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Treatment Program and Comparison Between Anticoagulants and Platelet Aggregation Inhibitors After Transient Ischemic Attack

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SUMMARY Transient cerebral ischemic attacks (TIA) are an important warning symptom of threatening stroke from cerebral infarction (CI). A local treatment program aimed at identifying as many individuals with TIA as possible and treating them in a uniform manner is desirable. Platelet aggregation inhibitors with a combination of acetylsalicylic acid and dipyridamole (ASA + DP) has been compared with anticoagulants (AC). The average length of treatment was 24 months and all patients received the treatment for at least 6 months. Sixty patients received AC and 65 ASA + DP. Four patients in the ASA + DP group (6 percent) and 2 in the AC group (3.3 percent) sustained cerebral infarction. These figures are essentially lower than the expected incidence of 15-20 percent.

TRANSIENT ischemic attacks (TIA) occur in 25-40 percent of patients who subsequently sustain a cerebral infarct. But not all of those afflicted consult a doctor before a stroke occurs.¹

To identify as many individuals as possible with TIA and treat them in a uniform manner within our health service district, a special program to evaluate treatment was designed and put in operation in February, 1974. The clinical definitions for TIA and stroke are those proposed by the Joint Committee for Stroke Facilities.² The diagnosis of TIA is based solely on the clinical evaluation. Angiography was reserved for patients with carotid TIA who were believed to be possible candidates for carotid surgery. The treatment program comprised 3 possibilities: anticoagulation, antiplatelet aggregant therapy and carotid endarterectomy.

Methods

One hundred and twenty-five patients with a clear history of TIA were included in the study. Sixty were given anticoagulants (AC) and 65 acetylsalicylic acid and dipyridamole (ASA + DP). All the patients were evaluated at the Department of Neurology at Borås Central Hospital. Patients with possible or suspected TIA were excluded, as were patients with minor symptoms and signs which persisted for more than 24 hours, which included patients who fell into the TIA + IR (incomplete recovery), RIND (reversible ischemic neurological deficit), and PNS (partial non-progressive stroke). The symptoms of the patients included in the study are listed in table 1.

All patients found to have TIA were immediately put on one of the 2 treatment regimes, depending on whether they were born on odd or even dates. Patients with several ischemic attacks in the acute phase, so-called malignant or excessive TIA, were also allocated to treatment.

Five patients with TIA in whom a non-atherosclerotic etiology (e.g., hemodynamic factors) was considered likely, were excluded. Three of these had intracerebral vascular anomalies which may have caused TIA, one had kinking in the internal carotid artery without atherosclerotic lesions of the vessel wall and one patient with vertebrobasilar TIA was believed to have symptoms due to severe cervical spondylosis.

Three patients with TIA with known collagen disease and 2 with advanced cancer were excluded, as were patients (n = 17) in whom AC were contraindicated.

Six patients born on odd dates stated that they had not taken their medicine according to directions; they had only taken one of the drugs. Two patients stopped taking the medicine owing to diffuse gastrointestinal discomfort, one patient felt "funny in his head" and one patient stated a basic fear of tablets as the reason for failing to comply with directions. These 8 patients were excluded from the study.

The concentration of acetylsalicylic acid in serum was analyzed and measurable levels found in 85 percent of random samples. This evidence of the level of
compliance is similar to that reported for the treatment of hypertension.

Despite well established routines for AC treatment, there were periods when thrombotest values were outside the therapeutic range. In the group of patients treated with anticoagulants, about 85 percent of the thrombotest values were within the 10-20 percent range.

**Results**

As shown in tables 1 and 2, the distribution of patients between the 2 groups for age, sex, length of treatment and symptoms showed good agreement. The prevalence of hypertension is somewhat higher in the ASA + DP group. Hypertension was not considered a contraindication to treatment with anticoagulants.

The 2 treatment groups were fairly comparable with respect to other relevant diseases.

It was not necessary to discontinue AC treatment owing to hemorrhage. Four patients on AC had transient hematuria. Treatment was stopped in one patient on ASA + DP who had transient melena.

As shown in Table 3, 2 patients (3.3 percent) in the group treated with AC and 4 (6 percent) in group treated with ASA + DP had a cerebral infarction during an average 2 years of treatment. No retinal infarction occurred. The difference between these 2 percentages is not statistically significant. All 6 patients who developed cerebral infarction (CI) had had carotid TIA with transient hemiparesis. The location of the cerebral infarct was consistent with the localization of TIA symptoms. One patient in the AC treatment group and 2 in the ASA + DP treatment group died as a result of the stroke.

One of the 4 patients in the ASA + DP treatment group who developed stroke had a stroke 4 months after the last TIA, while in the other 3, the interval between TIA and stroke was from one to 2 years. In the 2 patients in the AC group who developed a CI, the interval between the last TIA and stroke was 3 months and 9 months, respectively.

**Discussion**

The sample size in this study is not large enough to make statistical comparisons valid. In the absence of a group of untreated patients against which to compare

| Table 3. Treatment Program for TIA in Borås, Sweden. Number of Patients with More Than One TIA Before and With One or More TIA During the Treatment Period. Number of Patient Deaths |
|-----------------|-----------------|-----------------|-----------------|
| AC | ASA + DP |
| Recurrent TIA before treatment | 34 (57 per cent) | 37 (57 per cent) |
| Recurrent TIA during treatment | 10 (17 per cent) | 16 (25 per cent) |
| Cerebral infarction | 2 (3.3 per cent) | 3 men, 1 woman |
| DEATHS | 3 (5 per cent) | 8 (12 per cent) |
| infarctus cerebri | 1 | 2 men, 1 woman |
| infarctus cordis | 2 | 2 men |
| hemorrhagia cerebri | 0 | 2 men, 1 woman |
| lung embolus | 1 | 1 |
| cancer | 1 | 1 |
| pancreatitis | 1 | 1 |
our results no firm conclusions can be drawn about the value of treatments reported here.

This study does give some help in answering the question of how anticoagulants, or acetylsalicylic acid combined with dipyridamole, influence the natural course of TIA. To evaluate this, in the absence of a group of untreated patients, the AC group was used as a control group and the effect of ASA + DP was compared with it. In the “control” group 3.3 percent of patients had a CI after an average 2 years of treatment. In the study reported by Baker, the incidence of CI in patients treated with anticoagulant was 7 percent after 3 years or 2.3 percent per year. In his untreated group the incidence was 7.7 percent per year.

From 13 reports on the natural course of TIA, the data indicate that between 25 and 40 percent of patients with TIA have a stroke within 5 years or 5.3 percent per year. The risk is greatest during the first year after TIA.

A recently calculated incidence of stroke after TIA during the first year is greater than 15 percent. From these estimates, it is likely that without treatment, 10–16 percent of our patients might have had stroke. In 2 years of follow up, the results after both AC treatment and ASA + DP, show a cerebral infarct incidence of 3.3 and 6 percent respectively. These percentages are better than would have been obtained without treatment.

As a rule, TIA is a manifestation of arteriosclerotic disease. It is, therefore, important to treat the disease adequately and correct any risk factors.

Drugs which inhibit platelet aggregation offer new possibilities of long-term prophylaxis. A large study in the USA showed that 1.3 g per day of acetylsalicylic acid provided a significant reduction in the incidence of TIA. A Canadian study suggests that acetylsalicylic acid reduces the incidence of stroke in men.

The criticism raised against these 2 large scale multicenter studies, for example, at the Meeting of the International Committee on Thrombosis and Hemostasis in Leuven in 1978, shows how difficult it is to obtain a scientific basis for a treatment program for TIA.

Combination therapy with acetylsalicylic acid and dipyridamole is an interesting alternative to treatment with anticoagulants.

Our clinical experience may, therefore, be of some value although our comparative study of ASA + DP and AC does not permit statistical conclusions.

References
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