Nimodipine Increases Fibrinolytic Activity in Patients With Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose—The purpose of this study was first, to investigate which factor in the fibrinolytic cascade is responsible for the recently observed increase of fibrinolytic activity in patients with aneurysmal subarachnoid hemorrhage (SAH), and second, the cause of this increase.

Methods—Fibrinolytic activity and the main regulators of endogenous fibrinolytic activity, tissue plasminogen activator, and plasminogen activator inhibitor 1 (PAI-1) were measured in patients treated with and without nimodipine.

Results—In patients with aneurysmal SAH, fibrinolytic activity significantly increases from 2.7 IU/mL on admission to 4.2 IU/mL in week 3 (P<0.01, paired-sample t test), caused by a 1.6-fold decrease in plasma levels of PAI-1. The results also show that increased fibrinolytic activity is seen only in patients treated with nimodipine and that plasminogen activity and PAI-1 returned to baseline levels after treatment with nimodipine had been discontinued.

Conclusions—The mechanism of increased fibrinolytic activity in patients with aneurysmal SAH is a decrease in the level of PAI-1, which is most likely caused by treatment with nimodipine. (Stroke. 2001;32:1860-1862.)

Key Words: fibrinolysis • nimodipine • plasminogen activator inhibitor-1 • subarachnoid hemorrhage

As part of a recently completed placebo-controlled, randomized clinical trial investigating the effect of antifibrinolytic treatment on clinical outcome in patients with aneurysmal subarachnoid hemorrhage (SAH), plasma fibrinolytic activity was monitored in both antifibrinolytic-treated and placebo-treated patients.1 In the past, several studies investigating plasma fibrinolytic activity in patients with SAH did not demonstrate an increase in plasma fibrinolytic activity.2-4 However, in contrast to the results of these older studies, we observed in our study an unexplained 3-week increase in plasma fibrinolytic activity in placebo-treated patients.

The aim of the present study was first, to investigate which factor in the fibrinolytic cascade is directly responsible for the observed increase of fibrinolytic activity, and second, the cause of this increase in fibrinolytic activity.

A major difference between recent studies and the described older studies is the standard use of the calcium antagonist nimodipine to prevent cerebral ischemia. The question was therefore whether nimodipine could explain the observed increase in plasma fibrinolytic activity.

To investigate both questions, we measured in patients treated with and in patients treated without nimodipine the fibrinolytic activity and the main regulators of endogenous fibrinolytic activity, tissue plasminogen activator (TPA), and plasminogen activator inhibitor 1 (PAI-1).

Subjects and Methods

Patients

During the study period, 41 consecutively admitted patients with an angiographically proven aneurysmal SAH were included. Twenty-seven patients were included in the two participating centers in Amsterdam, The Netherlands (Academic Hospital of the Free University and The Academic Medical Center). In these centers, patients are routinely treated with nimodipine to prevent cerebral ischemia (360 mg per day orally [60 mg every 4 hours or 2 mg/h IV] for 3 weeks). In the other study center, (Royal Hallamshire Hospital, Sheffield, UK) 14 patients were included. In this center, calcium antagonists are not believed to have beneficial effects on cerebral ischemia; therefore, they are not used. In all participating centers, patients received modern standard care, including normal to hypertensive volemia and clipping or coiling of the ruptured aneurysm as soon as possible. None of the included patients was treated with antifibrinolytic agents. Because of ethical considerations, blood samples were collected only when blood was drawn for routine treatment: directly after admission, 4 days after SAH, and at 1-week intervals. During the whole study period, patients were identified by a unique patient identification number (PIN) to protect privacy. The code key to this PIN number remained the responsibility of the treating physician of the hospital where the patient was first seen during the study period and was destroyed after completion of the whole data set.

Laboratory Investigations and Analysis

Fibrinolytic activity was measured by detecting plasminogen activator activity (PA) with the use of an amidolytic assay.5 Briefly, 25 μL of plasma was mixed to a final volume of 250 μL.
with 0.1 mol/L Tris-HCl, pH 7.5, 0.1% (vol/vol) Tween-80, 0.3 mmol/L S-2251 (Chromogenix), 0.13 mol/L plasminogen, and 0.12 mg/mL CNBr fragments of fibrinogen (Chromogenix). The results are expressed as International Units per milliliter. TPA antigen (Asserachrom t-PA, Diagnostica Stago) and PAI-1 antigen (TintElize PAI-1, Biopool) were measured by ELISA tests. Individual patient results were grouped and averaged into 6 time windows (days 1 to 3; days 4 to 7; weeks 2, 3, and 4; and results obtained after 6 weeks). The samples were tested without knowledge of treatment or the timing of withdrawal of treatment. Statistical significance was tested with paired sample t tests and independent sample t tests where appropriate.

**Results**

The Figure shows that in patients with aneurysmal SAH treated with nimodipine, the mean value of the PA activity increased significantly over a 3-week period from 2.7 IU/mL on days 1 to 3 to 4.2 IU/mL in week 3 (Figure, P<0.01, paired sample t test). This increase in fibrinolytic activity is accompanied by a decrease of the mean value of the inhibitor (PAI-1) from 154 µg/L on days 1 to 3 to 96 µg/L in week 3 (P<0.01). After 6 weeks and after nimodipine treatment was stopped, both the PA activity and the PAI-1 returned to baseline values. Antigen levels of TPA (data not shown) did not change over time and were not different between the patient groups with and without nimodipine.

In contrast to the results in patients with nimodipine treatment, patients treated without nimodipine showed neither an increase in PA activity nor a decrease in the PAI-1 antigen levels. As a result, the Figure shows that 2 weeks after SAH, both mean PA activity and mean PAI-1 antigen levels were significantly different between the patient groups with and without nimodipine treatment (P<0.01, independent sample t test).

**Discussion**

Increased fibrinolytic activity in plasma from patients with aneurysmal SAH has never been reported. Fibrinolytic activity is not increased in patients with a poor or good clinical condition on admission, neither in patients with or without complications nor in those with poor or good outcome.3,6

The measurement of fibrinolytic activity in the cerebrospinal fluid (CSF) led to conflicting results.7 CSF samples were applied on fibrin plates, and after incubation, the diameter of the resulting zones of lysis were measured. With this method, increased fibrinolytic activity could be detected during the first week after SAH only if unheated plates were used and human fibrin was tested. Another method of testing fibrinolytic activity, the demonstration of fibrin-fibrinogen degradation products (FDPs), which result from the degradation of fibrin by plasmin, showed high levels of FDPs in the CSF after SAH up to the end of the third week. From all the studies on fibrinolysis and coagulation after SAH, high levels of FDPs in the CSF during the first weeks was the most consistent finding, but the interpretation of these results led to considerable debate. The presence of FDPs was independent from treatment with antifibrinolytic agents, whereas this treatment reduced the number of rebleeds. Moreover, plasminogen levels in the CSF were also raised in the CSF, which is not to be expected if there is an ongoing fibrinolytic activity by which plasminogen is converted to plasmin. After the demonstration of high FDP levels in the CSF of patients with other neurologic disorders, a more likely explanation for the presence of FDPs was that FDPs in the CSF reflect a damaged blood-CSF barrier and not local fibrinolytic activity in the subarachnoid space.

This study shows that in patients with SAH, increased fibrinolytic activity can be detected, that is, caused by decreasing levels of PAI-1, and that treatment with the calcium antagonist nimodipine is the most likely explanation for different results in comparison with earlier studies.

The group of patients treated without nimodipine was for logistic reasons limited to 14 patients and only had a 2-week follow-up, whereas 27 patients were treated with nimodipine and were followed for 6 weeks or longer. Despite the fact that the peak of increased fibrinolytic activity in patients treated with nimodipine is reached 3 weeks after SAH, the results showed already highly significant differences for both PA activity and PAI-1 antigen levels 2 weeks after SAH between patients treated with and without nimodipine.

If nimodipine has an effect on fibrinolytic activity, it is to be expected that bleeding complications are reported in patients who are taking nimodipine treatment. Indeed, this has been described: In a randomized clinical trial in patients with cardiac valve replacement surgery, more surgical bleed-
ings were observed in the group treated with nimodipine, and in hypertensive patients taking calcium antagonists, an increased occurrence of gastrointestinal hemorrhages was reported. Similar to our results, the calcium antagonists isradipine and amlodipine were shown to increase fibrinolytic activity by decreasing PAI-1 antigen levels in hypertensive patients.

However, in patients with SAH, an increased rate of rebleeding has not been observed in the nimodipine group of clinical trials. There are several possible explanations for this lack of relation between nimodipine and rebleeding. First, the increased fibrinolytic activity seen in patients taking nimodipine is gradually progressive after onset of treatment. It might be that the clot formation surrounding the aneurysm is affected too late to have an effect on rebleeding. Second, an explanation could be that the decreasing levels of PAI-1 have nothing to add to the activation of the fibrinolytic system, which has occurred in the acute phase after SAH. Although no increased fibrinolytic activity can be detected in the plasma of patients with SAH who are not treated with nimodipine and doubt exists about increased fibrinolytic activity in the CSF, there is no doubt about increased fibrinolytic activity surrounding the clot of the aneurysm. Large concentrations of TPA are probably released from the hemorrhage-damaged meninges, which results in less firm clots in and around the aneurysm. The clear effects of antifibrinolytic treatment on the rate of rebleeding supports this mechanism.

The increased fibrinolytic activity induced by nimodipine might also have beneficial effects in patients with SAH. Decreased fibrinolytic activity induced by tranexamic acid results in impaired recovery from cerebral ischemia. The other way around, increased fibrinolytic activity induced by nimodipine may have a beneficial effect on recovery from ischemia. We are currently testing this hypothesis in patients with SAH.

In conclusion, the mechanism of increased fibrinolytic activity in patients with SAH is a decrease in the level of PAI-1, which is most likely caused by treatment with nimodipine.

References
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