BRIEF REPORT

Aspirin Withdrawal and Acute Lower Limb Ischemia

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Aspirin is used mainly to prevent arterial events in patients with arteriopathy. Myocardial infarction and cerebrovascular events have been described after recent aspirin withdrawal. Experimental data suggest rebound platelet activity after aspirin discontinuation. Among a retrospective cohort of 181 patients admitted for acute lower limb ischemia for 4 yr, we studied 11 patients who had recently stopped taking aspirin. Aspirin was administered for vascular event prevention. The median duration of aspirin treatment without vascular events was 12 mo (range, 6–60 mo). The median time between aspirin withdrawal and lower limb ischemia was 23 days (range, 7–60 days). Four of the 11 patients stopped aspirin before a surgical procedure, without any substitution. In five patients, a recent diagnosis of neoplasia was observed. This study should alert clinicians to the risk of discontinuing chronic aspirin therapy in patients with severe peripheral vascular disease.

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Aspirin is used mainly to prevent arterial events in atherosclerotic patients. In primary prevention, aspirin is clearly indicated to prevent death and disability from stroke and myocardial infarction (1). However, no clear benefit has been shown for peripheral arterial events. In secondary prevention for peripheral ischemic events, chronic aspirin therapy reduces the risk of graft occlusion after vascular surgery (2–4).

Discontinuing aspirin therapy in the preoperative period is considered as a standard of care for avoiding hemorrhage during a surgical procedure (5). In this context of aspirin withdrawal, coronary and cerebral arterial events have been reported (6,7). In a cohort of 475 consecutive patients with acute myocardial infarction, Collet et al. (6) described 11 patients with recent aspirin withdrawal (median time of 10 days before the event; range, 3–15 days). These patients had stable coronary disease and had been free from acute coronary events for more than 3 yr before aspirin withdrawal. Aspirin was discontinued before a surgical procedure in 9 of these 11 patients. Second, Bachman (7) described 13 patients with cerebrovascular events that occurred within a few weeks after chronic aspirin therapy was stopped (approximate median time, 14 days; range, 2–56 days). We retrospectively studied a series of 11 patients with chronic obstructive arterial disease treated with aspirin who were admitted for acute lower limb ischemia after recent withdrawal of aspirin therapy.

Methods

Among a retrospective cohort of 181 patients admitted emergently in our institution for acute lower limb ischemia (from November 1998 to June 2002), we studied 11 patients who had recently stopped taking aspirin before a vascular event. IRB approval was not required because of the retrospective design of this study, and according to French legislation, no informed consent was needed to use data from a retrospective epidemiological study.

Aspirin (75–300 mg) was chronically administered for preventing vascular events in patients with peripheral vascular disease (at least second-stage Fontaine: intermittent claudication). These patients were considered stable for peripheral arterial disease before admission. Data on age, sex, vascular disease risk factors, and previous vascular events were collected. The aspirin treatment duration, the length of aspirin treatment without a vascular event, and the delay between the vascular event and aspirin withdrawal were noted. In relation to the small sample size and the fact that these data were not normally distributed, results are expressed as median and range.

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Results

Results are presented in Table 1. Eight of the 11 patients had a clinical history of severe peripheral arterial disease with vascular graft. Five patients had a recent diagnosis of neoplasia. The reason for discontinuing aspirin therapy was a surgical procedure in four patients (36%). Two patients chronically took oral anticoagulants (fluindione), and no patient received antiplatelet therapy other than aspirin. Nonsteroidal antiinflammatory drugs were not substituted for aspirin, and in this series of 11 patients, no patients were chronically treated with nonsteroidal antiinflammatory drugs. The median time between aspirin withdrawal and acute lower limb ischemia was 23 days (range, 7–60 days). In the 170 other cases of patients with acute lower limb ischemia, 3 patients were chronically treated with aspirin and had continued aspirin until the ischemic event occurred. Five of these 170 patients were taking nonsteroidal antiinflammatory medications.

Discussion

We describe 11 atherosclerotic patients chronically treated with aspirin and admitted for acute lower limb ischemia after discontinuing aspirin. These vascular events occurred in 36% of patients (4 of 11) in relation to a preoperative withdrawal of antiplatelet therapy.

Platelets play a major role in acute ischemic syndrome and peripheral vascular disease. They are involved in the development and progression of atherosclerosis and have a central role in graft thrombosis (8). Deposition of platelets is involved in failure of prosthetic grafts (9), and aspirin (associated with dipyridamole) reduces platelet deposition on vascular graft (10). In our report it is remarkable that, for patients with a previous vascular graft (8 of 11), graft occlusion occurred. Clinical observations of myocardial infarction or stroke, apparently related to aspirin or anticoagulant withdrawal, were noted in the setting of thrombocytosis or antiphospholipid syndrome (11,12), suggesting an abnormally high platelet aggregability.

Experimental studies have observed an enhancement of platelet aggregability after interruption of aspirin (13–15). Beving et al. (14) demonstrated that high levels of arachidonic acid metabolites were produced by platelets one to two weeks after discontinuation of acetyl salicylic acid. Similarly, Vial et al. (15) found a rebound increase in urinary thromboxane B2 excretion after aspirin withdrawal. *In vitro*, platelet thrombi produced after aspirin withdrawal seem to be more resistant to physiological fibrinolysis (13). The chronological link between aspirin withdrawal and acute arterial thrombosis may be partially explained by the timing of the biochemical mechanisms of rebound activity. In a report by Collet et al. (6) concerning acute myocardial infarction, the median delay was nine days. In Bachman's report (7), the median delay for cerebrovascular events was approximately 14 days, and in our study it was 23 days. These different delays may not be fortuitous, because arterial diameters and the possibility of vascular supply are different in these coronary, cerebral, and lower limb circulations.

Regarding the severity of arteritis, 72% of patients (8 of 11) had a history of severe arteritis with peripheral vascular graft, suggesting that peripheral blood flow was significantly compromised. Nevertheless, the duration of aspirin treatment without vascular events was 18.4 months (range, 6–60 months). Aspirin may have contributed to the apparent stabilization of arterial disease.

Many of the patients in the study of Collet et al. (6) and that of Bachman (7), as well as those in our study, had experienced arterial thrombosis in the perioperative setting (81%, 54%, and 36%, respectively). Surgery is a major inflammatory factor and may promote a procoagulant state (16). It is noteworthy that surgery has been recognized as a risk factor for coronary events (17) and stroke (18). In the preoperative period, antiplatelet drugs are usually interrupted at least five days before surgery to allow the generation of a sufficient number of naive platelets. Usually, aspirin is not substituted or is replaced either by a short-acting nonsteroidal antiinflammatory drug or by anticoagulant medications. In this study, short-acting antiplatelet drugs were not substituted for aspirin. The delay between aspirin withdrawal and arterial events is explained not only by the preoperative interruption of aspirin, but also by the reluctance to reintroduce antiplatelet drugs early in the postoperative period for fear of hemorrhagic surgical complications.

Interestingly, in our report, 45% of patients (5 of 11) had a recent clinical history of neoplasia. Malignant processes have been recognized as a classic risk factor for acute peripheral ischemia in relation to platelet activation and for an increase in platelet aggregability (19,20).

The association of common risk factors for arteriosclerosis and cancer (such as smoking) leads to the admission of patients with severe arteriosclerosis for oncological surgical indications. Hence, the question of aspirin withdrawal in the perioperative period must be managed carefully in patients with apparently increased arterial thrombosis risk factors.

This study does not establish a direct cause/effect relationship between aspirin withdrawal and arterial thrombosis. Unfortunately, because this occurrence seems to be rare, the critical number is the incidence of acute lower limb ischemia in patients who stop taking

Table 1. Description of 11 Patients with Arterial Ischemia After Recent Aspirin Withdrawal

Age (yr)/sex	Previous vascular disease	Comorbidity	Cancer	Aspirin dose (mg)
46/M	Arteritis	Diabetes mellitus Hypertension Hypercholesterolemia	Bladder tumor	100
74/F	Arteritis Femoropopliteal graft	Hypertension	Ovarian cancer	100
46/M	Arteritis Several vascular grafts	Hypertension Active smoking	No	100
53/M	Arteritis Femoropopliteal graft	Hypertension Active smoking Alcohol	No	100
72/M	Arteritis Several vascular grafts	Active smoking Alcohol	No	250
60/M	Arteritis Femoropopliteal graft	COPD Active smoking Alcohol	Esophageal cancer	100
62/M	Arteritis	Active smoking	Lung cancer	100
82/M	Arteritis Several vascular grafts	Diabetes mellitus Obesity Active smoking	No	100
74/M	Arteritis	Diabetes mellitus Hypertension Obesity	No	300
46/M	Arteritis Several vascular grafts	Diabetes mellitus Hypertension Hypercholesterolemia Active smoking Stroke	No	75
57/M	Arteritis Several vascular grafts	Active smoking Alcohol	Laryngeal cancer	100
Median time (range) 60 yr (46–82)				

COPD = chronic obstructive pulmonary disease.

aspirin. This number is not known. However, the expected rate of peripheral arterial ischemia in vascular patients still taking aspirin is also difficult to determine, and analysis of the literature does not permit answering this question.

In the perioperative context, aspirin is traditionally discontinued before elective surgery for fear of perioperative hemorrhagic complications. There are no conclusive data to answer this question. Several studies concerning specific surgical procedures have shown that antiplatelet drugs may increase the surgical site bleeding (21). Conversely, large studies have shown that an acceptable rate of bleeding complications may allow the perioperative use of antiplatelet drugs (22).

This observation needs to be confirmed by case-control studies to determine the role of aspirin withdrawal as an independent risk factor for peripheral arterial thrombosis. Nevertheless, this study should alert clinicians to the risk of discontinuing chronic aspirin therapy in patients with severe peripheral vascular disease who have had a recent diagnosis of cancer. In these cases, if aspirin withdrawal is required, the time off aspirin should be as short as possible, and early reintroduction is advocated.

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Table 1. Continued

Aspirin treatment duration (yr)	Treatment duration without vascular event (mo)	Time between vascular event and aspirin withdrawal (d)	Reason off aspirin	Vascular event and consequence
?	?	13	Surgery Bladder tumor resection	External iliac artery thrombosis Vascular surgery
1.5	16	60	Vomiting	Graft occlusion Amputation
7	36	9	Spontaneous	Graft occlusion Amputation
1	8	30	Spontaneous	Graft occlusion Vascular surgery
6	10	32	Neurosurgery	Graft occlusion Vascular surgery
?	12	23	Surgery Esophagectomy	Femoral artery thrombosis Death
?	?	60	Hemoptysis	Femoral artery thrombosis Vascular surgery
6	12	14	Spontaneous	Graft occlusion Vascular surgery
5	60	30	Spontaneous	Femoral artery thrombosis Vascular surgery
>2	6	21	Surgery Orthopedic procedure	Graft occlusion Vascular surgery
4	6	7	Gastric hemorrhage	Graft occlusion Vascular surgery
4.5 yr (1–7)	12 mo (6–60)	23 d (7–60)		

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