Thromboxane B$_2$ Levels in Serum During Continuous Administration of Nimodipine to Patients With Aneurysmal Subarachnoid Hemorrhage

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Twenty-four patients with subarachnoid hemorrhage due to rupture of a supratentorial aneurysm underwent surgery within 72 hours after subarachnoid hemorrhage. Immediately after clipping of the aneurysm the patients were treated with intravenous nimodipine for at least 7 days and then received the drug orally for another week. Nine patients had a documented or probable intake of aspirin or other nonsteroid anti-inflammatory drug during the days preceding admission. In all patients there was a gradual increase in serum thromboxane B$_2$ concentration from low to normal levels during the treatment period, the increase being most pronounced in patients with prior nonsteroid anti-inflammatory drug intake. Thromboxane B$_2$ concentrations were similar to those of four control patients not receiving nimodipine. In three patients who developed delayed ischemic dysfunction despite "therapeutic" nimodipine plasma concentrations, the thromboxane B$_2$ levels were low or normal. Our present results do not support the idea that nimodipine exerts an effect on platelet function in patients with aneurysmal subarachnoid hemorrhage. (Stroke 1988;19:644–647)

The beneficial effects of calcium antagonists in the treatment of coronary heart disease are often attributed to their potent relaxant action on vascular smooth muscle. This property has also been the rationale for clinical trials with calcium antagonists in the prevention of delayed cerebral vasoconstriction and delayed ischemic dysfunction (DID) following aneurysmal subarachnoid hemorrhage (SAH).1–3

However, in addition to the actions on smooth muscle, calcium antagonists may have other effects, for example, on platelet function,4 that may be of importance. Even if the role of platelets in the development of DID is unknown, it cannot be excluded that the vessel injury or tissue ischemia may activate platelets5 to release potent vasoconstrictors and proaggregatory substances such as thromboxane and serotonin, and this may in turn aggravate cerebrovascular damage.6 Although in vitro supratherapeutic concentrations of calcium antagonists are generally required to demonstrate effects on platelets, decreased platelet aggregation ex vivo following administration of low or normal therapeutic doses to volunteers or to patients have been reported.7–10 Others have failed to find any alterations in platelet aggregability.10–13

One platelet function assumed to depend on free intracellular calcium is the liberation of arachidonic acid from membrane phospholipids and hence the formation of prostaglandins and thromboxane. Human platelets exposed to calcium antagonists in vivo were reported to produce less thromboxane in response to stimulation by thrombin10 and collagen12 than before drug intake. Uehara and coworkers14 reported decreased levels of thromboxane B$_2$ (TXB$_2$) in plasma after treatment with nifedipine. These results are of particular interest in relation to the increased levels of urinary immunoreactive TXB$_2$ found in 30 patients with acute cerebral ischemia.15

Early surgical intervention in aneurysmal SAH with removal of blood clots combined with postoperative treatment with nimodipine has been reported to reduce the incidence of DID.16 The cerebral vasodilating action of nimodipine is well documented,16 but whether this drug in the doses used affects platelet function has not been established. In our present study of aneurysmal SAH patients, platelet function during continuous postoperative nimodipine administration was measured as thromboxane formation by platelets spontaneously activated during blood clotting.

Subjects and Methods

Twenty-four patients with a ruptured supratentorial aneurysm underwent operation within 72 hours after SAH. Clots and blood-contaminated cerebrospinal fluid (CSF) were evacuated from the basal cisterns. The exposed arteries were rinsed with 2.5 × 10$^{-5}$ M nimo-
Nimodipine. Immediately after clipping of the aneurysm, an intravenous infusion of the drug was started at 1 mg/hr and after 2 hours was increased to 2 mg/hr, which was continued for at least 7 days. Thereafter, nimodipine was given orally at 45 mg every 4 hours for at least another week.

Four patients similarly operated upon for aneurysms but not given nimodipine served as control patients. Two had ruptured supratentorial aneurysms, one had a ruptured basilar aneurysm, and one had a nonruptured aneurysm of the carotid artery.

Since acetylsalicylic acid (ASA) and other nonsteroid anti-inflammatory drugs (NSAIDs) are known to be potent inhibitors of TXB₂ formation, all patients were retrospectively classified according to the preoperative intake of these drugs. If such drug intake was not explicitly stated in the medical records and if there were no notes on headache or other symptoms during the days before admission, the patient was considered to be free of NSAIDs. Administration of NSAIDs was prohibited in the postoperative period.

During ongoing nimodipine infusion on Days 1, 3, 5, and 7 postoperatively, blood samples were collected for measurements of TXB₂ levels and of the concomitant concentrations of nimodipine in plasma. Blood samples were also taken from 12 patients immediately before an oral dose of nimodipine, usually on the third day of oral medication. Blood samples for TXB₂ measurements were taken from the four control patients on Days 1, 3, 5, 7, and 9 postoperatively. Blood samples were taken only on weekdays.

For TXB₂ measurements blood was allowed to clot at 37°C for 1 hour before serum was separated and stored at −20°C until immunoreactive TXB₂ was determined by radioimmunoassay (3H-Thromboxane B₂-RIA, New England Nuclear, Boston, Massachusetts). Nimodipine was measured by high-pressure liquid chromatography.² Fifty-two measurements in serum samples obtained from 14 healthy volunteers over 2 years served as normal references for TXB₂. In 13 of these volunteers, three to six measurements were made on separate occasions.

Platelets immediately before surgery were counted by using a routine method (Coulter-Counter, Coulter Corp., Hialeah, Florida) in the hospital laboratory.

**Results**

Nine patients treated with nimodipine had documented or probable intake of ASA or other NSAIDs during the days preceding admission. For 15 patients there was no information confirming or suggesting intake of NSAIDs. In several of these cases the onset of symptoms was so dramatic that any self-medication with analgesics was considered unlikely.

Among the control patients, intake of NSAID was probable in one, whereas the other three were considered to be free of NSAIDs.

TXB₂ levels in the serum of nimodipine-treated patients, with or without preceding intake of NSAIDs, are presented in Figure 1. On Day 1, six of six TXB₂ concentrations in serum obtained from patients who had taken NSAIDs were more than 2 SD from the mean of normal controls compared with two of twelve from patients free of NSAIDs. In a few patients, sudden drops to very low TXB₂ levels were found at the end of the treatment period. In each of these cases, scrutinization of the medical records revealed administration of single doses of ASA or other NSAIDs in the wards in spite of general instructions. The TXB₂ levels following these doses have not been included in the presentation of data. In two nimodipine-treated patients who had no documented or suspected intake of NSAIDs before admission, TXB₂ levels did not exceed 100 ng/ml at any measurement.

Nimodipine concentrations in plasma during the continuous infusion and after a single oral dose are shown in Figure 2. Data from patients considered to...
have taken NSAIDs are presented separately from those who had not. Details on pharmacokinetics have been presented elsewhere.23

Three patients developed DID. Their individual TXB2 levels are shown in Figure 3. Their nimodipine levels were close to the mean of all patients.

TXB2 levels in serum from the four control patients who did not receive nimodipine are presented in Figure 4. For one of the three control patients considered free of NSAIDs, the initial serum TXB2 was as low as for the control patient with NSAID.

The mean ± SD level of TXB2 from 52 measurements in healthy volunteers was 230 ± 92 ng/ml. The individual means varied between 165 and 386 ng/ml, and individual SDs varied between 8 and 127 (mean SD 54 ng/ml).

Mean ± SD platelet count in the eight nimodipine-treated patients who had taken NSAIDs was 215 ± 28 × 10^7/1 and in the 15 patients free of NSAIDs 214 ± 70 × 10^7/1. Platelet count was 400 × 10^7/1 in the control patient who had taken NSAIDs and 285 ± 22 × 10^7/1 in those considered free of these drugs.

The profile of TXB2 levels in serum during the postoperative period was essentially similar in patients who did and did not receive nimodipine, indicating that the increase in TXB2 levels was not caused by the drug.

The increase in TXB2, from very low to normal levels over a 1-week period in the patients considered to have taken NSAIDs is in agreement with the appearance of new platelets in the circulation following an episode of irreversible platelet damage, as seen after intake of ASA.24 Thus, TXB2 levels from this group of patients seem to confirm the assumption of drug intake made from anamnestic data.

However, also in patients who were considered free of NSAIDs, mean TXB2 levels were lower on the first postoperative day. It cannot be excluded that this reflects unrecorded intake of NSAIDs, possibly single doses of ASA for any reason in the week before the SAH. Alternative explanations might be that the platelets were refractory due to previous activation by the stress of the SAH or the operative trauma per se. Naesh et al25 reported that platelets were activated during cholecystectomy, and signs of refractoriness were noted in the postoperative period. Furthermore, inhibitory effects on the platelets by drugs used for anesthesia cannot be excluded.26

In our study, we had the opportunity to include three patients who developed symptoms of DID during nimodipine treatment. Their plasma concentrations of nimodipine did not differ from those of patients not developing DID. Two of the DID patients had low TXB2 levels throughout the observation period, whereas the third had levels within a normal range. Even if the number of patients developing DID is too

Discussion

Previous studies had suggested that nifedipine10 and nisoldipine15 decrease platelet aggregation and TXB2 formation. In our study, a third compound of the dihydropyridine group, nimodipine, was given to patients for > 1 week. During this time, the capacity of TXB2 formation was essentially unchanged in some patients, whereas it increased steadily in others. In no patient did an apparent spontaneous decline from high to low levels appear. At the end of the first postoperative week, TXB2 levels from most patients were in the same range as those from healthy volunteers. This argues against any clinically important depressant effect by nimodipine on platelet ability to form TXB2.

Antiplatelet effects of calcium antagonists in vivo usually have been reported shortly after intake of low single doses.7,9,10,12,13,15 In our study, a partial response could possibly have been obtained on Day 1, followed by development of tolerance. However, Uehara et al14 reported decreased aggregation and decreased plasma TXB2 levels after treatment of hypertensive patients with nifedipine for 8 weeks. After an equally long treatment period with nifedipine in patients with angina pectoris, others found inhibition of the platelet response to exercise but no change in the platelet response at rest.11 After 3 months' treatment with verapamil, on the other hand, Kristensen et al19 found no effects on platelets.

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low to allow conclusions, these data do not favor a relation between the TXB₂-forming capacity of the blood and the development of DID.

In conclusion, our results do not support the idea that nimodipine exerts effects on platelet function in patients with aneurysmal SAH.

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