ANEURYSMAL subarachnoid hemorrhage (SAH) accounts for approximately 8% of all acute cerebrovascular events, affecting approximately 26,000 Americans each year. Unlike other forms of cerebrovascular disease, the incidence of SAH is not declining. The ultimate mortality of this disease without treatment approaches 50%, most of the deaths occurring in the first two weeks after the hemorrhage, and disabling neurological sequelae are common among survivors. Death and disability result from the acute effects of SAH, including mass effects of a cerebral hematoma or cerebral edema. Acute hydrocephalus or convulsions may develop in the first few days after SAH. Fluid electrolyte imbalances secondary to inappropriate release of antidiuretic hormone may induce convulsions or coma. SAH causes profound rises in serum levels of catecholamines, which can lead to cardiac arrhythmias and myocardial infarction. Respiratory distress, hyperventilation, atelectasis, or pneumonia are known complications of SAH. The stress of the intracranial event may precipitate gastric mucosal ulceration and gastrointestinal hemorrhage. Cerebral vasospasm, a local or generalized narrowing of intracranial arteries, can complicate SAH and lead to cerebral infarction. Vasospasm reaches its peak severity during the first two weeks after SAH.

Recurrent hemorrhage is a major cause of death or serious morbidity among patients who survive the first SAH, reaching its highest incidence in the first 10 to 14 days after the initial hemorrhage. The mortality after a second hemorrhage is approximately twice the rate of a single SAH. Early treatment of patients with SAH should be aimed at prevention of the acute complications of the hemorrhage, especially amelioration of the consequences of cerebral vasospasm, as well as avoidance of rebleeding. While an effective measure to prevent cerebral vasospasm is not available, it has become possible to reduce the frequency of rebleeding.

Prevention of Recurrent Hemorrhage

Intracranial operative clipping of the aneurysmal neck, a procedure which secures the aneurysm from the arterial circulation, is unquestionably the optimal treatment to prevent rebleeding. However, intracranial operation on the aneurysm within the first several days after SAH has been associated with prohibitive morbidity and mortality, sometimes attributed to the aggravation of vasospasm by the operation. Delaying operation until two weeks after SAH allows the patient to recover from the acute effects of the hemorrhage before he is subjected to surgery, although it leaves the patient unprotected against rebleeding during the period of greatest risk of recurrent hemorrhage.

Medical management to prevent rebleeding during the first two weeks after SAH includes bed rest in a quiet environment, sedation, antieerebral edema therapy, anticonvulsant drugs, stool softening agents, analgesic drugs, and careful control of fluid-electrolyte balance. This method of management alone is associated with a 22.6% incidence of rebleeding and a 21% mortality during the first two weeks after SAH.\(^1\) The addition of drug-induced hypotension makes little difference; the frequency of rebleeding in the first 14 days is lowered to 18% and the mortality to 22.3%.\(^2\) Although induced hypotension probably reduces rebleeding by decreasing pressure on the aneurysmal wall, it may have a deleterious effect on patients with symptoms of cerebral ischemia secondary to vasospasm. Aggravation of cerebral ischemia may explain the failure of hypotensive therapy to reduce the early mortality following SAH.

Antifibrinolytic Therapy

The potential effectiveness of antifibrinolytic drugs in reducing early rebleeding from ruptured aneurysms was first reported in the 1960's. Although numerous series evaluating the effectiveness of antifibrinolytic therapy have subsequently appeared, the use of these agents remains controversial. This controversy has resulted partly because some studies show no benefit from antifibrinolytic therapy and because complications may accompany use of these agents.

The increased fibrinolytic activity of the cerebrospinal fluid (CSF) which follows SAH, may dissolve the naturally occurring perianeurysmal clot. Because rebleeding occurs with greatest frequency several days


Dr. Adams, Jr. is Associate Professor, Department of Neurology, University of Iowa College of Medicine, Iowa City, Iowa.

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after SAH, the clot may protect the patient during the first few days. Aminocaproic acid inhibits conversion of plasminogen to plasmin and partially blocks the activity of plasmin (fig. 1). Antifibrinolytic drugs inhibit the proteolytic activity of plasmin by reacting with receptor proteins of plasmin which are involved with fibrin binding. The drugs may also react with fibrin to prevent easy dissolution of the clot. Aminocaproic acid and other drugs, such as tranexamic acid, cross the blood-brain barrier to counteract the increased fibrinolytic activity of CSF. Preserving the intact perianeurysmal clot supports the wall, thus delaying or preventing a second rupture.

While aminocaproic acid and tranexamic acid are the drugs used in therapeutic trials among patients with SAH, only the former is available for patient care in the United States (fig. 2). Aminocaproic acid can be administered intravenously or orally. It is readily absorbed from the gastrointestinal tract, reaching maximum serum levels in two hours. Because a single intravenous dose of aminocaproic acid is rapidly cleared from the blood, it is usually given as a constant infusion. Virtually all of the aminocaproic acid is eliminated in the urine without being metabolized. The serum activity of aminocaproic acid can be monitored by the streptokinase-induced clot lysis time. Serum and CSF levels of aminocaproic acid have not been adequately standardized.

### Results of Clinical Trials

Sengupta et al.\(^5\) compared 76 patients with SAH who were treated with bed rest and sedation with 66 patients who also received aminocaproic acid at a daily dosage of 24 g. None of the patients given aminocaproic acid had recurrent hemorrhage, while 17 of the control patients rebled. Chowdhary et al.\(^5\) reported three instances of rebleeding among 83 patients treated with aminocaproic acid at a daily dosage of 36 g, while 22 of the 82 patients not given fibrinolytic drugs had recurrent hemorrhage. In a randomized controlled trial Fodstad et al.\(^6\) compared 23 patients treated with 6 g of tranexamic acid daily with 23 control patients. During the first six weeks after SAH, the clot may protect the patient during the first few days. Aminocaproic acid inhibits conversion of plasminogen to plasmin and partially blocks the activity of plasmin (fig. 1). Antifibrinolytic drugs inhibit the proteolytic activity of plasmin by reacting with receptor proteins of plasmin which are involved with fibrin binding. The drugs may also react with fibrin to prevent easy dissolution of the clot. Aminocaproic acid and other drugs, such as tranexamic acid, cross the blood-brain barrier to counteract the increased fibrinolytic activity of CSF. Preserving the intact perianeurysmal clot supports the wall, thus delaying or preventing a second rupture.

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### Current Status of Antifibrinolytic Therapy

SAH, rebleeding occurred in none control patients and in one patient treated with tranexamic acid. Maurice-Williams\(^7\) studied 25 patients given tranexamic acid after aneurysmal SAH and 25 patients treated by bed rest and sedation. Six patients given antifibrinolytic therapy had rebleeding, while 14 control patients rebled. In a randomized double-blind study Chandra\(^7\) reported recurrent hemorrhage in 1 of 20 patients given 6 g of tranexamic daily and in 4 of 19 patients receiving conventional therapy.

In a randomized trial of treatment of patients within seven days of SAH, the Cooperative Aneurysm Study initially found a 21.7% incidence of rebleeding within 14 days of SAH among patients treated by drug-induced hypotension compared with a 5.8% incidence of rebleeding among patients given antifibrinolytic therapy.\(^8\) The experience of the cooperative study suggested that antifibrinolytic therapy was superior to bed rest or drug-induced hypotension in the early preoperative management of patients with ruptured aneurysms. Among 471 patients treated with antifibrinolytic drugs within seven days of the initial bleed, the cooperative study found a 12.7% incidence of rebleeding and 11.6% mortality by the end of 14 days after SAH.\(^9\) In a summary report based on 1,114 patients treated with either tranexamic acid or aminocaproic acid, the cooperative study noted 10.0% rebleeding rate and 10.7% mortality within two weeks of SAH.\(^10\) Patients in poor condition or those admitted within three days of SAH had the highest frequency of second hemorrhage.

Other series have demonstrated no reduction in rebleeding with antifibrinolytic therapy. In 1973 Girvin reported no beneficial effect of antifibrinolytic therapy to prevent rebleeding.\(^11\) He noted 17 instances of rebleeding among 39 patients given aminocaproic acid and 3 instances of recurrent hemorrhage among 14 control patients. The dosage of administered aminocaproic acid was not reported. Recently, Shucart et al.\(^12\) compared results of treatment of 45 patients with aminocaproic acid with 55 control patients. All patients were treated within 48 hours of SAH. The daily dosage of aminocaproic acid was 36 g. Rebleeding was confirmed in 11 patients treated with aminocaproic acid and in 4 control patients. In a double-blind study by Van Rossum et al.,\(^13\) 26 patients given 4

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**Figure 1.** Schematic representation of the current theory of blood clot dissolution with the sites of activity of antifibrinolytic agents. (+) = activation; (−) = inhibition.

**Figure 2.** Chemical structures of aminocaproic acid and tranexamic acid.
g of tranexamic acid daily for 10 days were matched with 25 patients given placebo treatment. Rebleeding occurred in five patients given tranexamic acid and in four patients given placebo. Mortality rates were similar in both groups. However, this trial included patients other than those with ruptured aneurysms as the cause of SAH. Kaste and Ramsay\textsuperscript{14} noted no difference in rebleeding or mortality between 32 patients given 6 g of tranexamic acid daily and 32 patients given placebo. A recent report by Gelmers\textsuperscript{15} compared results of antifibrinolytic therapy in 31 patients given 4 g of tranexamic acid daily with 27 control patients. Recurrent hemorrhage developed in 16\% of patients given tranexamic acid and 35\% of control patients. The results did not reach statistical significance, and he concluded that antifibrinolytic therapy was not helpful.

As the previous reports attest, the question of the efficacy of antifibrinolytic therapy has not been resolved. The beneficial results of antifibrinolytic therapy in prevention of recurrent bleeding is suggested by a majority of studies, but the results have not satisfied modern statistical criteria.\textsuperscript{16} Ramirez-Lassepas\textsuperscript{17} in a recent review of the subject concluded that the data failed to demonstrate that antifibrinolytic drugs alter the natural history of the disease. Discrepancies in the results of the many series may be due to variables such as interval between hemorrhage and treatment, days at risk, clinical condition, dosage, and concomitant treatment. The controversy will not be resolved without another large, carefully controlled, randomized study of patients with recent aneurysmal SAH. At present, this writer feels that the use of antifibrinolytic therapy for patients with ruptured aneurysms appears justified by the available evidence. Its use in the preoperative care of patients with SAH complements other medical regimens utilizing bed rest, sedatives, analgesics, and antihypertensive drugs. It is not a substitute for operative repair of the aneurysm and should not be given to patients with SAH due to causes other than ruptured aneurysm.

The optimal daily dosage has not yet been established. The cooperative study used 36 g of aminocaproic acid or 12 g of tranexamic acid daily.\textsuperscript{18} Although larger daily dosages may be superior, further correlation of daily dosage, serum and CSF drug concentrations, and therapeutic response is required. If laboratory facilities are available, the streptokinase-induced clot lysis time can be monitored (therapeutic clot lysis time is in the range of 12 to 24 hours). Because the drugs are rapidly excreted, frequent administration is required to maintain adequate antifibrinolytic activity. In the cooperative study treatment was begun with continuous intravenous infusion and later converted to a regimen of divided oral doses every two hours when the patient’s condition permitted.

The possibility of serious complications of antifibrinolytic therapy has been the source of great concern. Despite large daily dosages the low incidence of serious complications of therapy attest to its relative safety.\textsuperscript{19} The most frequent side-effect is diarrhea, particularly with oral doses of tranexamic acid. Coagula-

Instances of myopathy developing during antifibrinolytic therapy have been reported. This is a particular problem in patients on prolonged therapy (several weeks) with aminocaproic acid. Psychiatric disturbances and restlessness may complicate antifibrinolytic therapy, which can create diagnostic difficulties in a patient with SAH. If a hematological disorder, myopathy, or acute delirium develops in a patient receiving an antifibrinolytic agent, the drug should be discontinued. Convulsions may complicate antifibrinolytic therapy, even though most convulsions in patients with SAH result from the disease itself.

In the cooperative study’s series of 1,114 patients, focal neurological symptoms appeared in approximately 30\% of treated patients.\textsuperscript{18} These symptoms probably reflect complications of the initial hemorrhage, including cerebral vasospasm, rather than consequences of therapy. Instances of cerebral arterial thrombosis attributed to antifibrinolytic drugs have been reported.\textsuperscript{18} While the potential of cerebral ischemia secondary to vasospasm provoked by antifibrinolytic therapy exists, increased frequency of cerebral infarction among treated patients has not been demonstrated. Evidence that antifibrinolytic drugs induce the arterial changes consistent with cerebral vasospasm has not emerged. Unless there are indications of progressive cerebral arterial thrombosis, the development of focal neurological signs is not a reason for discontinuing treatment in a patient who is receiving antifibrinolytic therapy for SAH.

Because these drugs block fibrinolysis, retained clots surrounding the arachnoid villi may induce scarring and decreased CSF absorption, thus predisposing to the development of hydrocephalus. Park has reported a higher frequency of hydrocephalus among patients treated with aminocaproic acid.\textsuperscript{19} Further consideration of this potential complication is warranted.

While the above conditions undoubtedly occur, updated information indicates that antifibrinolytic therapy is not accompanied by frequent major neurological or medical complications.

Conclusions

Early medical therapy after SAH allows the patient’s condition to stabilize before operative repair of the aneurysm. It does not replace neurosurgical treatment. Aminocaproic acid may be a useful drug in the total preoperative care of a patient with ruptured aneurysm. Complete bed rest with a quiet environment, sedatives, analgesics, anticonvulsants, and stool softeners are also necessary. Maintenance of normal blood pressure (but not hypotensive levels) should be achieved. Monitoring of vital signs, level of consciousness, and neurological status and frequent
observations for development of new headache or neurological deficits are required to detect rebleeding or other complications. Fluid-electrolyte balance must be carefully managed and anticerebral edema therapy may also be needed.

Aminocaproic acid should be administered initially as a constant intravenous infusion at a daily dosage of 36 g (usually 18 g in 400 ml of 5% dextrose in water administered over every 12 hours). Later, the drug may be given by the oral route, the usual dosage being 1.5 g every two hours. Fourteen days after SAH, daily dosage is tapered to 24 g, and the drug is discontinued after three weeks. The drug is withdrawn approximately 12 hours before operation.

The patient should be closely followed for the development of abnormalities in blood clotting studies, serum osmolality, serum fibrinogen, complete blood count, platelet count, blood urea nitrogen, serum creatine kinase, and serum electrolytes. The patient should also be closely watched for the development of superficial or deep thrombophlebitis.

References

Current status of antifibrinolytic therapy for treatment of patients with aneurysmal subarachnoid hemorrhage.

H P Adams, Jr

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