entry into the study and at each follow-up visit, similar packages containing the drugs. Each drug was prepared in the form of tasteless tablets which were identical in form, weight, color and size. These were supplied by the statistics center without the investigator knowing which drug was given. The patients and their physicians were discouraged from using other drugs with antiaggregant action, and a list of these was given to each patient. Compliance was evaluated by counting the number of tablets returned at each follow-up visit, and for the patients on sulfinpyrazone treatment by evaluating the decrease of uric acid blood levels compared with baseline values. To maintain the double-blind condition, the investigator was not told these values.

Follow-up visits were at 1, 2, 4, and 6 months, and then at three months’ intervals for a maximum of two years. Blood chemistry tests were repeated at alternate follow-up visits, and an ECG at least once a year. At each visit, the patient was asked if any events or side-effects had occurred since the last visit, and if he was taking the tablets regularly. In addition, a neurologic examination was performed and any risk factors were checked.

Since it is probable that sulfinpyrazone’s antiaggregant effect manifests after a week of treatment at the full dose, it was decided to consider any event, and to attribute it to the relative treatment, only after 15 days from start of treatment.

As regards recurrence of TIA, their frequency and clinical severity (assessed on the extent of symptoms and their duration) in the three months preceding entry in the study were compared with those reported after the 15th day from start of treatment. TIAs were considered as minor events when the frequency and/or clinical severity were the same or increased.

A diagnosis of stroke was made when the symptoms and neurologic signs persisted for more than 24 hr. A diagnosis of myocardial infarction was given when the clinical case history was associated with the presence of ECG and enzymatic alterations concordant with such a diagnosis, which had been absent at entry in the study. Deaths were documented and classified according to their cause. Diagnosis of the test events was always checked by one neurologist at least who was unaware of the patients’ treatments. Statistical analysis was performed using appropriate parametric and non-parametric tests, including the method for complex contingency tables. Outcome analyses were performed by means of clinical life-tables according to Cutler and Ederer. The Gehan test was used to calculate z values.

Results

Six university and hospital clinics participated in the study, which enrolled a total of 127 patients. The patient enrollment period lasted from June 1976 to December 1978, and follow-up finished in December 1979. Three patients were subsequently excluded from the series, since it was considered in retrospect that they did not correspond to the protocol characteristics. Homogeneity of the baseline variables was analyzed: their distribution was found to be substantially homogeneous in the two treatment groups (tables 1 and 2) and also between the series from the various centers. Thirty-two patients were considered to be withdrawals (reasons for withdrawals and their distribution in the two groups are reported in table 3). Information was collected from these patients to ascertain if, by the end of the study, major events had occurred: one patient in the ASA group had died of cardiac decompensation and one in the sulfinpyra-
The sulfinpyrazone group of pulmonary thromboembolism. The average time of follow-up, from entry of the patients in the study to their withdrawal for any reason, was 11.23 months (11.19 months in the ASA treatment group, 11.28 months in the sulfinpyrazone treatment group). The incidence of major and minor events is reported in table 4. In view of their low total number, they were considered globally in the statistical evaluation. There were no other deaths in the study group. No events occurred during the first 15 days of treatment. No statistically significant difference was noted in the occurrence of events between the two treatment groups. There was no correlation between the incidence of events and the presence of risk factors (arterial hypertension, smoking, diabetes, dyslipidemia) in the two groups. Table 5 shows the results of non-parametric analysis of the data reported in table 4. Only the interaction between treatment, sex of the patients, and incidence of events has provided a statistically significant result ($X^2 = 9.53, p < 0.01$).

Further analysis was done to assess the efficacy of the two drugs tested. This may be due to the low number of patients included in the study. Unfortunately, it was not possible to extend the duration of this study, and the careful selection of patients (carried out according to the criteria described) resulted in the enrolment of a population which was clinically homogeneous but smaller than estimated. Our results corroborate those obtained by the CCSG and regards the difference in ASA's efficacy according to the sex of the patients. If our data were expressed in terms of risk reduction of events (as they were by CCSG), it can be seen that in male patients there is a risk reduction of 53%, while there is no benefit to female patients. Since these results were obtained by comparing two groups treated exclusively with ASA or with sulfinpyrazone, there was no possibility of an interaction between the drugs — a point which raised criticism in the CCSG's statistical evaluation.

Our study supports various indications that ASA's efficacy as an antithrombotic drug is limited to male subjects. Various hypotheses have been put forward to explain this differential action of ASA. In addition to hormonal differences, a possible difference has been suggested in the sensitivity of cyclooxygenase inhibition at the platelet and endothelial level, as well as the greater importance of extra-platelet factors in the pathogenesis of thromboembolic disease in women. Such differences could explain the

### Discussion

Our study has not shown a significant difference in the efficacy of the two drugs tested. This may be due to the low number of patients included in the study. Unfortunately, it was not possible to extend the duration of this study, and the careful selection of patients (carried out according to the criteria described) resulted in the enrolment of a population which was clinically homogeneous but smaller than estimated.

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### Table 3. Withdrawals: Distribution and Causes in the Two Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>ASA (n = 63)</th>
<th>Sulfinpyrazone (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric side effects</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Other side effects</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Non-compliance</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Causes not connected with treatment*</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>15 (24%)</td>
<td>17 (28%)</td>
</tr>
</tbody>
</table>

*Moving away, arbitrary suspension of treatment, concomitant administration of synergic drugs.

### Table 4. Distribution of Events at the End of Follow-up in the Two Treatment Groups, According to Sex

<table>
<thead>
<tr>
<th></th>
<th>ASA (Males)</th>
<th>ASA (Females)</th>
<th>Total</th>
<th>Sulfinpyrazone (Males)</th>
<th>Sulfinpyrazone (Females)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vascular death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Recurrence of TIA</td>
<td>8</td>
<td>13</td>
<td>21</td>
<td>16</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>Total number of events</td>
<td>9</td>
<td>14</td>
<td>23</td>
<td>20</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Free of events</td>
<td>33</td>
<td>7</td>
<td>40</td>
<td>24</td>
<td>12</td>
<td>36</td>
</tr>
</tbody>
</table>

### Table 5. Chi-square Analysis of the Data Reported in Table 4

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Chi-square value</th>
<th>d.f.</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment and sex</td>
<td>1.215</td>
<td>1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Treatment and events</td>
<td>0.230</td>
<td>1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex and events</td>
<td>2.367</td>
<td>1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Treatment and sex and events</td>
<td>9.530</td>
<td>1</td>
<td>$p &lt; 0.01$</td>
</tr>
</tbody>
</table>

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results obtained with the other drug, sulfinpyrazone, in female patients. Also in this respect, our results agree with those of the CCSG in demonstrating a favorable trend, even though not statistically significant, in the outcome of female patients treated with sulfinpyrazone. The lesser incidence of TIA in women, and thus the reduced number of subjects included in the case series, does not allow us to draw any definite conclusion. However, a study performed on a larger number of female patients only might be helpful in assessing the potential usefulness of this drug in patients for whom adequate preventive treatment does not at present seem available.

Acknowledgements

The authors wish to thank Drs. Luigi Baroni and Paola Beggi for their methodological and technical assistance.

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The Effect of Combined Aspirin and Dipyridamole Therapy on Thrombus Formation in an Arterial Thrombogenic Lesion in The Dog

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SUMMARY We investigated the potential of aspirin and dipyridamole in combination to inhibit thrombus formation by comparing endarterectomized segments of 20 dog carotid arteries in animals treated with pre- and post-operative aspirin and dipyridamole to 20 arteries from untreated animals and 20 arteries from animals receiving intra-operative heparin. The temporal profile of thrombus formation was assessed by means of angiography, light microscopy, and scanning electron microscopy at time intervals ranging from 30 minutes to three months from the time of surgery. All of the aspirin-dipyridamole vessels remained patent and only one had significant gross thrombus formation. This contrasted to six occlusions and six significant gross thrombi in the control group and one occlusion and six significant gross thrombi in the heparin group. The combination of oral aspirin and dipyridamole minimizes thrombus formation in the highly thrombogenic lesion created by carotid endarterectomy in the dog.

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PLATELET PHYSIOLOGY and the pharmacology of platelet-affecting drugs have been the subject of considerable recent interest. Several major clinical trials have been recently completed or are currently in progress to evaluate the potential of drugs inhibiting platelet activity to lower the morbidity and mortality associated with cardiovascular and cerebrovascular disease.1, 2 Much of the purported value of these drugs relates to their ability to inhibit thrombus formation on intravascular thrombogenic lesions. Such effects may be more readily quantitated in the laboratory environment than in a clinical setting. We selected a reliable in vivo thrombogenic lesion,3 the endarterectomized canine carotid artery, to compare the purported antithrombotic properties of two of these agents in combination, aspirin and dipyridamole, to no treatment and heparin. It seemed reasonable to postulate that if these drugs could favorably alter the temporal profile of clot formation on a highly thrombogenic surface in the laboratory animal, then they might be expected to do so in thrombogenic atherosclerotic ulcers encountered in clinical practice.
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