Differences in the Occurrence of Carotid Transient Ischemic Attacks Associated With Antiplatelet Aggregation Therapy

BY MARK L. DYKEN, M.D., OLDRICH J. KOLAR, M.D., AND F. HAVEN JONES, M.D.*

Abstract: Differences in the Occurrence of Carotid Transient Ischemic Attacks Associated With Antiplatelet Aggregation Therapy

Twenty-six of 117 consecutive patients with a provisional diagnosis of transient ischemic attacks answered the following criteria: (1) transient hypofunction of an area supplied by a branch of an internal carotid artery, (2) no evidence of infarction, (3) carotid and vertebral arterial systems visualized angiographically, (4) cerebral blood flow and metabolism studies performed, (5) followed a minimum of three months, (6) other causes of transient dysfunction had been ruled out, and (7) no carotid arterial system surgery. Only six (23%) had occlusion greater than 50% and 21 (81%) had evidence of irregularity or ulceration of an atherosclerotic plaque in the appropriate internal carotid artery. It was noted in retrospect that 15 of the patients were treated with aspirin (300 mg b.i.d.) and 11 were not. No difference in ultimate infarction or death was noted, but only two (13%) of those treated with aspirin had an additional attack compared to nine (82%) of those who had no aspirin. These findings suggest that fibrin-platelet emboli may be a major contributor to transient ischemic attacks in the carotid circulation. The authors stress that this is a retrospective study and its importance is to further support the need for prospective studies before antiplatelet aggregating drugs are used indiscriminately.

Additional Key Words: acetylsalicylic acid, adenosine diphosphate, intimal repair, arterial injury, thrombosis, platelet-fibrin emboli.

The exact etiology, the natural history, and the ideal treatment of transient ischemic attacks have not been clearly established. All case series are influenced by selection factors and by diagnostic criteria. Frequently the number of transient ischemic attacks prior to entry into the study, risk factors, diagnostic tests performed, angiographical findings, and types of treatment are not recorded. In most studies, the diagnosis has been made because of transient dysfunction of the nervous system usually lasting less than 24 hours, but this is not a universal criterion. The presence of many other diseases—migraine, cardiac arrhythmia, epilepsy, hypoglycemia, syncope, end-organ disease, hyperventilation, tumor, psychiatric disturbances, etc.—may or may not have been excluded. Frequently patients with posterior circulation insufficiencies are mixed with those with anterior circulation insufficiencies and the final results reported in total despite some evidence that transient ischemic attacks in the anterior and posterior circulation may be quite different. Unfortunately, any complaint that may be referable to the posterior circulation including such nonspecific symptoms as syncope, dizziness, tinnitus, etc., have been included but without more likely diseases having been excluded. Because of this variation in recording and the paucity of well-defined series, after reviewing the great amount of conflicting or nebulous data, the authors reviewed all their patients admitted to a clinical cerebral vascular disease ward from 1969 to June of 1972 who had been admitted with the provisional diagnosis of transient ischemic attacks. Before the review was performed, the following criteria were established for inclusion of these patients in the study:

1. Transient (less than 24 hours) hypofunction of an area supplied by a branch of an internal carotid artery.

2. No evidence of infarction at the time of hospitalization. This was determined by normal neurological examinations by at least two neurologist, including one of the authors.

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3. Carotid and vertebral arterial systems were visualized angiographically.

4. Cerebral blood flow and metabolism studies were performed.

5. Each patient had been followed a minimum of three months and one of the authors examined the patient at the time of each follow-up.

6. Diseases such as cardiac arrhythmia, hypoglycemia, epilepsy, other primary diseases of the nervous system and diseases secondarily affecting the nervous system had been ruled out as possible causes of the transient dysfunction.

7. No carotid arterial system surgery.

A total of 117 patients had the provisional diagnosis of transient ischemic attacks, but only 26 answered all of the above criteria. Upon review of these 26 a marked difference in the number of transient ischemic attacks was noted between those who were treated with an antiplatelet aggregating agent (acetylsalicylic acid) and those who were not. An additional 15 patients answered all of the criteria except for 7.

Methods

The strict criteria for admission to the study were met by 26 of the 117 patients admitted to the Cerebral Vascular Disease Center with the provisional diagnosis of transient ischemic attacks. After these 26 patients were admitted to the study, review demonstrated technically unsatisfactory cerebral blood flow curves on one patient. In addition, all patients had the following studies: extracranial artery auscultation, cuff brachial blood pressure determinations in each arm, ophthalmodynamometry, ophthalmosonometry using the directional Doppler unit, electrocardiography, electroencephalography, skull and chest radiograms, fasting blood sugar, two-hour postprandial blood sugar, complete blood count, sedimentation rate, urinalysis, serology, serum electrolytes, serum calcium and phosphorus, SGOT, blood urea nitrogen, bleeding and clotting time, PBI, prothrombin time, blood cholesterol, blood triglycerides, serum lipoprotein electrophoresis, A-scan echoencephalography, cerebrospinal fluid analysis for cells, protein, sugar, colloidal gold, electrophoresis and immunoelectrophoresis, spinal fluid cholesterol, serum electrophoresis, rapid and delayed radiosotope brain scan, genetic consultation and neuropsychological testing. Most had retinal blood flow and retinal vascular reactivity studies. Each patient had a weekly complete blood count, blood urea nitrogen, urinalysis, serum cholesterol, blood triglycerides and fasting blood sugar and two-hour postprandial blood sugar. Every patient on the second week of hospitalization had a repeat electrocardiogram and SGOT and most had a repeat brain scan on the third week. All the patients were followed a mean of 20 ± 11 months. Those who were treated with aspirin were followed 14 ± 8 months and those not treated with aspirin were followed 29 ± 9 months. The patients who were not treated with aspirin were evaluated for a 14-month period following the hospitalization.

The time from the first attack to admission ranged from hours to ten years with a median of 35 days. The most attacks were two a day and the least one every two years. Five patients had had attacks for longer than one year and 16 had had episodes for one month or longer. Of these 16, the attacks ranged from three per week to one every two years. The median frequency was two per month. Four patients had only one attack before admission. All patients were white despite the observation that 5% of the patients admitted to the unit were black. Each patient was followed within a minimum of three months following hospitalization, a second visit within six months, the third visit within a year and from then on at a minimum of yearly intervals.

Results

Twenty of the 26 patients had associated illnesses. These included: diabetes mellitus, congestive heart failure, arteriosclerotic heart disease, hyperlipidemia of various types, hypertensive cardiovascular disease, emphysema, genitourinary tract infections, herniated intervertebral lumbar disk, obesity, hypothyroidism, alcoholism, polyneuropathy, angina pectoris, aortic stenosis, atrial fibrillation, and myocardial infarction.

Two patients had cerebral infarctions during follow-up. One of them was receiving aspirin and the other was not receiving aspirin. One patient who did not receive aspirin died with a massive myocardial infarction. Of the 25 survivors, 23 were completely independent in their activities and were essentially within normal limits.

Two (13%) patients of the aspirin-treated group continued having transient ischemic attacks. While nine (82%) of those not receiving aspirin had subsequent TIAs. Because of the marked difference in the incidence of transient ischemic attacks in this retrospective study between those who were treated with aspirin and those who were not, the patients were analyzed concerning the important parameters. No significant differences in age, sex, cerebral blood flow, cerebral oxygen utilization, cerebral vascular resistance, cerebral reactivity to 100% oxygen and 5% carbon dioxide, mean arterial pressure, infarction or death were noted. Those patients who received aspirin had an increased incidence of transient ischemic attacks in the distribution of the left internal carotid artery and those who did not had an increased incidence on the right. Of those treated with aspirin, four had attacks in the distribution of the right internal carotid and 11 in the left. Of those who were not treated with aspirin, six had attacks in the distribution of the right internal carotid artery, three in the left and two on both sides. The cerebral vascular index as described by Bloor averaged 3.3 ± 2.3 as compared to 4.3 ± 3.9 in those who were not treated with aspirin. This difference is not significant.

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Review of the angiograms revealed irregular and/or ulcerated plaques in the appropriate internal carotid artery in 21 cases and a smooth plaque in five. Only six (23%) had greater than 50% occlusion of the artery. In table 1 it is seen that these changes were not different in those who received aspirin and in those who did not receive aspirin.

Of the 15 patients who received aspirin, only two or 13% continued having attacks; of the 11 who did not receive aspirin, nine (82%) had at least one further attack (table 1). A Chi square test indicates that this difference is significant (P < 0.001). Although the patients in the control group said that they did not take drugs known to contain aspirin, we were unable in retrospect to establish this by laboratory tests.

The two patients who did receive aspirin and continued having transient ischemic attacks were interesting as they stopped having attacks when aspirin dosage was increased from 300 mg twice a day to 600 mg twice a day. The first patient was a 57-year-old man who one month before admission began having episodes, lasting approximately 30 minutes, of inability to read and comprehend language with sensory loss over the right upper extremity. Neurological examination was normal as was the complete work-up. He was placed on aspirin 300 mg twice a day and had two attacks during the first three months of follow-up. At this time, aspirin was increased to 600 mg twice a day and he has had no further attacks in seven months of follow-up.

The next patient was a 54-year-old female who had episodes of weakness over the right side of the body with difficulty speaking. These occurred two or three times a week and lasted 30 to 60 seconds. She had had these attacks for two months before her admission. She was placed on aspirin 300 mg twice a day and had three episodes during the first two months following this medication. At this time her aspirin dosage was increased to 600 mg twice a day and she has now been followed for nine months on this dosage without further episodes.

**Discussion**

The fact that one patient receiving aspirin and one patient not receiving aspirin developed cerebral infarction means that there was no difference in the two groups as far as this important endpoint (cerebral infarction) was concerned. The decrease in the occurrence of transient ischemic attacks following treatment with an antiplatelet aggregating drug gives support to the theory that platelet-fibrin emboli from ulcerated atherosclerotic plaques are a major contributor to transient ischemic attacks in the anterior cerebral circulation distribution. In this study of 26 well-verified cases, 20 had less than 50% occlusion of an appropriate internal carotid artery. It has been shown by a number of studies that no decrease in flow or in pressure occurs distal to an occluded carotid artery until the diameter has decreased to at least 70%. In addition, 21 demonstrated definite irregularities and/or ulceration of the plaque by angiography. These anatomical observations give further support to a hematological effect rather than an interference with blood flow by the plaque itself. Studies in animals indicate antiplatelet aggregation drugs decrease thrombosis following arterial injury and preliminary studies in humans suggest that transient ischemic attacks also may be decreased.

The initial factor in arterial thrombus formation appears to be platelet adhesion to collagen exposed by damage to the intima. Adhesion of platelets is associated with release of substances, including adenosine diphosphate (ADP), which causes rounding, aggregation and consequent release reaction in other platelets in a progressive chain reaction. The platelet aggregation is followed by

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**Table 1**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Plaque Occlusion</th>
<th>TIA*</th>
<th>Infarct</th>
<th>Death</th>
<th>Smooth</th>
<th>Irreg</th>
<th>Less than 50%</th>
<th>50%+</th>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
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<td>45</td>
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<td>107</td>
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<tr>
<td>SD</td>
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<td>0.5</td>
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<tr>
<td>N</td>
<td>15</td>
<td>11</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>3(13%)</td>
<td>1(7%)</td>
<td>0</td>
<td>3(20%)</td>
</tr>
<tr>
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<td>45</td>
<td>3.1</td>
<td>109</td>
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<tr>
<td>N</td>
<td>11</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>9(82%)</td>
<td>1(9%)</td>
<td>1(9%)</td>
<td>2(18%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9(82%)</td>
<td></td>
<td>8(73%)</td>
<td>3(27%)</td>
</tr>
</tbody>
</table>

*Significance of difference ASA versus No ASA P < 0.001.
CBF = cerebral blood flow, ml/100 gm brain per minute.
MAP = mean arterial pressure in mm Hg.
CMRO₂ = cerebral oxygen utilization, ml O₂/100 gm per minute.
deposition of fibrin in and around the original platelet mass with possible microembolization of platelet-fibrin emboli. Aspirin prevents the release reactions\textsuperscript{11, 12} and synthesis of the prostaglandin E\textsubscript{1} and E\textsubscript{2} in platelets.\textsuperscript{13} The prostaglandin E\textsubscript{2} inhibits ADP-induced platelet aggregation in blood\textsuperscript{14} and increases the amount of the cyclic adenosine monophosphate.\textsuperscript{15}

Aspirin does not have significant effects on prevention of postoperative venous thrombosis.\textsuperscript{16}

It is highly probable that various phases of the arterial mural thrombus formation occur simultaneously in the multiple arteriosclerotic vessel wall lesions of the carotid, vertebral and/or the intracranial circulation. The interference of biochemical substances released in various stages of the arterial thrombotic process with their possible regulative feedback effects is poorly understood.

Regarding the results of our observations, the relatively constant level of the antiaggregating agent in the range of 600 to 1,200 mg of aspirin per day evidently prevents initiation of further platelet aggregation over the intimal lesions.

The already existing fibrin deposits in the arterial mural thrombus and/or the arteriosclerotic defects involving the intima with the consequent collagen exposure remain unaffected.

Clinical judgment and periodic screening for abnormal hemostatic conditions\textsuperscript{17} appear to be, at the present time, the most practical aspects in determination of the daily dose of aspirin in patients with transient ischemic attacks.

The decreased incidence of transient ischemic attacks associated with aspirin therapy in our study would be highly significant if this were not a retrospective study. Despite the excellent matching of known variables, it is possible that variables not recognized other than aspirin account for the difference in attacks. Nevertheless, the drug might be beneficial in treating transient ischemic attacks in the anterior circulation but might have no effect on ultimate infarction or death. The authors stress that the importance of this communication is to underline the need for prospective studies with good controls before antiplatelet aggregating drugs are used indiscriminately.

**Summary**

Twenty-six of 117 consecutive patients with a provisional diagnosis of transient ischemic attacks answered the following criteria: (1) transient (less than 24 hours) hypofunction of an area supplied by a branch of an internal carotid artery; (2) no evidence of infarction at the time of hospitalization; (3) carotid and vertebral arterial systems visualized angiographically; (4) cerebral blood flow and metabolism studies were performed; (5) each patient had been followed a minimum of three months; (6) other primary and secondary diseases of the nervous system had been ruled out as possible causes of the transient dysfunction; and (7) no carotid arterial system surgery.

It was noted in retrospect that 15 of the patients were treated with aspirin, 300 mg twice a day, and 11 were not. No difference in ultimate infarction or death was noted between the two groups; only two of those treated with aspirin had an additional transient ischemic attack compared to nine of those who were not treated with aspirin. Only six of the total group had stenosis greater than 50\% and 21 had evidence of irregularity or ulceration of an atherosclerotic plaque in the appropriate internal carotid artery. These findings suggest that fibrin-platelet emboli may be a major contributor to transient ischemic attacks in the carotid circulation and that these attacks may be effectively decreased by an antiplatelet aggregating agent. The authors stress that this is a retrospective study and, while there was no difference in the prevention of cerebral infarction or death in the two groups of patients, the results of the observations do support the need for prospective studies before antiplatelet aggregating drugs are used indiscriminately.

**References**

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