Antifibrinolytic Therapy for Intracranial Aneurysms*

S. Mullan, M.D., and J. Dawley, M.D.

Division of Neurological Surgery, University of Chicago Hospitals and Clinics, Chicago, Illinois

It has long been known and it has been recently documented in an admirable fashion that patients who sustain a subarachnoid hemorrhage from a ruptured berry aneurysm have a tendency to rebleed, that this tendency is minimal during the first 2 days, rises to a maximum about the end of the first week, falls to a relatively low level during the third week, and to a very low figure after the third month. Pathologically speaking, what does this mean? It probably means that the initial hemorrhage stops by means of the formation of a blood clot (possibly aided by arterial spasm), that this blood clot is intact for 2 days and then shows evidence of dissolution. Dissolution may allow a second hemorrhage to occur. If the second hemorrhage does not occur early, fibrous tissue and endothelial repair take place, thus providing the patient once more with a reasonable, if perhaps restricted, life expectancy.

Therapeutically, there is little that can be done for the patient’s initial hemorrhage beyond good medical and nursing care and the occasional evacuation of an intracranial hematoma. Most effort has been directed toward preventing the incidence and consequent mortality and morbidity of the second and subsequent hemorrhages. The classical surgical methods of clip, ligation, and encapsulation are well known. Medical reduction of blood pressure has also been advocated. Another reasonable method that suggests itself is a prolongation of the duration of the naturally occurring hemostatic blood clot within and about the wall of the aneurysm. This prolongation might be expected to provide protection against hemorrhage while fibrous tissue and endothelial repair got under way. In the course of experimental work designed to induce controlled thrombosis within intracranial aneurysms, we noted that electrically induced thrombi in the femoral artery of the dog were of short duration but could, in fact, be persuaded to last longer when EACA (epsilon-aminocaproic acid) was given in daily doses of 0.34 gm per kilogram. Later we used it clinically to prolong the duration of the thrombus in an electrically thrombosed aneurysm. Since that time we have used it in an attempt to prevent recurrent hemorrhage in patients who have recently bled. Meyer has used it in patients with cerebral thrombosis to counteract the effects of excessive fibrinolysis and anticoagulant therapy. He was pleased to note that it did so effectively and did not produce any evidence of further cerebrovascular thrombosis. Uihlein et al., have used it to inhibit plasminogen activation in patients whose aneurysms were surgically treated under deep hypothermia. Porter, et al., have shown that the drug is capable of eliminating all measurable fibrinolytic activity in the spinal fluid in dogs and have suggested its clinical use in a manner similar to ours.

EACA is a mono amino carboxylic acid lacking the alpha amino group but otherwise structurally similar to lycine, and was first synthesized about the beginning of the present century in Germany. Its anti-plasmin role was first identified in Japan in 1948. Since then, it has undergone a very extensive laboratory and clinical investigation and has been found clinically useful in the management of excessive bleeding from systemic hyperfibrinolysis and urinary fibrinolysis. The literature is now an extensive one. Useful reviews will be found in the articles by Beller, Pechet, and others. Pharmacologically, it acts by competitive inhibition of the activator, which converts plasminogen into the proteolytic enzyme plasmin. It also appears to inhibit (but to a lesser extent) the direct action of plasmin, namely, the breakdown of the fibrin molecule into plyypeptides and amimo acids. It is largely excreted unchanged in the urine. Toxic reports have been minimal. It is contraindicated in situations of endovascular thrombosis and in situations of

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defective renal excretion. Minimal side effects such as dizziness have been encountered.

**Materials and Methods**

In view of its possible role in preventing or delaying the enzymatic dissolution of the hemostatic clot and considering the very minimal risk of toxic change, we have administered the drug to 35 patients with a recent subarachnoid hemorrhage in a dose of 24 gm per day (4 gm every 4 hours). Those who were able to drink had it administered orally. Others had it by intravenous infusion. This dose of 24 gm daily provides a blood level of 13 mg/100 ml, and blocks a high concentration of activator.\(^9,13\) It was maintained for periods of several days up to 6 weeks. Thirty of these patients had a demonstrable aneurysm. There were 16 internal carotid, nine anterior cerebral, two middle cerebral, and one vertebral aneurysm, and two instances of multiple aneurysm. This group included those who were ineligible for surgery, refused surgery, or awaited surgery.

**Results**

Two patients bled again. One woman had an aneurysm on the internal carotid artery at the posterior communicating junction. She was initially unconscious but awoke on the third day. Her elevated blood pressure was controlled by reserpine. She was kept continuously in bed. Her headache eased by about the 20th day, and she was otherwise well and normotensive when she died suddenly on the 25th day. Another patient with a similarly situated aneurysm developed a headache on the seventh day, was somewhat confused for a few hours, and it was thought that her right hemiparesis temporarily increased. She did not lose consciousness.

Several other patients had intermittent exacerbation of headache while on the drug. These raised the possibilities of minute hemorrhages, but none could be documented by lumbar puncture or by alteration in neurological signs. Three of our patients who were practically moribund on admission died of their initial hemorrhage. In one of these in whom there was an extensive temporal hematoma, some thrombosis was present in one of the branches of the middle cerebral artery. It was not certain whether this was an ante-mortem or a postmortem phenomenon.

Fourteen patients had surgery at times ranging from a few days up to 21 days after commencement of the EACA. Patients with a blood pressure over 175 systolic had antihypertensive medication (reserpine or methyl-dopa) in an attempt to reduce the figure toward normal. No attempt was made to lower blood pressure below normal in the manner recommended by Slosberg.\(^17\) The only definitive complication was a tendency towards local thrombosis in those veins receiving the drug systemically.

**Discussion**

These results do not, of course, prove that EACA was effective in preventing a second hemorrhage. This series is much too uncontrollable for that. The purpose of the paper is rather to present the idea, to draw attention to the possibility of prophylactic therapy by inhibition of clot dissolution, and to show that EACA, a drug of possible merit in this regard, is sufficiently free of complications for an adequate trial. Its final role may be evaluated more quickly and more effectively by neurological and neurosurgical services that handle more patients with aneurysm than we do.

Undoubtedly more effective methods of fibrinolysis inhibition will develop.\(^1\)\(^–\)\(^3,10\) Other amino acids with a primary amino and a terminal carboxyl group, such as amino methyl cyclohexane, may be more effective. There are, in addition, some well-known proteolytic enzyme inhibitors extracted from animal and vegetable tissue. A purified polypeptide of a molecular weight of 11,000, obtained from the bovine parotid, has recently been investigated in some detail. It acts directly on the plasmin rather than upon the activation of plasminogen, as does EACA. There is evidence that a combination of EACA and this kallikrein inhibitor (K.1) may be superior to either acting alone; K.1, like EACA, seems to be remarkable free of toxic effects. Other substances such as toluidine blue, protamine sulphate, and corticosteroids have some anti-fibrinolytic inhibition and may have some role in combination.

One of the limitations of the antifibrinolytic therapy is that the normal clot contains within it sufficient enzymes for its own dissolution (as in vitro). Only circulating enzymes are inhibited. Should a patient bleed while under the influence of inhibitors, then if he survives,
Antifibrinolytic Therapy for Intracranial Aneurysms

this new clot should be more resistant to dissolution than the first one. The crucial problem is that of survival. This inevitably leads to a search for some material to limit the bleeding episode itself. The peanut extract, which has been reported to reduce by 25% the bleeding time in the transected cheek pouch arteriole of the hamster, is a possibility.\(^6\) Although spasm has been noted with this substance, the enhanced activity seems to lie in the platelets, and hemostasis occurs before this spasm is evident.

**Summary**

It is suggested that the known tendency for ruptured intracranial aneurysms to rebleed within a short period of time is related to the dissolution of hemostatic clot by the normal fibrinolytic mechanism. It is further suggested that inhibition of this fibrinolytic system should give the aneurysm a better chance to heal its defect by fibrous tissue and endothelium. Thirty-five patients with recent subarachnoid hemorrhage were treated by the known antifibrinolytic agent, EACA (epsilon amino caproic acid), in a dose of 24 gm per day during the period of maximum risk. Two of these had a second hemorrhage; in one it was fatal and in the other it was very mild. We have discussed the need for a more detailed study of EACA and the possible use of a more potent antifibrinolytic system and of agents to reduce bleeding time.

**References**


