Effect of Sulfinpyrazone on Platelet Survival Time in Patients with Transient Cerebral Ischemic Attacks

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SUMMARY Platelet suppressant drugs have been suggested as beneficial for patients with transient cerebral ischemic attacks and these drugs have been shown to lengthen shorted platelet survival time. In the present study platelet survival time (autologous labeling with ¹¹⁰ Chromium) was measured in 25 patients with transient cerebral ischemia involving a carotid distribution. Platelet survival was shortened in all patients (2.5 ± 0.10 days; AVE t ½ ± SEM; Normal 3.7 ± 0.04 days P < 0.001). Sulfinpyrazone increased platelet survival in 9 of 19 (47%) of patients (2.4 ± 0.10 to 2.8 ± 0.16 days; P < 0.01).

EVIDENCE IS AVAILABLE to suggest that platelet thromboemboli may be involved in transient cerebral ischemia. In 1959 Fisher observed white bodies moving in the retinal arterial circulation in a patient with transient monocular blindness. Similar observations have been made by Ashby et al., Bunning et al., and Russell and these authors established a relationship between extracranial carotid atherosclerosis and ipsilateral monocular blindness.

In the experimental animal, Honour and Russell were able to show arterial thrombosis and cerebral emboli after injury to the carotid artery.

Several laboratory tests of platelet reactivity have been developed and applied to patients with thromboembolism and a number of drugs have been identified which alter these tests. In patients with cerebrovascular disease clinical studies of platelet suppressant drugs have shown benefit in some studies and no apparent effect in others. In the present study platelet survival time was measured in patients with transient cerebral attacks and the effect of a platelet suppressant drug, sulfinpyrazone, on the frequency of ischemic episodes and on platelet survival time was assessed.

Patients

Observations were made on 25 patients with clinically defined transient cerebral ischemia. All patients had multiple episodes of cerebral ischemia suggesting a carotid arterial distribution — aphasia, hemiparesis. Three had transient monocular blindness. Twenty-one patients were men. Nine patients underwent carotid arteriography and occlusive atherosclerosis of the carotid artery was demonstrated in all of these patients. Nineteen were 55 years or older; 3 were aged 40-54 years and 3 women were less than 40 years of age. There were no known predisposing factors to thrombosis in any patient (e.g. oral contraceptive use, carcinoma) except for atherosclerosis. Seventeen men had clinical or arteriographic evidence of coronary artery disease.

Methods

Platelet survival time was measured by labeling the platelets from about 450 ml of the patient's venous blood with 100-150 microcuries of ¹¹⁰ Chromium. Following re-infusion of labeled platelets samples were drawn daily for 7 days. A single exponent was fitted to the 7 days of platelet count-rate data by computer-assisted least-squares analysis and the half-time computed. In 18 normal subjects platelet survival half-time averaged 3.7 ± 0.19 days (±sd).

Twenty-five patients had platelet survival measured once and in 19 patients platelet survival time was measured a second time after three to four months of treatment with sulfinpyrazone (400 mg qd). Treatment with sulfinpyrazone was continued in all of these 19 patients and they have been followed for an average of 27 months (range 13-38 months). The six patients who did not take sulfinpyrazone have been followed for a similar period of time (average 30 months, range 8-55 months). Sulfinpyrazone was offered to all patients for the purpose of defining the effect of the drug on platelet survival time. It was suggested to all patients that benefit might occur in terms of avoiding stroke and decreasing the frequency of ischemic episodes. Of the six patients who were not re-studied, four did not want to participate and the other two were begun on the drug, but subsequently discontinued sulfinpyrazone and decided they did not want to participate.

Patients gave their consent to the performance of platelet survival time and appreciated the experimental nature of therapy with sulfinpyrazone.

Student's t-test was used to compare the various groups statistically.

Results

Platelet survival half-time was shortened in all 25 patients and the average (2.5 ± 0.10 days; AVE ± SEM) was significantly different from normal (3.7 ± 0.04 days;
SULFINPYRAZONE AND PLATELET SURVIVAL TIME/Steere el al.

Sulfinpyrazone significantly increased platelet survival time (2.4 ± 0.10 to 2.8 ± 0.16 days; \( p < 0.01 \)) and nine of 19 (47%) patients given the drug had an alteration of platelet survival time by 0.20 days or more. Four patients (21%) had normalization of platelet survival (> 3.2 days).

Of the 19 patients treated with sulfinpyrazone 10 observed a marked beneficial effect on the frequency of ischemic attacks, noting no more episodes. This initial good clinical result has been maintained. An additional six patients had a reduction in the frequency of ischemic episodes by at least one-half of their pre-treatment level. All 19 patients had at least four episodes per month prior to sulfinpyrazone treatment. Three patients observed no effect of sulfinpyrazone on the frequency of their ischemic attacks. No patient who was treated with sulfinpyrazone had stroke.

Of the six patients who did not receive sulfinpyrazone, two have had stroke, one had a reduction and three no change in the frequency of their cerebral ischemia. These patients also had at least four episodes per month prior to measurement of platelet survival time.

The clinical effect of sulfinpyrazone could be predicted from the alteration in platelet survival time. In the 10 patients who had a marked reduction in their frequency of ischemia, seven (70%) had an increase in platelet survival time (2.6 ± 0.16 to 3.1 ± 0.22 days; \( p < 0.01 \)) and four (40%) had normalization of platelet survival. None of the three patients who failed to receive benefit from sulfinpyrazone had a change in platelet survival time. Two of the six (33%) patients who noted some clinical improvement with sulfinpyrazone had an alteration of platelet survival time (2.4 ± 0.23 to 2.5 ± 0.17 days; NS) but neither was normalized by the drug.

Sulfinpyrazone capsules (200 mg) were given to the patients every 2–3 months. Patient compliance in taking medication was inquired about and re-enforced every two to three months.

Discussion

The results of this study suggest that platelet survival time is shortened in patients with transient cerebral ischemia, that sulfinpyrazone lengthens platelet survival in these patients, that this drug appears to be associated with a reduction in the frequency of ischemic episodes, and that there appears to be a relationship between alteration of platelet survival time and reduction in the frequency of ischemic attacks.

The observation that platelet survival time is shortened in patients with transient cerebral ischemia is probably not surprising in that between 50 and 60% of patients with coronary artery disease have shortened platelet survival,\(^7\) and coronary and cerebral atherosclerosis frequently coexist. Seventeen of our patients had coronary disease. Sulfinpyrazone lengthens shortened platelet survival time in about the same number of patients with cerebrovascular disease as in patients with coronary artery disease.\(^7\)

The apparent beneficial effect of sulfinpyrazone in reducing the frequency of transient ischemia is open to question because this study was not controlled. Both patients and authors knew that sulfinpyrazone was being administered and that the drug was supposed to be effective. The results of this study should not be construed as an attempt to establish that sulfinpyrazone has clinical benefit in patients with cerebrovascular disease.

Evans carried out a blinded crossover study of 20 patients with transient monocular blindness in which sulfinpyrazone and placebo were administered for six weeks each.\(^8\) Evans noted a statistically significant reduction in ischemic episodes during the sulfinpyrazone treatment period.\(^9\) Blakely and Gent randomly allocated 291 older men to sulfinpyrazone or placebo and observed a significant reduction in death from apparent vascular causes in the sulfinpyrazone treated group.\(^10\) Thus, there is some evidence that sulfinpyrazone is therapeutically effective in patients with cerebrovascular disease.

Two other prospective clinical trials using platelet suppressant drugs have not shown clinical benefit. Acheson et al. did not observe a reduction in frequency of ischemic attacks in patients treated with dipyridamole\(^11\) and Acheson and Hutchinson were unable to show that clofibrate decreased the frequency of cerebral ischemic episodes.\(^12\) Platelet survival time is lengthened by both dipyridamole\(^6\), \(^13\) and clofibrate.\(^1\) Platelet survival time was not measured in the patients of Acheson et al. and Acheson and Hutchinson. Perhaps the conflicting results observed with platelet suppressants will be clarified when the results of the multicenter trials with sulfinpyrazone and aspirin become available.

The relationship between alteration of platelet survival

\[\text{Platelet Survival Time (t/2), days} \]

\[\text{Normal} \quad \text{TIA} \]

\[\begin{array}{c}
\text{N = 25} \\
p < 0.001
\end{array} \]

\[\text{Normal} \quad \text{TIA} \]

\[\begin{array}{c}
\text{N = 25} \\
p < 0.001
\end{array} \]

\[\text{Normal} \quad \text{TIA} \]

\[\begin{array}{c}
\text{N = 25} \\
p < 0.001
\end{array} \]

\[\text{Normal} \quad \text{TIA} \]

\[\begin{array}{c}
\text{N = 25} \\
p < 0.001
\end{array} \]
and the apparent clinical effectiveness of sulfinpyrazone is of interest. Sulfinpyrazone is probably acting to prevent the interaction of platelets with the atherosclerotic arterial surface. Platelet survival time should measure this interaction, but the reasons for the failure of sulfinpyrazone to decrease platelet-surface interaction (increase platelet survival time) in all patients with atherosclerosis are not clear.

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