Effect of Discontinuing Aspirin Therapy on the Risk of Brain Ischemic Stroke

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Background: Aspirin, or acetylsalicylic acid, is widely used to prevent ischemic vascular disease. Clinical and experimental data suggest that a rebound effect occurs 4 or fewer weeks after interruption of aspirin therapy.

Objective: To study the discontinuation of aspirin therapy as a risk factor for ischemic stroke (IS).

Design: Case-control study.

Setting: Stroke unit.

Participants: Three hundred nine patients with IS or transient ischemic attack undergoing long-term aspirin treatment before their index event and 309 age-, sex-, and antiplatelet therapy–matched controls who had not had an IS in the previous 6 months.

Methods: We compared the frequency of aspirin therapy discontinuation during the 4 weeks before an ischemic cerebral event in patients and the 4 weeks before interview in controls.

Results: The 2 groups had a similar frequency of risk factors, except for coronary heart disease, which was more frequent in patients (36% vs 18%; P<.001). Aspirin use had been discontinued in 13 patients and 4 controls. Aspirin interruption yielded an odds ratio for IS/transient ischemic attack of 3.4 (95% confidence interval, 1.08-10.63; P<.005) after adjustment in a multivariable model.

Conclusions: These results highlight the importance of aspirin therapy compliance and give an estimate of the risk associated with the discontinuation of aspirin therapy in patients at risk for IS, particularly those with coronary heart disease.

Arch Neurol. 2005;62:1217-1220

THE PROTECTIVE EFFECTS OF
antiplatelet agents against atherothrombotic disease
are well documented, and the use of such agents results in a reduction in atherothrombotic disease of approximately 25% in patients at high risk.1 However, early thromboembolic complications after the interruption of treatment with aspirin have been reported in experimental studies2-4 and case reports5-7 and have been suggested in uncontrolled surveys.8-11 Acute arterial thrombosis has been associated with hypertriglyceridemia,12 low high-density lipoprotein cholesterol levels,12 catecholamine activity,13 hyperfibrinogemia,14 hyperglycemia,15 nephrotic syndrome,16 inflammation,17 the postpartum period,18 and infections.19 However, the discontinuation of antiplatelet agents as a risk factor for acute ischemic disease is rarely mentioned, and any association is not clear. On the other hand, many clinical situations are associated with the discontinuation of aspirin therapy: before surgical interventions, hemorrhagic disorders, interactions with other drugs, the patient’s negligence, dementia, and drug intolerance. Given the widespread use of aspirin and the practice of stopping antiplatelet therapy for the previously mentioned reasons, the existence of a prothrombotic effect after the discontinuation of aspirin therapy could play an important role in triggering ischemic cerebrovascular disease.

METHODS

The medical records of all patients admitted to the stroke unit at Centre Hospitalier Universitaire Vaudois between January 1, 2002, and April 30, 2004, with a stroke or transient ischemic attack were reviewed, and patients who received aspirin either as monotherapy or combined with other antithrombotic drugs before these events were selected. Patients who used other antiplatelet drugs (clopidogrel bisulfate, ticlopidine hydrochloride, or dipyridamole) as monotherapy were excluded because no experimental studies, to our knowledge, have suggested a prothrombotic effect.
after their withdrawal. Patients with previous cerebrovascular risk factors and poor compliance were also excluded because, in all the controls, medication was controlled by regular medical follow-up. The following information was collected: sex, age, cerebrovascular risk factors, cause of ischemic stroke (IS), and type and dosage of antiplatelet drug therapy. Hypertension was defined as blood pressure greater than 140/90 mm Hg. Participants were classified as having diabetes mellitus if they had 2 or more fasting blood glucose levels greater than 108 mg/dL (>6.0 mmol/L). Smoking history was coded as never, previous, or current. Hypercholesterolemia was defined as a fasting cholesterol level greater than 251 mg/dL (>6.5 mmol/L). A positive cardiovascular history was defined as the presence of 1 or more of the following: myocardial infarction, coronary angioplasty, coronary artery bypass graft surgery, or lower limb arterial disease. When antiplatelet drug therapy was discontinued, we recorded the reason for discontinuation and the delay between interruption and the onset of the ischemic event. The 4 weeks before the index event was chosen because it has been suggested to be the probable interval in which a rebound effect will occur on the basis of an experimental survey. The control group, selected from outpatients with a history of stroke who had not had a stroke or transient ischemic attack in the previous 6 months and who were taking long-term aspirin for cerebrovascular secondary prevention, underwent a cross-sectional prevalence survey by telephone on the presence of cerebrovascular risk factors and the discontinuation of antiplatelet drug treatment during the previous 4 weeks. For each patient receiving aspirin alone or in combination with other antithrombotic agents, we selected 1 control matched for age, sex, and treatment.

Statistical analyses were performed using a software program (SPSS 12.0 for Windows; SPSS Inc, Chicago, Ill). The Mann-Whitney test was used to calculate the mean for nonparametric variables, and the unpaired t test with the Welch correction was used for normal variables. The \( \chi^2 \) test was performed on the aspirin discontinuation variable, and the odds ratio was calculated. Variables were entered into a multivariate model if they were significant in the univariate analysis (\( P<.05 \)).

 Nine hundred seventy-eight patients with IS or transient ischemic attacks were admitted to the stroke unit during the study period. On the basis of the elimination criteria, we excluded 669 patients (513 not undergoing antithrombotic therapy, 86 taking oral anticoagulant agents alone, 34 receiving clopidogrel alone, 31 showing poor compliance with treatment for previous cardiovascular and cerebrovascular risk factors, and 5 receiving heparin therapy alone), leaving 309 for analysis. The distribution of clinical features is summarized in Table 1.

Thirteen patients discontinued aspirin therapy in the 4 weeks before the IS, whereas only 4 controls discontinued aspirin use in the 4 weeks before the interview. This represents a discontinuation frequency of 4.2% in all patients hospitalized for ischemic events while receiving long-term aspirin treatment and of 1.3% in controls.

Stopping aspirin use (\( P=.03 \)) and coronary heart disease (CHD) (\( P=.001 \)) were the only significant variables. After adjusting for CHD in a multivariate model, discontinuation of aspirin therapy remained a significant variable (\( P=.04 \)). Furthermore, we analyzed the frequency of CHD specifically in the 2 groups of patients who had stopped taking aspirin and found that the difference was not significant (46% in the patient group and 25% in the control group; \( P=.56 \)).

The demographics, cause of stroke, aspirin dosage, delay between aspirin withdrawal and cerebral ischemia, and the reason for drug interruption are listed in Table 2. In 7 patients, aspirin use was discontinued on the advice of the patient’s physician either before a surgical procedure or because the physician decided that there was no clinical indication for aspirin therapy. In 5 patients, the patients themselves decided to discontinue treatment because of bleeding complications, and in the remaining 5, the reason was negligence or dementia. The mean±SD age of the patients who stopped taking aspirin was 69±13 years in the patient group and 62±19 years in the control group (\( P=.41 \)). The frequency of males was 85% in the patient group but only 25% in the control group (\( P=.05 \)). The mean±SD interval between treatment disruption and cerebral infarction in the patient group was 9.5±7 days. The mean aspirin dose in the patients and controls was 200 and 212 mg, respectively (\( P=.75 \)). The most common cause of stroke associated with aspirin discontinuation was cardioembolic (46%).

Aspirin acts pharmacologically as a noncompetitive inhibitor of platelet and endothelial cyclooxygenase and has an effect on the balance between thromboxane \( A_2 \), released from platelets, and prostacyclin, produced by the endothelium. Prostacyclin induces vasodilatation and inhibits platelet aggregation, whereas thromboxane \( A_2 \) is a powerful vasoconstrictor and promoter of platelet aggregation. The dose-related selectivity of aspirin is at-
thrombotic effects are seen at 8 to 10 days. Beving et al suggested an antithrombotic effect is seen in the 3 days after the administration of a single dose of aspirin. Whereas platelets cannot make fresh cyclooxygenase until they are replaced. The dose-related selectivity of the effect of aspirin on platelet and vascular cyclooxygenase raises the question of the dose producing the most beneficial therapeutic effect. The prothrombogenic effects observed after aspirin treatment might have practical relevance in clinical practice when the aspirin concentration in the microvasculature is extremely low, and may be explained by the presence of residual small amounts of aspirin in the endothelium that still inhibit prostacyclin production. Aguejouf et al demonstrated experimentally that an antithrombotic effect is seen in the 3 days after administration of a single dose of aspirin, whereas prothrombotic effects are seen at 8 to 10 days. Beving et al reported a stimulatory effect on platelet basal production of arachidonic acid metabolites when measured 3 weeks after stopping aspirin therapy and suggested the induction of a new platelet population with higher cyclooxygenase activity. Mousa et al found some rebound increase in the binding of fibrinogen to platelets after the administration of a single dose of aspirin. The possible prothrombotic rebound effects seen after stopping aspirin use might limit its therapeutic benefit and might explain some thromboembolic complications observed in the previously mentioned studies.

Using a retrospective cross-sectional case-control design, we found an increased IS risk in the 4 weeks after aspirin discontinuation in patients with multiple risk factors for cerebrovascular disease (odds ratio, 3.34; 95% confidence interval, 1.07-10.39). This result persisted after adjusting for the increased frequency of CHD (odds ratio, 3.4; 95% confidence interval, 1.08-10.63). The presence of CHD was also statistically significant, and this factor may be responsible for the higher frequency of ischemic events seen in the patient group. Although separate analysis of the frequency of CHD in the 2 groups showed that the difference was not statistically significant, these data may be incorrect owing to the restricted number of patients with aspirin discontinuation in both groups. On the other hand, CHD may be an independent risk factor for IS after the interruption of aspirin treatment. The main cause of stroke in the individuals who discontinued aspirin use was cardioembolic. This is surprising because, in most patients, antiplatelet agents are not the first choice for the secondary prevention of cardioembolic strokes. However, aspirin has proven efficacy in the prevention of cardioembolic strokes, and the withdrawal of aspirin therapy may precipitate acute coronary events and consequently cardioembolic strokes. Seventy percent of ISs occurred fewer than 10 days after discontinuation (mean ± SD, 9 ± 7 days). This delay is in accordance with a pharmacologic study suggesting prothrombotic effects after discontinuing aspirin use. Although Beving et al suggested that the rebound phenomenon may be associated with higher doses, we did not find a statistically significant difference in aspirin dosage between the 2 groups.

The results of this case-control study reinforce those of previous studies that reported a rebound effect after aspirin withdrawal. However, this is the only controlled study, to our knowledge, to measure the magnitude of the association between aspirin therapy discontinuation and the risk of developing IS. Sibon and Orgogozo reported a frequency of 4.49% of strokes related to recent antiplatelet drug therapy discontinuation, and Bachman described 13 patients with cerebrovascular events occurring within 4 weeks of stopping long-term aspirin intake. In cardiologic studies, acute ischemic coronary events after aspirin withdrawal have been noted in 2.3% to 4.1% of cases. However, none of these surveys quantified this problem. The common practice of withdrawing antiplatelet agents is now being challenged because an increase in myocardial infarctions has been reported in patients in whom treatment was interrupted. Recent guidelines recommend that aspirin not

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**Table 2. Clinical Characteristics of the Participants Who Discontinued Using Aspirin**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Cause of Stroke</th>
<th>Aspirin Dosage, mg/d</th>
<th>Delay of Interruption, d</th>
<th>Reason for Interruption</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/91</td>
<td>Control</td>
<td>300</td>
<td>5</td>
<td>Knee arthroscopy</td>
</tr>
<tr>
<td>2/F/49</td>
<td>Control</td>
<td>300</td>
<td>14</td>
<td>Noncompliance</td>
</tr>
<tr>
<td>3/F/50</td>
<td>Control</td>
<td>150</td>
<td>20</td>
<td>Noncompliance</td>
</tr>
<tr>
<td>4/F/59</td>
<td>Control</td>
<td>100</td>
<td>10</td>
<td>Skin biopsy</td>
</tr>
<tr>
<td>5/M/82</td>
<td>Hypotension</td>
<td>100</td>
<td>7</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>6/M/84</td>
<td>Cardioembolic</td>
<td>100</td>
<td>5</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>7/M/58</td>
<td>Cardioembolic</td>
<td>300</td>
<td>4</td>
<td>Noncompliance</td>
</tr>
<tr>
<td>8/M/84</td>
<td>Cardioembolic</td>
<td>100</td>
<td>3</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>9/F/70</td>
<td>Cardioembolic</td>
<td>100</td>
<td>20</td>
<td>Noncompliance</td>
</tr>
<tr>
<td>10/M/65</td>
<td>Lacunar</td>
<td>300</td>
<td>20</td>
<td>Intestinal bleeding</td>
</tr>
<tr>
<td>11/F/86</td>
<td>Undetermined</td>
<td>300</td>
<td>25</td>
<td>Dementia</td>
</tr>
<tr>
<td>12/M/70</td>
<td>Undetermined</td>
<td>Unknown</td>
<td>15</td>
<td>Hematuria</td>
</tr>
<tr>
<td>13/M/64</td>
<td>Lacunar</td>
<td>300</td>
<td>5</td>
<td>Urologic procedure</td>
</tr>
<tr>
<td>14/M/39</td>
<td>Atherothrombotic</td>
<td>300</td>
<td>3</td>
<td>Physician decided treatment not clinically relevant</td>
</tr>
<tr>
<td>15/M/74</td>
<td>Cardioembolic</td>
<td>300</td>
<td>3</td>
<td>Carotid surgery</td>
</tr>
<tr>
<td>16/M/66</td>
<td>Undetermined</td>
<td>100</td>
<td>8</td>
<td>Coronary angioplasty</td>
</tr>
<tr>
<td>17/M/57</td>
<td>Cardioembolic</td>
<td>100</td>
<td>7</td>
<td>Gastric surgery</td>
</tr>
</tbody>
</table>
be withdrawn for most vascular procedures and in several additional settings. Collet et al\textsuperscript{10} showed that the discontinuation of long-term aspirin therapy in patients with stable coronary artery disease, especially before surgery, may be associated with a substantial risk of acute myocardial infarction. Other studies\textsuperscript{6,22} have suggested continuation of aspirin treatment before dermatologic and ophthalmologic procedures.

There are limitations to this study, some of which are inherent to a case-control design in which differential errors are hard to avoid because the information for the patients and controls is obtained under different circumstances. The first limitation of this study may, therefore, be a risk of a selection bias toward controls with higher health awareness. However, with the exception of CHD, the 2 groups were comparable. The second limitation is that the frequency of aspirin therapy discontinuation in the patients may have been underestimated because some patients with acute stroke leading to aphasia, confusion, and deterioration of consciousness may not report treatment compliance correctly, and individuals with non-compliance or dementia may not report drug discontinuation. The delay between treatment cessation and cerebral infarct may be underestimated for the same reasons. Because of the small number of patients who stopped taking aspirin in both groups, we cannot exclude the possibility that aspirin dosage may be important in the development of the rebound phenomenon. Another limitation is the original indication for taking aspirin. Although the groups had similar cardiovascular risk factors, all the controls were taking aspirin for secondary stroke prevention, and the patients were taking aspirin for diverse reasons.

In conclusion, the discontinuation of aspirin therapy could increase the risk of IS in patients with multiple cardiovascular risk factors, mainly in those with CHD, and we should be aware of the indications, adverse effects, and potential complications of stopping aspirin use. Preoperative withholding of antiplatelet drug therapy in patients with ischemic heart disease may not always be the best solution and requires further study.

Accepted for Publication: February 25, 2005.

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Obtained funding: Maulaz. Administrative, technical, and material support: Bezerra, Michel, and Bogousslavsky. Study supervision: Michel and Bogousslavsky.

Funding/Support: This study was supported in part by grants from the Switzerland Federal Commission for Scholarships for Foreign Students (Dr. Maulaz).

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