A randomized placebo-controlled double-blind trial of nimodipine after SAH in monkeys

Part 1: Clinical and radiological findings

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The authors have developed a method to induce chronic cerebral vasospasm after subarachnoid hemorrhage (SAH) in monkeys. With microsurgical techniques, 33 monkeys had a frontotemporal craniectomy and unilateral opening of the subarachnoid cisterns. Cerebrospinal fluid was drained and a fresh hematoma, obtained from an average of 7 ml of autologous blood, was carefully placed against the major arteries of the anterior circulation on one side. The 30 monkeys studied for 7 to 14 days after the SAH were allocated randomly to two treatment groups of 15: one group received placebo and the other nimodipine, 1 mg/kg every 8 hours. Indices monitored before and after SAH included neurological status, cerebral blood flow, computerized tomography, and angiographic vessel caliber.

In the placebo group, delayed ischemic neurological deficit developed in one monkey 4 days after clot placement and was present at sacrifice on Day 14. No such deficit occurred in the nimodipine group. The effect of nimodipine on vessel caliber at this dosage was equivocal. Significant vasospasm (31% to 100% reduction in vessel caliber) developed in 87% (26 of 30) of the animals. Overall, vasospasm was slightly more common in the placebo group: in this group, on Days 7 and 14, the incidence of vasospasm was significantly higher (p < 0.05) than in the nimodipine group. However, the average percentage reduction in vessel caliber of the maximally constricted vessel in each monkey was not significantly different between the two groups.

Key Words: subarachnoid hemorrhage • cerebral vasospasm • nimodipine • computerized tomography

A large collection of blood in the basal cisterns of patients with ruptured aneurysms and of experimental animals has been considered to be the single most important factor governing the development of chronic severe cerebral vasospasm and delayed ischemic neurological deficits. At present, there is no definitive treatment to prevent the deterioration in neurological status which can result from vasospasm. Numerous pharmacological agents have been tried in order to relieve vasospasm, usually unsuccessfully. There is some recent evidence, however, that the calcium entry blocker, nimodipine, given orally in doses of 0.35 mg/kg every 4 hours is effective in preventing neurological deficits produced by cerebral arterial spasm in humans. The present study in monkeys was designed to create a reproducible model of chronic cerebral vasospasm by mimicking a large localized subarachnoid hemorrhage (SAH), and to investigate the efficacy of nimodipine in preventing cerebral vasospasm.

Materials and Methods

Preparation

We studied 33 female cynomolgus monkeys (Macaca fascicularis) with an average weight of 3.2 kg (range 2.5 to 4.3 kg). Three monkeys died shortly after the induction of SAH; the remaining 30 monkeys, studied for 7 to 14 days post-SAH, are the subject of this report. The pathological study is described in Part 2 of this paper.
mography (CT) scans. Baseline values were established, and neurological assessment and CT scanning were performed (during the control period) 3 to 7 days before the SAH was created on Day 0. Neurological assessment was performed daily thereafter and the other investigations were carried out on Days 7 and 14. For each monkey, alterations in vessel caliber, CBF, and MABP after creation of the SAH were calculated as percentage changes from baseline values.

Anesthesia was induced with ketamine hydrochloride, 6 to 10 mg/kg given intramuscularly (control period and Days 7 and 14), or sodium pentobarbital, 26 mg/kg given intravenously (Day 0) and supplemented with a 2:1 mixture of N₂O:O₂ administered with a variable-phase respirator* via an endotracheal tube. The cephalic vein was cannulated for the administration of drugs and fluids. Paralysis was induced and maintained with intravenous gallamine, 2 mg/kg repeated every 45 minutes. Procaine penicillin, 100,000 units/kg, was injected intramuscularly 30 to 60 minutes before surgery. Body temperature was monitored with a rectal thermometer† and was maintained at 37°C by means of a heating pad beneath the monkey. Sterile surgical technique was employed. The femoral artery on either side was catheterized for retrograde femorocerebral angiography with a No. 5 French radiopaque, sigmoid-tip polyethylene catheter. Under fluoroscopic control, the catheter was placed in the innominate artery and intermittent flushing was carried out with 1.0 ml of 0.9% saline with heparin (10 U/ml). When variables were tested, PaCO₂ was kept as close as possible to 38 mm Hg and, when the SAH was induced, it was maintained between 30 and 35 mm Hg. The catheter was connected to a three-way stopcock and to an injector for the administration of xenon-133 (¹³³Xe), a Cordis injector‡ for administering iothalamate meglumine, and a pressure transducer for monitoring arterial blood pressure.§

Induction of Subarachnoid Hemorrhage

A right frontotemporal craniectomy was carried out in 28 animals and a left approach was utilized in two. With the use of an operating microscope, the arachnoid cisterns over the internal carotid artery (ICA), posterior communicating artery (PCoA), middle cerebral artery (MCA), and anterior cerebral artery (ACA) were very carefully opened. Cerebrospinal fluid (CSF), 3 to 4 ml, was drained by suction. The clot, from an average of 7 ml (range 5 to 9 ml) of arterial blood, was placed (maximum volume possible) over the exposed arteries (Fig. 1). The dura was closed in a watertight fashion with 7-0 silk and the incision was closed in layers with 2-0 silk and 3-0 nylon. At the end of the experiment, the paralysis was reversed with prostigmine (0.07 mg/kg) and atropine (0.02 mg/kg) administered intravenously, and the catheters and endotracheal tube were removed.

Preparation and Administration of Drugs

The medication was prepared by a pharmacist (Faculty of Pharmacy, University of Alberta) not otherwise connected with the study, who maintained the codes sealed until the experiments and statistical evaluation were completed. A solution of polyethylene glycol 400 was prepared, and each of the 30 animals received 50 ml; the preparation for 15 monkeys contained nimodipine in a concentration of 3 mg/ml. Drugs were prepared and administered to the monkeys under gold light,¶ and protected in amber bottles. The medication was started 20 hours after the SAH and given at 0730, 1530, and 2330 hours daily until Day 14 post-SAH.

The animals would not swallow food containing nimodipine and therefore both groups were sedated with ketamine, 6 to 10 mg/kg intramuscularly. A nasogastric tube was then passed and the drug or placebo administered.

Neurological Assessment

Each monkey underwent neurological examination before and 5 hours after SAH, and daily thereafter until it was sacrificed under general anesthesia. A five-division neurological grading system was used for evaluation;¹² in this system Grade 1 indicated normal and Grade 5 moribund.

Radiological Assessment

Cranial CT studies were performed and graded as in our previous study.⁶ Retrograde femorocerebral angiography was performed (after CBF studies) using the catheter previously described. One anteroposterior film was obtained during the arterial phase, 1 week before creation of the SAH, and on Days 7 and 14. Cerebral vessels were measured bilaterally at 10 points: the extradural ICA (just before entrance into the cavernous sinus), the segment of the ICA between the PCoA and ophthalmic artery, the sphenoidal MCA, the ACA, and the proximal and distal pericallosal arteries. Conray 60 (iothalamate meglumine) was injected at a rate of approximately 10 ml/sec for 1 second at 300 psi. Magnification factors were constant and a radiopaque control tube was used to correct for variation in films, exposure, and development. A previously calibrated (1:1) optical measuring system was used to measure each arterial point six times and the mean value was calculated. Serial measurements were plotted as percentage change in vessel caliber and vasospasm was graded as

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* Variable-phase respirator manufactured by Harvard Apparatus, Inc., Dover Road, Milis, Massachusetts.
† Tele-Thermometer manufactured by Yellow Springs Instrument Co., Yellow Springs, Ohio.
‡ Injector manufactured by Cordis Corp., Miami, Florida.
§ Pressure transducer, P23dB, manufactured by Statham Instrument Co., 2230 Statham Boulevard, Oxnard, California.

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FIG. 1. Operative pictures taken through the microscope. **Upper Left:** Normal intracranial structures are seen after the arachnoid membrane was opened. 2 = optic nerve; c = internal carotid artery; m = middle cerebral artery; a = anterior cerebral artery. Notice that there is no vasospasm and no bleeding from surgery. **Upper Right:** A small fragment of blood clot has been placed against c. **Lower Left:** A larger volume of blood clot has been placed against c, m, and a. Notice acute vasospasm induced by the hematoma. **Lower Right:** A clot from 7 ml of blood fills the middle fossa.

follows: -1% to -10% = none; -11% to -30% = mild; -31% to -50% = moderate; and 51% or greater reduction = severe. At the end of the study, we determined the overall incidence of vasospasm, its time course, and the reduction in vessel caliber (based on the maximally constricted vessel) in each monkey. The angiographic appearance of collateral circulation was assessed on Days 7 and 14 by angiography and graded as follows: 0 = none; + = small vessel not previously seen on control or mild dilation in previously apparent vessel; ++ = medium-sized new channel; +++ = large-sized new channel.

**Cerebral Blood Flow**

Two CBF measurements were made before cerebral angiography on each occasion, and 2 to 3 hours or 6 to 7 hours after medication. Hemispheric CBF was determined bilaterally by intra-arterial $^{133}$Xe clearance technique, using a single collimated scintillation detector (1 in. in diameter, activated with NaI-thallium) which recorded the radioactivity from the dorsolateral frontal-parietal brain regions. The CBF values were calculated by the initial slope index method and were corrected to a PaCO$_2$ of 40 mm Hg.

**Analysis of Data**

Data for all monkeys were coded, entered into a computer, and edited. Descriptive statistics and frequencies were determined for each variable at each time period. Relationships between vasospasm and CBF at each time period were determined by Pearson's correlation coefficient.

Changes in CBF were compared between the two groups by two-sample t-tests. The incidence of vasospasm within each group and collateral circulation were analyzed by the Fisher-Irwin test. The degree of vasospasm across time and between groups was compared by the analysis of variance, and changes in MABP across time were assessed by analysis of covariance with the covariate being the initial value of MABP. The level of significance for all tests of comparison or association was $p < 0.05$. 

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TABLE 1

Control values for measured and observed indices*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Group</th>
<th>Nimodipine Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of monkeys</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>body weight (kg)</td>
<td>3.3 ± 0.4</td>
<td>3.2 ± 0.4</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>119 ± 9</td>
<td>126 ± 14</td>
</tr>
<tr>
<td>heart rate (/min)</td>
<td>172 ± 20</td>
<td>184 ± 20</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>38 ± 2</td>
<td>36 ± 2</td>
</tr>
<tr>
<td>vessel caliber (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.6 ± 0.2</td>
<td>1.5 ± 0.3</td>
</tr>
<tr>
<td>2</td>
<td>1.6 ± 0.2</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>3</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>4</td>
<td>1.3 ± 0.2</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>ACA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.8 ± 0.2</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>6</td>
<td>0.9 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
<tr>
<td>MCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>8</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>PCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>10</td>
<td>0.8 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>hemispheric CBF (ml/100 gm/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>right</td>
<td>44 ± 10</td>
<td>43 ± 10</td>
</tr>
<tr>
<td>left</td>
<td>42 ± 10</td>
<td>44 ± 14</td>
</tr>
<tr>
<td>size of hematoma (cc)</td>
<td>7.3 ± 1.1</td>
<td>7.1 ± 1.1</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviation. MABP = mean arterial blood pressure; ICA = internal carotid artery (1 = right extradural ICA, 2 = left extradural ICA, 3 = right supracranial ICA, 4 = left supracranial ICA); ACA = anterior cerebral artery (5 = right ACA, 6 = left ACA); MCA = middle cerebral artery (7 = right sphenoidal MCA, 8 = left sphenoidal MCA); PCA = pericallosal artery (9 = proximal pericallosal artery, 10 = distal pericallosal artery); CBF = cerebral blood flow.

Results

A total of 121 sets of measurements were completed on the 30 monkeys within a 6-month period. Two animals in the nimodipine group died; one from a lethal dose of contrast medium associated with a difficult catheterization on Day 7, and the other, after being well throughout the study, suffocated itself with the cage's food container on Day 13.

The hemorrhage as seen on the first CT scan after its creation was graded as large in all 30 monkeys. Comparisons of the two groups showed no significant differences in pre-SAH values for body weight, the measured physiological indices, cerebral vessel caliber, or volume of the hematoma placed intracranially (Table 1). There were no significant alterations between groups in average values for body weight, PaCO₂, PaO₂, or MABP. There were no side effects from either nimodipine or placebo in any animal.

Neurological Assessment

In one animal from the placebo group, delayed hemiparesis developed on Day 4, contralateral to the side of clot placement (Fig. 2). Function in its leg improved by Day 10, but the arm remained severely weak until sacrifice on Day 14. The angiograms (Fig. 3) showed severe vasospasm of the right MCA on both Days 4 and 7. The CT scans (Fig. 4) showed a wedge-shaped low-density area in the distribution of the right MCA on Days 7 and 13. No animal in the nimodipine group had a delayed ischemic neurological deficit.

Incidence of Vasospasm

Vasospasm was considered to be present when the vessel caliber showed a greater than 10% reduction from the control value. It was seen in the placebo group in all 15 monkeys on Day 7, and in 12 (80%) of 15 on Day 14. In the nimodipine group, it was seen in all 15 animals on Day 7, and in 12 (92%) of 13 on Day 14. Moderate vasospasm (31% to 50% reduction in vessel caliber) was more common in the nimodipine group (the difference was not significant). It was seen in the placebo group in 12 (80%) of 15 animals on Day 7, and in four (27%) of 15 on Day 14. In the nimodipine group, moderate vasospasm was seen in 13 (87%) of 15 monkeys on Day 7, and in five (38%) of 13 on Day 14. Severe vasospasm (≥ 51% reduction in vessel caliber) was more common in the placebo group (the difference was not significant). It was apparent in the placebo

Fig. 2. Picture of Monkey 58 taken on Day 7 post-subarachnoid hemorrhage. A left hemiparesis developed in this monkey on Day 4 and persisted until Day 10. From Day 11 to 14, the paresis in its leg improved but remained the same in its upper limb until sacrifice. Note craniectomy incision on the right. Pups were equal and symmetrical.
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FIG. 3. Anteroposterior cerebral angiograms of Monkey 58 which was allocated to the placebo group. C = control angiogram. Note severe vasospasm of the sphenoidal segment of the middle cerebral artery and of the supraclinoid internal carotid artery (large arrows) on Days 4 and 7. There is also moderate spasm of the anterior cerebral artery (medium arrow) and of the extradural internal carotid artery (small arrows) on Days 4 and 7. Note partial reversal of vasospasm which is mild on Day 14.

group in five (33%) of 15 animals on Day 7, and in one (7%) of 15 on Day 14. In the nimodipine group, it was seen in two (13%) of 15 monkeys on Day 7, and in 0 of 13 on Day 14.

Significant vasospasm (31% to 100% reduction in vessel caliber) developed in 26 (87%) of 30 animals (13 in each group). In the placebo group, the average vasospasm (± standard error) was 47% ± 5%, and in the nimodipine group it was 43% ± 5%.

The most frequently and severely affected vessel on Day 7 in the placebo group was the MCA on the clot side (47% of the time). The intradural ICA and the ACA on the clot side were next in frequency (20% each), and the extradural ICA was last in frequency.

FIG. 4. Serial computerized tomography scans of Monkey 58. C = control scan. Thick layers of blood are seen on Day 0 (large arrows) and a wedge-shaped low density area in the distribution of the right middle cerebral artery on Days 7 and 14 (small arrows). Note that the territories of the brain supplied by the anterior cerebral and posterior cerebral arteries are not affected.

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FIG. 5. Incidence of vasospasm (more than 10% reduction in vessel caliber) based on data at the 10 arterial sites in 38 angiograms of the 30 monkeys. Vasospasm was significantly more common on Days 7 and 14 in the placebo group. Figures above the columns indicate the number of animals studied at those times. SAH = subarachnoid hemorrhage; * = p < 0.05.

In the nimodipine group, the most affected vessels were the MCA and intradural ICA (31% of each) on the clot side, followed by the ACA on the same side in frequency (25%), with the pericallosal artery being last in frequency (13%). Calculation of the incidence of vasospasm at the 10 arterial sites in 56 angiograms of 30 monkeys showed that vasospasm occurred significantly more frequently in the placebo group on Days 7 and 14 (p < 0.05) (Fig. 5). Within groups, vasospasm was more frequently seen on the clot side than the non-clot side (p < 0.0001). Intergroup comparison for incidence of vasospasm on the clot side showed no difference but, in the non-clot side, vasospasm was more common in the placebo group than in the nimodipine group (p < 0.01, Fig. 6).

Time Course and Degree of Vasospasm

Overall, vasospasm on the clot side was more common on Day 7 than on Day 14 (p < 0.01) (Figs. 6 and 7). Intergroup comparison showed no difference in severity of vasospasm at any time (Fig. 7). In the placebo group, vasospasm was maximal (mean vessel caliber = 53% of control) on Day 7 and decreased thereafter (Fig. 7). Figures 3 and 8 illustrate the cerebral angiograms of monkeys in the placebo group. In the nimodipine group, vasospasm was also maximal (mean vessel caliber = 57% of control) on Day 7 and decreased by Day 14. Figures 9 and 10 depict angiograms of monkeys in the nimodipine group.

Collateral Circulation

Collateral circulation seen angiographically was an incidental finding. It was maximal on Day 7 and usually returned to the control appearance by Day 14. Figure 8 illustrates a representative case from the placebo group.

<table>
<thead>
<tr>
<th>Grade of Collateral Circulation</th>
<th>Placebo</th>
<th>Nimodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 7</td>
<td>Day 14</td>
</tr>
<tr>
<td></td>
<td>Clot Side</td>
<td>Non-Clot Side</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>+</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>++</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>+++</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Total animals</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

*0 = collateral circulation not seen; + = small new vessel not previously seen on control; ++ = medium-sized new channel; +++ = large-sized new channel; — = absent.

†Two animals died before Day 14 (see text).
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Fig. 7. Time course of vasospasm and mean (± SE) percentage change in vessel caliber based on measurements of the vessel maximally constricted in each monkey. In both groups, vasospasm was significantly greater (p < 0.001) on the clot side on Day 7. Between groups, there was no significant difference in degree of vasospasm. Figures above and below standard error bars indicate number of animals studied at those times. SAH = subarachnoid hemorrhage; ns = not significant.

Group with both severe vasospasm and increased collateral circulation on Day 7. Figures 9 and 10 depict representative cases from the nimodipine group with both severe vasospasm and increased collateral circulation on Day 7. Intergroup comparison for the presence of collateral circulation showed no significant difference (Table 2).

Cerebral Blood Flow

Hemispheric CBF was not significantly different between sides, days post-SAH, or treatment groups. Nimodipine had not increased CBF when measured 2 and 6 hours after it was given on Days 7 and 14 post-SAH.

Discussion

The high reproducibility with which cerebral vasospasm occurred in this primate model makes it an attractive and reliable one for assessing various therapies for prevention and treatment of vasospasm in man. The time course, the association with a large collection of blood in the subarachnoid space, and the fact that vasospasm can cause obvious neurological deficits of delayed onset are all features which are identical to the human syndrome. However, when assessing any treatment for neurological deficits from vasospasm, we have to take into account the anatomical and physiological variations of the collateral circulation between species.

The failure to demonstrate a reduction in hemispheric CBF was probably due to the collateral circulation which compensated for the vasospasm present. In addition, the size of the detectors did not permit selective assessment of CBF supply to the territory of the MCA. Harper, et al., reported increases in CBF while nimodipine was being administered through an intravenous or intra-arterial catheter, and up to 20 minutes after the drug was stopped. We did not observe any significant increase in CBF by 2 and 6 hours after nimodipine was given orally (1 gm/kg) on Days 7 and 14 post-SAH.

Cerebral arterial spasm likely originates from the interaction of multiple factors that ultimately induce contraction by increasing the concentration of free intracellular calcium. It might be expected that, by blocking the ingress of calcium to the smooth-muscle cell, cerebral vasospasm can be prevented or diminished despite its multiplex origin. In vitro studies using dog basilar and femoral arteries have demonstrated that nifedipine and nimodipine inhibit contractions induced...
by serotonin, phenylephrine, and KCl. In that study, nimodipine had a more potent effect on the basilar artery and it showed a greater inhibitory effect than nifedipine. The preferential effect of nimodipine on cerebral vessels has been confirmed by others. In vivo studies have also reported a beneficial effect of both nifedipine and nimodipine in the prevention and treatment of cerebral vasospasm in dogs. In these studies, nifedipine in a dose of 1 mg/kg reversed both the acute and early chronic (2-day) phases of vasospasm. Also, nimodipine proved to be more effective than nifedipine in reversing acute vasospasm when both drugs were given in a dose of 0.28 mg/kg. Nimodipine was not tested at 2 days or longer after SAH.

Our results do not entirely agree with previous investigations. Compared to placebo, nimodipine in a dose of 1 mg/kg given orally every 8 hours reduced the overall number of vessels in spasm on Days 7 and 14 post-SAH. However, when assessing vasospasm by side, nimodipine did not improve the incidence or the severity of chronic vasospasm on the clot side. The beneficial effect of nimodipine was observed only on the control or non-clot side. This suggests that the trial drug (at the given doses) prevents acute and chronic spasm of vessels exposed to low concentrations of vasoactive substances derived from blood. This applies to our control or non-clot side, and perhaps to the experiments of Cohen and Allen in which they used 2.5 ml of autogenous blood to create an SAH in dogs. These

Fig. 9. Anteroposterior cerebral angiograms of Monkey 57 which was allocated to the nimodipine group. C = control angiogram. There is moderate vasospasm of the middle cerebral and internal carotid arteries (arrows) on Day 7. Note new large-sized collateral circulation (open arrowhead) on Days 7 and 14. Vasospasm is gone by Day 14.

Fig. 10. Anteroposterior cerebral angiograms of Monkey 68 which was allocated to the nimodipine group. C = control angiogram. There is severe vasospasm of the middle cerebral and internal carotid arteries (large arrows) and of the anterior cerebral artery (medium arrow) on Day 7, but spasm is gone by Day 14. Note medium-sized new collateral circulation (open arrowhead) on Day 7 when spasm is maximal. There is also dilation (W) of the insular middle cerebral artery on Day 7.
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authors assessed the efficacy of nimodipine in reversing acute vasospasm (at 80 minutes post-SAH) rather than chronic vasospasm (7 to 14 days after SAH); the factors involved in the genesis of acute and chronic vasospasm may be different. It is chronic vasospasm that causes ischemia of delayed onset.8,13

In a recent clinical trial of nimodipine by Allen, et al.,2 severe, delayed, and persistent neurological deficits or death were caused by vasospasm alone in nine (7.2%) of 125 patients; it was seen in eight who were given placebo and in one who received nimodipine 0.35 mg/kg every 4 hours. The authors concluded that nimodipine significantly improved the neurological outcome of patients who developed deficits from vasospasm.

In our study, delayed ischemic neurological deficit occurred in one monkey only (3.3%). Presumably one of the factors that prevented the deterioration in neurological status from vasospasm in these young female monkeys is the ability of collateral circulation to develop at the time when vasospasm is maximal.

Although we used a larger dose of nimodipine (1 mg/kg every 8 hours) compared to the clinical study (0.35 mg/kg every 4 hours), nimodipine did not improve the incidence or reduce the severity of chronic vasospasm (clot side) when compared to placebo. It is possible that nimodipine may not be as effective when given every 8 hours as when it is administered every 4 hours. The most effective dosage of nimodipine remains to be determined. Since no clear beneficial or negative side effects were observed with 1 mg/kg every 8 hours, further trials with increased doses of this calcium entry blocker are under way in our laboratory.

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References


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