Combination of Aminocaproic Acid and Nicardipine in Treatment of Aneurysmal Subarachnoid Hemorrhage

David W. Beck, MD, Harold P. Adams, MD, Eugene S. Flamm, MD, John C. Godersky, MD, and Christopher M. Loftus, MD

Antifibrinolytic drugs reduce the risk of rebleeding during the first 2 weeks after aneurysmal subarachnoid hemorrhage. However, they do not lower overall mortality, largely because of an increased incidence of cerebral ischemia. The usefulness of antifibrinolytic drugs might be increased if a method to prevent or control vasospasm in patients were to be developed. We recently completed late Phase I and Phase II studies of the calcium ion blocking drug nicardipine in 67 patients treated within 1 week of subarachnoid hemorrhage. Of these 67 patients, 42 had delayed operations and were treated concomitantly with the antifibrinolytic drug aminocaproic acid (1.5 g/hr) for an average of 6 days before surgery. The outcome of these 42 patients is the subject of this report. Fifteen of 42 patients were treated with the lower dosage levels of nicardipine (0.4-4.5 mg/m²/hr), and 27 patients were treated at the highest dosage level (6.0 mg/m²/hr). Using the World Federation of Neurological Surgeons scale for subarachnoid hemorrhage, at admission 18 patients were Grade I, 15 were Grade II, 6 were Grade III, and 3 were Grade IV. Five patients (12%) developed clinical signs of deterioration suggestive of cerebral ischemia with concomitant evidence of vasospasm on arteriography. These patients were all treated with hypervolemic hypertensive therapy. Only one patient (2%) developed an infarction from vasospasm. Two patients developed symptomatic hydrocephalus requiring ventriculoperitoneal shunting, and a third patient required a temporary ventriculostomy. The 3-month postoperative outcomes were excellent. Three patients (7%) rebled. Three patients died, two from rebleeding of the aneurysm and one who never regained consciousness from the initial hemorrhage. Thirty-two patients (76%) were Grade I at 3 months after the subarachnoid hemorrhage. These data suggest that the incidence of vasospasm and cerebral ischemia among patients with antifibrinolytic drugs can be lowered by the concomitant use of a calcium ion blocker. Further investigation of this combination of drugs in patients with recent subarachnoid hemorrhage is warranted. (Stroke 1988;19:63-67)

The use of antifibrinolytic drugs in the management of aneurysmal subarachnoid hemorrhage (SAH) is controversial. Recently two large multicenter trials showed that the risk of rebleeding was substantially reduced in patients receiving antifibrinolytic drugs compared with a comparable group of patients not receiving antifibrinolytic drugs. However, the overall mortality rate at 3 months between the groups was similar. The reduction of mortality due to rebleeding was negated by increased mortality due to cerebral ischemia among the patients given antifibrinolytic drugs. Antifibrinolytic drugs could become a useful preoperative therapy in patients with recent SAH if the risks of vasospasm and cerebral ischemia could be reduced.

We recently performed a prospective dosage escalation study of nicardipine, a dihydropyridine calcium ion entry blocking agent that preferentially binds to cerebrovascular smooth muscle, in 67 patients with recent SAH. Forty-two patients had delayed operations planned for the treatment of the aneurysm and were given aminocaproic acid before surgery. These 42 patients were studied for any effect on the incidence and severity of symptomatic vasospasm by the concomitant administration of nicardipine and aminocaproic acid.

Subjects and Methods

Patients between the ages of 18 and 75 admitted to University of Iowa Hospitals or to New York University Medical Center within 7 calendar days of SAH from a documented cerebral aneurysm were included in the study. The details of this study are described elsewhere. In all cases, blood in the subarachnoid space was evident on either computed tomography (CT) or nontraumatic lumbar puncture. Cerebral angiography to demonstrate the presence of a saccular aneurysm and the absence of vasospasm was performed before patients were entered into the study. Patients were excluded if they were deeply comatose, if they had a large intracerebral hemorrhage, or if arterial narrowing was found on the initial arteriogram. Patients were also excluded if they were taking a calcium ion blocking...
drug before entry into the study. Informed consent was obtained from the patient or next of kin.

Patients were admitted to either an intensive care unit or to a stroke care unit. Nicardipine, donated by Syntex Research (Palo Alto, California), was given intravenously in normal saline as a constant infusion until 14 days after SAH. Seven dosage levels of nicardipine were evaluated, and patients were observed for any side effects at each level before escalation to a higher one. The details of this dosage escalation study are described in another publication. The treating neurosurgeon opted for early or delayed operation on a case-by-case basis; no specific criteria were used. Aminocaproic acid was given initially as a 5-g bolus either intravenously or orally, followed by 1.5 g/hr in patients for whom delayed surgery was planned.

Other therapies were prescribed as indicated. Hypervolemic therapy or drug-induced hypertensive therapy was prescribed for patients with symptoms of cerebral ischemia. Hypervolemic therapy included expansion of intravascular fluids with colloid solutions or plasmapheresis to a central venous pressure of 8–12 cm water or a pulmonary wedge pressure of 16–20 mm Hg. If systolic blood pressure was not raised sufficiently by these means, vasopressors, primarily dopamine, were given to raise systolic blood pressure by 20–50 mm Hg. The decisions for symptomatic treatment of vasospasm with hypervolemic and hypertensive agents were made on a case-by-case basis and followed the guidelines outlined previously. Aminocaproic acid was discontinued if ischemic symptoms appeared.

All patients underwent repeat arteriography 7–10 days after SAH to assess evidence of angiographic vasospasm. Severity of vasospasm seen by arteriography was measured by the scale used by the Cooperative Aneurysm Study (N.F. Kassell, "Cooperative study on timing of aneurysm surgery," presented at the annual meeting of the American Association of Neurological Surgeons, Atlanta, Georgia, April 23, 1985).

Twelve patients (29%) developed arterial narrowing 7–10 days after SAH and 3 months later to record infarction or the presence of hydrocephalus. The World Federation of Neurological Surgeons (WFNS) grading scale for SAH was recorded daily during hospitalization. At 3 months the Glasgow Outcome Scale was used to record the degree of recovery.

Results

Forty-two patients were treated concomitantly with aminocaproic acid and nicardipine. The average duration of treatment with aminocaproic acid was 6 (range 2–13) days. The patients ranged in age from 30 to 72 (mean 48.5) years. Twenty-five patients were men and 17 were women. The interval from SAH until hospital admission and institution of medical treatment was 0–1 days in 9 patients, 2–3 days in 11 patients, and 4–7 days in 22 patients. Using the WFNS scale, at admission 18 patients were Grade I, 15 were Grade II, 5 were Grade III-A, 1 was Grade III-B, and 3 were Grade IV. Sites of the ruptured aneurysms are listed in Table 2. CT scans on admission were categorized using the criteria of Fisher et al and demonstrated diffuse thick subarachnoid collections of blood in 12 patients, diffuse thin collections in 11, focal thick collections in 2, and focal thin subarachnoid blood in 7; 1 patient had an intraparenchymal hematoma, and 9 had normal CT studies. Seven dosage levels of nicardipine were used, with 27 of the 42 patients receiving nicardipine at the highest level (Table 3). Nicardipine was administered until the fourteenth day after SAH. All but one patient underwent operative repair of the aneurysm. The timing of surgery after SAH is shown in Table 4.

Twelve patients (29%) developed arterial narrowing demonstrated by arteriography performed 7–10 days after SAH (Table 5). This includes 8 of 15 patients (53%) who received nicardipine at dosage levels I–VI.

### Table 1. World Federation of Neurological Surgeons Grading Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Unruptured aneurysm in subarachnoid space</td>
</tr>
<tr>
<td>1</td>
<td>Neurologically intact except for cranial nerve palsy (Glasgow Coma Scale 15)</td>
</tr>
<tr>
<td>I-A</td>
<td>Persistent neurologic deficit &gt;3 weeks after subarachnoid hemorrhage</td>
</tr>
<tr>
<td>II</td>
<td>Neurologically intact except for cranial nerve palsy, with neck stiffness, headache, or both (Glasgow Coma Scale 15)</td>
</tr>
<tr>
<td>III</td>
<td>Glasgow Coma Scale 13–14</td>
</tr>
<tr>
<td>III-A</td>
<td>Without focal neurologic deficit</td>
</tr>
<tr>
<td>III-B</td>
<td>With focal neurologic deficit</td>
</tr>
<tr>
<td>IV</td>
<td>Glasgow Coma Scale 8–12, with or without focal neurologic deficit</td>
</tr>
<tr>
<td>V</td>
<td>Unresponsive coma with or without abnormal posturing (Glasgow Coma Scale less than 8)</td>
</tr>
</tbody>
</table>

### Table 2. Site of Aneurysm Responsible for Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Site</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmic artery</td>
<td>2</td>
</tr>
<tr>
<td>Posterior communicating artery</td>
<td>11</td>
</tr>
<tr>
<td>Carotid bifurcation</td>
<td>2</td>
</tr>
<tr>
<td>Anterior communicating artery</td>
<td>15</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>3</td>
</tr>
<tr>
<td>Anterior choroidal artery</td>
<td>1</td>
</tr>
<tr>
<td>Basilar artery tip</td>
<td>3</td>
</tr>
<tr>
<td>Basilar artery trunk</td>
<td>1</td>
</tr>
<tr>
<td>Vertebral junction</td>
<td>2</td>
</tr>
<tr>
<td>Posterior inferior cerebellar artery</td>
<td>2</td>
</tr>
</tbody>
</table>
and 4 of 27 patients (15%) who received nicardipine at the highest level, VII. The severity of the angiographic vasospasm using the Cooperative Aneurysm Study scale is also shown in Table 5.

Five patients (12%) developed clinical signs of deterioration suggestive of cerebral ischemia with concomitant evidence of vasospasm on arteriography. These patients were all treated with hypervolemic hypertensive therapy. Only one of these patients (4%) received nicardipine at the highest dosage level (Table 5). That patient had a left posterior communicating artery aneurysm and developed an infarction from vasospasm in the left anterior cerebral artery distribution demonstrated on CT scan. The other four patients did well, and their signs of cerebral ischemia resolved. These four patients had normal CT scans and normal neurologic examinations on 3-month follow-up.

Three patients developed symptomatic hydrocephalus; two underwent ventriculoperitoneal shunting and one underwent ventriculostomy. This patient did not require a shunt after his ventriculostomy was removed.

Aminocaproic acid and nicardipine were very well tolerated. No permanent sequelae could be attributed to either drug. Symptomatic hypotension was rarely seen, although isolated systolic blood pressure of ≤100 mm Hg was noted in 19 patients, 15 of whom were treated at dosage level VII. Possible side effects among our patients receiving nicardipine with and without concomitant antifibrinolytic therapy are described in another paper.7

The outcomes at 3 months after SAH are shown in Table 6. Three patients (7%) rebled. Three patients died, two from rebleeding of the aneurysm and one who never regained consciousness after the initial SAH. This patient died in a nursing home of congestive heart failure. Thirty-two patients (76%) were Grade I at 3 months after SAH.

### Discussion

The two major complications from aneurysmal SAH in patients who survive the initial hemorrhage are rebleeding from the aneurysm and cerebral ischemia secondary to vasospasm. In patients for whom delayed surgery is planned, antifibrinolytic therapy has been used in an attempt to prevent rebleeding from the aneurysm. Several small uncontrolled studies have shown favorable results.12,13 The efficacy of antifibrinolytic drugs in the prevention of rebleeding has been clarified by recent reports.4,6 In the Dutch-British study, 285 patients with angiographically proven aneurysmal SAH were randomized to tranexamic acid (130 patients) or placebo (155 patients). In the tranexamic acid-treated group, 13 patients (10%) rebled compared with 35 patients (23%) in the placebo group.5 The Cooperative Aneurysm Study compared the rebleeding rate of 672 matched patients who received antifibrinolytic drugs (467 patients) or no antifibrinolytic drugs (205 patients).4,6 All 672 patients had delayed intracranial operations. The incidence of rebleeding by 14 days after SAH was significantly reduced in the antifi-
Table 6. Clinical Outcome at 3 Months After Subarachnoid Hemorrhage Using the Glasgow Outcome Scale in Patients Receiving Aminocaproic Acid and Nicardipine

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dosage levels I–VI</th>
<th>n = 15</th>
<th>%</th>
<th>Dosage level VII</th>
<th>n = 27</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td>12</td>
<td>80</td>
<td></td>
<td>20</td>
<td>74</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td>2</td>
<td>13</td>
<td></td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td></td>
<td>1</td>
<td>7</td>
<td></td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

brinolytic-treated group (11.7%) compared with the group that received no antifibrinolytic drug (19.4%).

Unfortunately, while antifibrinolytic drugs reduced the risk of rebleeding, the overall management outcome was not significantly different, primarily because of a high incidence of cerebral infarction due to vasospasm. Similar results were recorded by Fodstad in a randomized study of tranexamic acid. This group found that the mortality rate was higher in patients who received antifibrinolytic therapy, despite a lower rebleeding rate. Most of the patients in the antifibrinolytic-treated group developed cerebral infarction, a cause for the increased mortality rate. Ameen and Illingworth noted similar results.

The interaction between antifibrinolytic agents and the development of vasospasm is not known. It is speculated that antifibrinolytic drugs delay clearance of the blood from the subarachnoid space and allow the factors that cause vasospasm to persist. The severity of vasospasm appears to be related to the amount and duration of blood in the basal cisterns.

The overall management outcome in patients with aneurysmal SAH for whom delayed surgery is planned may be improved if the reduced risk of rebleeding brought about by antifibrinolytic drug administration could be combined with an agent that would prevent ischemic complications. Recent work on vasospasm has centered on the use of drugs that increase intracellular calcium or that decrease calcium entry into vascular smooth muscle. Nicardipine appears to be an ideal calcium ion entry blocking drug for use in SAH because its major effect is on cerebral vascular smooth muscle and because experimentally it has been shown to reverse experimental cerebral vasoconstriction and to prevent ischemic damage. We found that the incidence of symptomatic vasospasm was quite low (12%) in patients receiving both aminocaproic acid and nicardipine. At the highest dosage level of nicardipine, the incidence of ischemic complications was only 4%; this is in contrast to the Cooperative Aneurysm Study, which reported a 34% incidence of focal ischemic deficits in 467 patients receiving only antifibrinolytic agents, and to the Dutch-British study, which reported a 24% incidence of cerebral infarction secondary to vasospasm in patients treated with antifibrinolytic drugs.

The overall management outcome in our patients was excellent, with a mortality rate of 7%; 76% of the survivors had no neurologic deficit 3 months after SAH. Again, these results compare quite favorably with the Cooperative Aneurysm Study, which reported a 22% 30-day mortality rate in patients receiving antifibrinolytic drugs, and with the Dutch-British study, which reported a 28% mortality rate at 3 months after aneurysmal SAH in patients receiving antifibrinolytic drugs.

The results of our study are very promising. They suggest that the high rate of ischemic complications seen with the use of antifibrinolytic agents can be markedly reduced by the concomitant administration of the calcium channel blocking agent nicardipine. These data provide a strong impetus for a randomized double-blind clinical trial of nicardipine in conjunction with antifibrinolytic drugs in patients with SAH to determine the efficacy of this combination therapy. For surgeons who prefer to delay surgery in the treatment of aneurysmal SAH, this information may be critical to the overall management.

References
15. Ameen AA, Illingworth R: Antifibrinolytic treatment in the pre-operative management of subarachnoid hemorrhage.

KEY WORDS • calcium channel blockers • antifibrinolytic agents • nicardipine • subarachnoid hemorrhage • cerebral vasospasm • aminocaproic acid
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