Antifibrinolytic Activity During Administration of Epsilon-Aminocaproic Acid

BY DONALD W. NIBBELINK, M.D.

Abstract: Antifibrinolytic Activity During Administration of Epsilon-Aminocaproic Acid

Utilizing an in vitro method for activated and nonactivated whole blood clot-lysis determinations, the antifibrinolytic effect of epsilon-aminocaproic acid therapy was evaluated. Initially, the induced antifibrinolytic activity diminished within two hours after the previous dose. Continuing therapy for three to six days resulted in sustained fibrinolytic inhibition.

ADDITIONAL KEY WORDS
clot-lysis determination  antifibrinolysis  cerebral aneurysm  streptokinase

Epsilon-aminocaproic acid (EACA), a known inhibitor of fibrinolysis, is now used extensively in a variety of fibrinolytic disorders.1-4 The effect of EACA has been shown to produce greater strength of an experimental intra-aortic clot without significant change in size.5 Previous reports6,7 have generated considerable interest in the use of EACA in treatment of subarachnoid hemorrhage due to ruptured cerebral aneurysm. One of the problems with EACA therapy has been to determine the degree of inhibition of fibrinolysis in the patient under treatment. Plasma EACA activity has been determined with amino acid chromatography using resin-loaded paper,8 measurement of antifibrinolytic properties in an in vitro system,9 chemical measurements using column chromatography,10 and by inhibition of streptokinase in vitro.11

This report describes a method for monitoring the antifibrinolytic effect in patients treated with EACA. A modification of the whole blood clot-lysis time12-18 has proved to be quite satisfactory.

Methods

Nine patients were given intravenous or oral EACA. Six patients had a subarachnoid hemorrhage due to ruptured aneurysm and one had a bleeding intraventricular neoplasm. Oral doses of 4 to 6 gm every four or six hours were also given to two patients with unrelated neurological disorders for three days or less, one with mild organic brain syndrome and one with peripheral neuropathy associated with alcoholism. The purpose for administration of EACA to these patients was to substantiate the pattern of antifibrinolytic effect with single and multiple oral doses in patients without subarachnoid hemorrhage. Informed consent was obtained from each patient.

Oral or intravenous administration of EACA was given in various dosages of 1 to 3 gm every two to four hours. Combinations of dosages were such that no patient received more than 36 gm nor less than 12 gm every 24 hours. Blood (4.5 ml) was obtained by venipuncture into sterile vacuum tubes containing 0.5 ml of 3.8% sodium citrate between 8 and 10 A.M. These samples of 1:10 dilution (citrate: blood) were immediately placed in ice water and processed within 30 minutes. In 10 x 75 mm test tubes, 1.7 ml of phosphate buffer,* pH 7.4 (9.47 g of Na₂HPO₄ dissolved in 1.0 liter of distilled water mixed with 3.02 g of K₂HPO₄ dissolved in 250 ml distilled water), 0.1 ml of streptokinase,1 flask 0.2 ml of thrombin solution: 5,000 units of Parke-Davis topical thrombin was dissolved in 100 ml 0.9% saline. This was diluted to 1:10 solution at time of use.

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Table 1

Data From a Representative Patient Receiving Oral EACA

<table>
<thead>
<tr>
<th>Day</th>
<th>Grams of EACA every two hours</th>
<th>Hours from last dose</th>
<th>Hours to complete lysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>1½</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>1½</td>
<td>8½½</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>13</td>
<td>2</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>15</td>
<td>No EACA</td>
<td>for 20 hrs</td>
<td>7</td>
</tr>
</tbody>
</table>

Data From a Representative Patient Receiving Intravenous EACA

<table>
<thead>
<tr>
<th>Day</th>
<th>Grams of EACA every two hours</th>
<th>Hours from last dose</th>
<th>Hours to complete lysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>—</td>
<td>—</td>
<td>3½</td>
</tr>
<tr>
<td>3</td>
<td>—</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>½</td>
<td>&gt;103</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>½</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>½</td>
<td>72</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>2</td>
<td>12½½</td>
</tr>
<tr>
<td>15</td>
<td>2 (oral)</td>
<td>¾</td>
<td>&gt;96</td>
</tr>
<tr>
<td>15</td>
<td>2 (oral)</td>
<td>2</td>
<td>&gt;96</td>
</tr>
</tbody>
</table>

Day after onset of subarachnoid hemorrhage, dosage of EACA (epsilon-aminocaproic acid), interval from last dose blood sample taken, and hours to complete lysis in specimens with and without SSV (Streptokinase-Streptodornase Varidase, Lederle).

Results

Table 1 (upper portion) shows clot-lysis times tabulated with respect to dosage and interval from last dose in a typical patient who was treated with oral EACA for 15 days. After control values were determined, EACA therapy was started on the fourth day after onset of subarachnoid hemorrhage. Twenty-four hours later (day 5, table 1) the activated clot-lysis time remained at control values in the specimen taken two hours from the previous dose. From day six through 11, 3 gm every two hours were prescribed, but by the eighth day the activated clot-lysis time increased to 24 hours in the sample taken two hours after the last dose. Thereafter, the activated clot-lysis time remained stable through day 11 and the nonactivated determination was prolonged to 51 hours. Decreasing the dosage to 2 gm every two hours during the next 24-hour interval produced an activated clot-lysis time of 31 hours on day 13 in the sample taken two hours after the previous dose, and 48 hours for the nonactivated sample. After EACA was discontinued for a period of 20 hours, clot-lysis time on day 15 was diminishing rapidly toward control values.

The tabulation in the lower portion of Table 1 represents the results of induced antifibrinolytic effect in a patient treated with intravenous EACA. Initial dosage of 3 gm every two hours was started on the fourth day after onset of subarachnoid hemorrhage. On the fifth day, the blood sample taken one-half hour after the previous dose revealed a prolonged clot-lysis time over 103 hours for the activated and nonactivated specimens. The sample taken one and one-half hours later

At 0°C for ten minutes. After clotting, the tubes were rotated in order to free the clots from the walls of the tube, and then placed in a 37°C water bath. Clot lysis was observed at two-hour intervals until lysis was complete. $^8$

The same procedure was followed for nonactivated whole blood clot-lysis determinations by omission of streptokinase, and 1.8 ml of buffer used instead of 1.7 ml.
showed shortened lysis times to 12 and 27 hours respectively. Thereafter, the dose was decreased to 2 gm every two hours for five days, and on day ten the two-hour specimen had an activated clot-lysis time of 28 hours and a nonactivated clot-lysis time over 96 hours. After further reduction in dose to 1 gm every two hours for a 24-hour period, activated clot-lysis time diminished to 12½ hours on day 11, two hours after the previous dose. Increasing the dosage again to 2 gm orally every two hours for three days (day 12 to 15) resulted in greatly prolonged activated and nonactivated clot-lysis times to more than 96 hours. Thereafter, EACA was discontinued for 24 hours and the patient underwent successful craniotomy for an internal carotid aneurysm.

All tests were performed in duplicate for both the activated and nonactivated determinations. The activated samples were more reliable with unsatisfactory discrepancies occurring in less than 10% of specimens. Greater variability was observed with whole blood clot-lysis determinations. Further disadvantage in these determinations was evident with respect to the time utilized for complete lysis to occur. Any bacterial infections caused clot-lysis to occur more rapidly than expected.

**Discussion**

Oral EACA given in divided doses for 24 hours or less resulted in activated clot-lysis times approximating control values in samples taken more than two hours after the previous dose. Clot-lysis times were always most prolonged when specimens were taken within the first hour after receiving the drug, whereupon it would decrease toward baseline values during the second and third hours. This response was found both in patients with subarachnoid hemorrhage due to ruptured aneurysm and in the two patients given EACA with unrelated neurological disorders. Although continuous intravenous therapy has been a common route of administration of EACA in fibrinolytic disorders, it has been more desirable to give EACA in divided dosage in most patients with subarachnoid hemorrhage, especially in those who are able to take oral medication. It became evident in the early phase of this investigation that EACA should be given at frequent intervals of two hours or less in order to produce a sustained antifibrinolytic effect.

All patients with subarachnoid hemorrhage remained on EACA therapy for 10 to 15 days. In three patients intravenous administration every two hours produced a more rapid rise in clot-lysis time two hours after the previous dose in contrast to oral therapy in the three other patients. Oral EACA, 3 gm given every two hours during initial days of treatment, did not prolong clot-lysis time to more than 24 hours until five to seven days of therapy. Therefore, the main advantage of intravenous administration was the more rapid rise to continuous antifibrinolysis during the initial treatment interval. Thereafter, clot-lysis times could be maintained on reduced oral or intravenous dosage of 1 or 2 gm every two or three hours.

Antifibrinolytic activity was regarded as adequate when the activated clot-lysis time was in the range of 12 to 24 hours. This prolongation in clot lysis was an arbitrary endpoint used in patients with subarachnoid hemorrhage due to ruptured aneurysm. In several instances activated clot-lysis time far exceeded 24 hours. No complications were observed during or after such occasions. No rebleeding episodes occurred and all patients tolerated the drug well. All patients with subarachnoid hemorrhage were given approximately one liter of fluid every 24 hours and four patients received antihypertensive therapy. One patient with a left middle cerebral aneurysm had an intracerebral hematoma diagnosed by cerebral angiography. All patients had four-vessel angiography prior to treatment. One additional patient not in this series was treated with antihypertensive medication without EACA. Clot-lysis times remained at control values during the two-week interval after rupture of an internal carotid aneurysm. Two other patients, one with a subarachnoid hemorrhage due to a hemorrhagic cerebral vascular accident and one with a ruptured aneurysm on the superior cerebellar artery, had clot-lysis times which remained at control values during hospitalization. However, the latter patient had a prolonged whole blood clot-lysis time up to 48 hours for one week, which thereafter diminished spontaneously to 15 hours. This was the only patient who had elevations in plasminogen which were twice the normal range.

No undesirable effects occurred in any patient while on EACA. Electrolytes, platelet
counts, and prothrombin times remained stable. The relationship of plasma fibrinogen to EACA therapy is in process of evaluation in conjunction with plasminogen levels, partial thromboplastin times, euglobulin clot-lysis time, and factor VIII assays. An analysis of these items as related to patients with ruptured cerebral aneurysm is in preparation.

Acknowledgment
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References
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