Intracarotid slow bolus injection of nimodipine during angiography for treatment of cerebral vasospasm after SAH

A preliminary report

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Nimodipine was given as an intracarotid slow bolus injection in six patients with subarachnoid hemorrhage (SAH) due to rupture of a cerebral aneurysm, with angiographically demonstrated vasospasm. The patients were followed by serial angiograms for demonstration of the effect of nimodipine on vasospasm. After angiography, all patients were treated with a constant venous infusion of this new calcium antagonist. Although the therapeutic regimen was started only a few hours after onset of vasospasm, there was no change in cerebral vessel caliber detectable on angiograms following the intracarotid injection. Three patients died, two patients finally recovered with neurological deficits due to cerebral ischemia, and one patient with asymptomatic vasospasm remained symptom-free. Although nimodipine may act to prevent cerebral vasospasm after SAH, the authors believe that the intracarotid application is not effective after vasospasm has occurred.

Key Words: cerebral vasospasm • subarachnoid hemorrhage • nimodipine • aneurysm • angiography • calcium antagonist

Cerebral vasospasm has been recognized as a major complication of ruptured cerebral aneurysms. In spite of extensive research, the pathogenesis of cerebral vasospasm remains obscure, and the clinical management has so far been extremely difficult. Although the search for causative factors has prompted the use of various therapeutic regimens, the results have in general been disappointing, probably because cerebral vasospasm has a multifactorial etiology.

Nimodipine, isopropyl (2-methoxy-ethyl) 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate, is a new calcium antagonist with special affinity for the receptor-operated calcium channels in cerebral vessels. In a clinical trial, we have tested the efficacy of an intracarotid slow bolus injection of nimodipine during angiography in patients in whom angiograms unequivocally showed rupture of a cerebral aneurysm and marked cerebral vasospasms.

Clinical Material and Methods

This investigation was carried out as an open pilot study with six patients of both sexes, aged between 15 and 62 years. Patients admitted to the study had to meet the following requirements: on initial neurological examination, patients must have been classified in Grades I to IV according to Hunt and Hess; subarachnoid hemorrhage (SAH) should have been clearly identified by lumbar puncture and/or by computerized tomography (CT); cerebral vasospasm must have been demonstrated unequivocally by angiography; and the treatment must have been started within 24 hours after onset of cerebral vasospasm. Patients with renal or liver insufficiency, cardiac decompensation, cardiac arrhythmias, angina pectoris, cerebral edema, or cerebral infarction were excluded from the study. Pregnancy and concomitant administration of β-blockers also led to exclusion.

Cerebral panangiography was performed through the femoral artery by the Seldinger technique; the contrast medium used in all patients was Angiografin (meglumaminidotsirozate). Nimodipine was injected into the carotid artery via a heparinized polyurethane or polyethylene catheter. It was diluted with 10 ml of isotonic saline solution, and was given as a slow bolus injection over 10 minutes.
Angiography was repeated 10 minutes after the end of the bolus injection. In two patients a second intracarotid slow bolus injection was given and angiography was again repeated 10 minutes after the injection was completed. Constant venous infusion of nimodipine was started immediately after completion of angiography and was planned to last at least 5 days. Finally, nimodipine was administered orally for 3 days. For the venous infusion a dose of 2 mg/hr was chosen; for oral administration a dose of 60 mg every 6 hours was given. Serial CT scans were made at the onset of vasospasm and during the course of nimodipine therapy.

Results of Treatment

All clinical data are summarized in Table 1. In these six cases, the onset of cerebral vasospasm was within 24 hours in three patients, within 1 week in two, and 9 days after SAH in one patient. Onset of vasospasm within 24 hours after SAH was defined as early vasospasm, and onset of vasospasm more than 4 days after SAH as late vasospasm.

Early vasospasm occurred in Cases 3, 4, and 5. Cases 3 and 4 were classified in neurological Grade III at admission, having a massive intracerebral hematoma and ventricular hemorrhage. Both patients deteriorated...
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within several hours after admission. Angiography performed before deterioration did not demonstrate vasospasm, but repeat angiography shortly after deterioration showed marked vasospasm. Rapid deterioration of patients in poor clinical condition in general is thought to be caused by intracerebral hematoma or by ventricular hemorrhage. There is often no time to perform angiography. These two cases showed that early vasospasm does play a role in the rapid deterioration of such patients.

Early vasospasm also occurred in Case 5. In this patient, angiography was performed on the day of SAH. There were no clinical signs of vasospasm, but the angiogram showed marked vasospasm of the left middle cerebral artery (MCA). This case was classified as early asymptomatic vasospasm.

Late vasospasm occurred in Cases 1, 2, and 6. In these patients, initial angiography after SAH did not show signs of vasospasm, but marked cerebral vasospasm could be demonstrated unequivocally by angiography at the time of deterioration. These three cases will now be described in detail.

Representative Case Reports

Case 1
This 58-year-old woman sustained an SAH on November 11, 1982. She developed a moderately stiff neck but no neurological deficit. There was no initial loss of consciousness. She was not hypertensive. A CT scan showed obstructed cisterns and a small intracerebral hematoma in the right temporal region. Angiography on November 13 (Fig. 1) showed an aneurysm of the right MCA, but no evidence of intracranial arterial spasm.

On November 18, 7 days after the SAH, the patient suddenly became restless and developed a left hemiparesis. Repeat CT gave no evidence of rebleeding. Angiography was then performed immediately (Fig. 2) and revealed severe vasospasm of the intracranial part of the internal carotid artery (ICA) on the right, and a nearly total reduction in caliber of the right anterior cerebral artery (ACA) and MCA.

Intracarotid nimodipine was given in a dose of 0.034 mg, and angiography was repeated (Fig. 3 left). There was no change in vessel caliber. A second dose of 0.034 mg nimodipine was given and angiography was performed again, 30 minutes after the end of the slow bolus injection (Fig. 3 right). Cerebral vasospasm remained unchanged. About 18 hours after onset of vasospasm, CT showed a hypodense area in the right hemisphere (Fig. 4 left).

Fig. 4. Computerized tomography scans in Case 1. Left: Eighteen hours after onset of vasospasm there is a hypodense area (arrows) in the right hemisphere. Right: Four days after onset of vasospasm there is complete infarction in the area supplied by the middle cerebral artery.
Fig. 5. Lateral angiograms of Case 1. Left: During continuous intravenous application of nimodipine, 11 days after SAH and 4 days after onset of vasospasm. Vasospasm is nearly unchanged along the precommunicating portion of the anterior cerebral artery (closed arrowheads) and internal carotid artery (open arrowheads). There is less severe spasm of the right middle cerebral artery (arrows). Center: Fourteen days after onset of vasospasm and 6 days after completion of the intravenous and oral nimodipine therapy. There is regression of the vasospasm. Right: Two months after onset of vasospasm, 1 day before operation on the aneurysm, there are no signs of vasospasm.

A constant intravenous infusion of nimodipine, which was started immediately after the last angiography, was given over 5 days, followed by oral administration of 60 mg every 6 hours for 3 days. On November 22, 11 days after SAH and 4 days after the onset of vasospasm, angiography was repeated (Fig. 5 left). At that time the patient was fully alert, but had a left hemiplegia and homonymous hemianopsia. The angiogram showed that the vasospasm of the A1 segment of the ACA was nearly unchanged but the spasm of the MCA and ICA was less severe. A CT scan showed a complete infarction in the area supplied by the right MCA (Fig. 4 right).

Six days after completion of the nimodipine therapy, on December 1, regression of vasospasm was seen in the angiogram (Fig. 5 center). After the clinical status had stabilized, the aneurysm of the right MCA was clipped on January 18, 1983. A preoperative angiogram showed no signs of vasospasm (Fig. 5 right). At that time the left hemiplegia and homonymous hemianopsia showed a slight regression.

Case 2

This 15-year-old girl suddenly lost consciousness at school for a few minutes on November 24, 1982, and fell and fractured her jaw. She was admitted to a department for oral surgery. During the oral surgery she became unconscious again. Examination revealed a stiff neck, and about 30 minutes later she was admitted to our department. At admission, the patient was awake and fully alert. She had a moderately stiff neck but there was no neurological deficit. A CT scan revealed SAH (Fig. 6 left). Angiography was performed on November 25, and an aneurysm was found at the top of the basilar artery (Fig. 7). There were no signs of vasospasm.

On November 30, the girl suddenly became comatose while being brought to the operating room for the aneurysm operation. She had respiratory arrest, fixed pupils, and extensor responses to pain on both sides. A CT scan showed hydrocephalus; the blood in the subarachnoid space had been partially resorbed (Fig. 6 right). A ventriculoperitoneal shunt (Pudenz-Heyer system) was inserted, and angiography about 4 hours after the onset of deterioration showed no alteration of the basilar artery aneurysm; now there was marked spasm of the right posterior cerebral artery, ICA, ACA, and MCA (Fig. 8). After simultaneous intravertebral and intracarotid slow bolus injection of nimodipine there was no change in vessel caliber. The patient suffered no neurological deficit, and did well for the next 3 days. On December 3, 1982, during treatment...
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FIG. 7. Case 2. Anteroposterior (left) and lateral (right) views of a vertebral artery angiogram 1 day after subarachnoid hemorrhage showing the aneurysm at the top of the basilar artery (arrows). No signs of vasospasm are seen.

with nimodipine, angiography was repeated. The spasm was apparently less severe in all areas of the carotid and vertebrobasilar systems (Fig. 9). Several hours later the girl suddenly became comatose again, with respiratory arrest. A CT scan revealed rebleeding with opacified cisterns and massive ventricular hemorrhage. She died 4 days later.

Case 6

This 62-year-old man experienced a spontaneous SAH on February 23, 1983. There was initial loss of consciousness. On March 3, 8 days after SAH, he became restless and confused. Lumbar puncture then showed xanthochromic cerebrospinal fluid and the patient was admitted to our department the same day. At admission he was fully alert. There were no signs of confusion, stiff neck, or neurological deficits. A CT scan showed no abnormalities.

Angiography on March 4 revealed an aneurysm of the right MCA, and marked spasm of the right MCA, the left ICA, and the left ACA (Fig. 10). The spasm remained unchanged after two intracarotid slow bolus injections of 0.5 mg nimodipine (Fig. 11). At that time there were no clinical signs of cerebral ischemia. After angiography a constant venous infusion of 2 mg/hr nimodipine was given.

FIG. 8. Case 2. Anteroposterior (left) and lateral (right) views of a brachial artery angiogram showing severe vasospasm of the vertebrobasilar system, especially the right posterior cerebral artery (arrow), but also spasm of the right internal carotid artery and anterior cerebral artery (closed arrowhead), and middle cerebral artery (open arrowheads).
FIG. 9. Case 2. Brachial artery angiogram, lateral view, 4 days after onset of vasospasm, during treatment with continuous intravenous application of nimodipine. Vasospasm is less severe in all areas of the carotid and vertebrobasilar system.

On March 6, 11 days after SAH and the 2nd day of nimodipine treatment, the patient developed a left hemiparesis. The dose of nimodipine was increased to 10 mg/hr, but there was no regression of symptoms and the hemiparesis gradually became worse during the following days. A CT scan 4 days later showed a small hypodense area in the right postcentral region (Fig. 12). Angiography on March 11, 7 days after the first angiography, showed that the vasospasm was less severe (Fig. 13), but there was no change of clinical condition.

The aneurysm was clipped on March 14. Postoperatively, the patient’s left hemiparesis remained unchanged. Six months later, regression of the hemiparesis was noticed and he was able to walk.

Discussion

Until now, various agents have been identified that constrict cerebral vessels; these include serotonin, its metabolites, prostaglandins, thromboxane A2, whole blood, hemoglobin, erythrocyte breakdown products, fibrinogen degradation products, uridine triphosphate, and many others. Mechanical factors are also thought to play a role in the pathogenesis of cerebral vasospasm. All these known vasoconstrictive agents may act by many different mechanisms, but they all induce contraction of the smooth muscle of the cerebral vessel by increasing the free intracellular concentration of calcium. Whenever extracellular calcium ions are needed for activation, the vasoconstriction can be prevented or inhibited by calcium antagonistic drugs.

Experiments have shown that there are different populations of calcium channels in membranes of different vessels and that the receptor-operated calcium channels in brain vessels substantially differ from those of peripheral vessels. In vitro and in vivo investigations have shown dilatation of constricted vessels following intravenous and topical application of calcium antagonists, especially nimodipine. In this clinical trial, we could not achieve any direct change in caliber of the angiographically demonstrated constricted cerebral vessels. We found that intracarotid injections of nimodipine did not prevent ischemia, in spite of the fact that treatment was started very soon after onset of vasospasm.

Tolerance to the intracarotid slow bolus injection of nimodipine was good. We did not see any adverse side-effects other than a slight fall of systolic blood pressure, which started 4 to 8 minutes after the start of the slow bolus injection (Fig. 14). There was no significant alteration of pulse rate.

Although it is beyond the scope of this preliminary
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FIG. 11. Case 6. Angiogram, anteroposterior view, after the first of two slow bolus injections of nimodipine, showing no change of vessel caliber. There were no clinical signs of cerebral ischemia at that time.

FIG. 12. Case 6. Computerized tomography scan showing a small hypodense area (arrows) in the right postcentral region.

FIG. 13. Case 6. Angiograms, anteroposterior (left) and lateral (right) views 7 days after the first angiogram and 5 days after development of left hemiparesis. Regression of spasm can be observed.

FIG. 14. Registration of systolic blood pressure. Left: Pressures for Cases 2, 3, 4, and 5 at admission (A), during slow bolus injection of nimodipine (inject.), and for 50 minutes after the end of injection. Right: Pressures for Cases 1 and 6 at admission (A), during the first slow bolus injection of nimodipine (1.inj.), for 30 minutes after the end of the first injection, during the second slow bolus injection of nimodipine (2.inj.), and for 50 minutes after the end of the second injection.
TABLE 1

Summary of clinical data of six patients with SAH and vasospasm treated with nimodipine (NDP)*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Site of Aneurysm</th>
<th>Clinical Grade</th>
<th>SAH to Admission</th>
<th>SAH to Onset of VS</th>
<th>VS to Start of NDP</th>
<th>Localization of Spasm</th>
<th>Intravenous NDP (mg)</th>
<th>Oral NDP (mg)</th>
<th>Response to NDP</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58, F</td>
<td>rt MCA</td>
<td>I</td>
<td>III</td>
<td>19 hrs</td>
<td>7 days</td>
<td>2 hrs</td>
<td>bilat A1, A2, MCA, ICA</td>
<td>0.068</td>
<td>1090</td>
<td>720</td>
</tr>
<tr>
<td>2</td>
<td>15, F</td>
<td>basilar artery</td>
<td>I</td>
<td>IV-V</td>
<td>died</td>
<td>6 hrs</td>
<td>6 days</td>
<td>rt A2, MCA, ICA, PCA</td>
<td>0.5</td>
<td>560</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>41, F</td>
<td>lt MCA</td>
<td>III</td>
<td>IV</td>
<td>died</td>
<td>4 hrs</td>
<td>6 hrs</td>
<td>lt A1, A2, MCA, ICA, PCA</td>
<td>0.5</td>
<td>280</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>55, M</td>
<td>ACoA</td>
<td>III</td>
<td>IV</td>
<td>died</td>
<td>10 hrs</td>
<td>20 hrs</td>
<td>rt A1, A2, ICA, ICA</td>
<td>0.5</td>
<td>220</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>41, M</td>
<td>lt MCA</td>
<td>I</td>
<td>I</td>
<td>7 hrs</td>
<td>1 day</td>
<td>4 hrs</td>
<td>lt MCA</td>
<td>0.5</td>
<td>1200</td>
<td>1200</td>
</tr>
<tr>
<td>6</td>
<td>62, M</td>
<td>rt MCA</td>
<td>I</td>
<td>II</td>
<td>8 days</td>
<td>9 days</td>
<td>5 hrs</td>
<td>rt MCA, lt A1, lt ICA</td>
<td>1.0</td>
<td>1190</td>
<td>720</td>
</tr>
</tbody>
</table>

* Abbreviations: SAH = subarachnoid hemorrhage; VS = cerebral vasospasm; MCA = middle cerebral artery; A1 = precommunicating portion of anterior cerebral artery (ACA); A2 = pericallosal ACA; ICA = internal carotid artery; PCA = posterior cerebral artery; ACoA = anterior communicating artery.

report to make general statements, one can say that the primary changes in the vessel wall that lead to vasospasm occur at an early stage after SAH, and that the nature of these changes is thus far unknown. Vasospasm may, at the time we are able to diagnose it because of the appearance of clinical signs, be accompanied by structural swelling of the vessel wall. Mizukami, et al.,28 showed that, in the acute stage of vasospasm, narrowing of cerebral vessels is caused by contraction of smooth-muscle cells. But in the subacute stage there are histological changes in the vessel wall caused by the long-lasting muscle contraction, with medial thickening, intimal edema, and corrugation of the internal elastic lamina.

Angiographic demonstration of cerebral arterial luminal narrowing at the subacute stage, which is considered as cerebral arterial spasm, therefore is more likely to be a luminal narrowing caused by swelling of the vessel wall and will not be reversible by muscle relaxation alone. This is confirmed by our study, although our findings must be regarded as preliminary and in need of confirmation. Furthermore, the dilatation of previously vasospastic vessels, as seen in our patients, could be explained as a beneficial effect of intravenous application of nimodipine, but it can also be explained as a dilatation caused by necrosis of the smooth-muscle cells as a natural course of the vasospasm, as was shown in the study of Mizukami, et al.28 From a theoretical point of view, it seems possible to prevent vasospasm if the smooth-muscle contraction can be prevented within a few hours after the SAH. A recent study1 has shown a beneficial effect of prophylactic oral administration of nimodipine. The results of a study with constant intravenous application of nimodipine within 24 hours after SAH, as performed in our clinic since April, 1983, will be published later.

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