The authors present a case of proximal myopathy secondary to epsilon-aminocaproic acid (EACA) administration. This well recognized entity does not occur immediately after institution of therapy, but follows a delay of several days and a cumulative dose. Its consequences include a spectrum of symptoms from myalgias to severe myopathy with rhabdomyolysis, myoglobinuria, and acute tubular necrosis. A presenting symptom of calf pain in a patient receiving EACA should not automatically imply deep vein thrombosis. Serial creatine phosphokinase measurements are essential in monitoring a patient undergoing EACA therapy, especially after 2 weeks of treatment and a total dose of greater than 500 gm.

**KEY WORDS** • epsilon-aminocaproic acid • myopathy • myoglobinuria • subarachnoid hemorrhage

Epsilon-aminocaproic acid (EACA) is a mono-aminocarboxylic acid that inhibits the activation of plasminogen to plasmin, thus inhibiting fibrinolysis.\(^24,25\) It has been reported to reduce the incidence of recurrent hemorrhage following recent rupture of intracranial aneurysms and before operative repair.\(^25,26\)

An uncommon complication of its use is a proximal limb and truncal myopathy. Eighteen such cases have been documented\(^4,6-8,10,14-20,22,28,29\) since the first report in 1969 by Korsan-Bengsten, *et al.*,\(^19\) We present an additional case, and summarize the findings of those cases already reported.

**Case Report**

This 72-year-old woman was in good health until December 24, 1978, when she experienced a severe occipital headache followed by loss of consciousness.

*First Admission.* Lumbar puncture on admission to the hospital confirmed the presence of a subarachnoid hemorrhage (SAH). Angiography demonstrated a bilobular aneurysm arising from the right posterior communicating artery. In addition, the patient was found to have a third-degree heart block requiring insertion of a transvenous pacemaker.

Because of her age and cardiac status, the patient was treated with EACA and an operation was not performed. She received 36 gm/day EACA intravenously for 2 weeks, tapered to 30 gm/day intravenously for 1 week; thereafter, 24 gm/day was given orally, but was discontinued 1 month after starting therapy, after an episode of orthostatic hypotension (total cumulative dose 900 gm). Several days later, the patient developed aching shoulder and arm pains and general weakness.

She was discharged from the hospital on January 24, 1979, but for the next 7 days she continued to have pain and weakness, now involving the shoulder girdle, trunk, and proximal aspect of the legs. She had difficulty rising from a chair, sitting up, and ascending stairs. At this point, her urine became dark and the output was diminished.

*Second Admission.* The patient was rereadmitted on February 2, 1979. Examination revealed the biceps, triceps, quadriceps, gastrocnemius, and soleus muscles to be tender bilaterally. Proximal shoulder girdle and hip flexor strength was decreased, but the distal hand...
**EACA-induced myopathy**

**Fig. 1.** Frozen cross section of deltoid muscle biopsy from our patient. Degenerating myofibers containing macrophages are scattered randomly among normal fibers. Endomysial lymphocytes were not present in this biopsy specimen. H & E, × 325.

Strength was normal. Upper extremity reflexes were 2++ and lower extremity reflexes were 1+. Laboratory tests performed on the day of hospital admission revealed abnormal results as shown in Table 1. The following tests were within normal limits: sodium, potassium, chlorine, calcium, total bilirubin, alkaline phosphatase, total protein and albumin, hematocrit and hemoglobin, free thyroxin (T4) index, and total T4. The Doppler venous examination showed normal spontaneous flow, normal augmentation, and valvular competence of the popliteal and femoral veins. Electromyography revealed increased muscle irritability and pseudomyotonic discharges, with normal motor unit morphology.

Biopsy of the right gastrocnemius muscle on February 2 revealed necrotic muscle fibers filled with macrophages, but with no lymphocytic infiltrate around the fibers or vessels. The necrotic muscle fibers were all at the same state of degeneration, suggesting a single insult. Mild Type II atrophy was demonstrated by adenosine triphosphatase stain. There was no increase in endomysial collagen (Fig. 1).

**Course.** The patient was treated by restriction of fluid intake, and prednisone was begun for possible polymyositis and acute tubular necrosis secondary to rhabdomyolysis. Urine output returned to normal, and no dialysis was required. Prednisone was gradually discontinued. By the 26th day after admission, clinical symptoms had resolved. By the 46th day after admission, the creatine phosphokinase (CPK) was normal.

The patient died 9 months later as a result of recurrent SAH. Despite extensive search, the autopsy revealed no histological evidence of residual myopathy or previous muscle injury.

**Discussion**

The role of EACA in inhibiting plasmin synthesis has been known since 1948. Side effects during its long-term usage include nausea, nasal stuffiness, diarrhea, rash, and transient orthostatic hypotension. In dogs and monkeys treated with high-dose intravenous EACA for 3 weeks, subendocardial hemorrhages and myocardial fatty degeneration were noted. This has not been found in humans at autopsy. Since 1969, 13 different articles have documented 18 cases of EACA-induced myopathy (the patient of Korsan-Bengsten, et al., received a second confirming EACA challenge, and is considered as two cases). Findings from these patients and those of ours are summarized in Table 2.

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value in Our Patient</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood CO₂ level (mEq/liter)</td>
<td>19</td>
<td>23–30</td>
</tr>
<tr>
<td>blood urea nitrogen (mg/dl)</td>
<td>59</td>
<td>7–20</td>
</tr>
<tr>
<td>creatinine (mg/dl)</td>
<td>4.7</td>
<td>0.5–1.4</td>
</tr>
<tr>
<td>uric acid (mg/dl)</td>
<td>9.9</td>
<td>2–8.5</td>
</tr>
<tr>
<td>lactate dehydrogenase (IU)</td>
<td>415</td>
<td>12–55</td>
</tr>
<tr>
<td>serum glutamic oxaloacetic</td>
<td>1023</td>
<td>0–35</td>
</tr>
<tr>
<td>transaminase (IU)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>serum glutamic pyruvic</td>
<td>627</td>
<td>0–35</td>
</tr>
<tr>
<td>transaminase (IU)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>creatine phosphokinase (IU)</td>
<td>29,800</td>
<td>8–150</td>
</tr>
<tr>
<td>erythrocyte sedimentation rate (mm/hr)</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2

Summary of 19 cases of proximal myopathy secondary to EACA administration*

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Duration of Therapy (days)</th>
<th>Dose/ Day (gm)</th>
<th>Total Dose (gm)</th>
<th>CPK (IU)</th>
<th>SGOT (IU)</th>
<th>SGPT (IU)</th>
<th>LDH (IU)</th>
<th>ESR (mm/hr)</th>
<th>Pain &amp; Tenderness Alone</th>
<th>Pain, Tenderness, &amp; Weakness</th>
<th>Weakness Alone</th>
<th>Pattern of Myopathy</th>
<th>Calf Muscle Tenderness</th>
<th>Muscle Biopsy Results</th>
<th>Myoglobinuria</th>
<th>Acute Tubular Necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korsan-Bengsten, et al., 1969</td>
<td>31, M</td>
<td>35</td>
<td>30</td>
<td>1100</td>
<td>1080</td>
<td>13</td>
<td>15</td>
<td>difficulty walking</td>
<td>+</td>
<td>hyaline degeneration &amp; necrosis</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bennet, 1972</td>
<td>32, M</td>
<td>63</td>
<td>24</td>
<td>1500</td>
<td>1360</td>
<td>25</td>
<td>40</td>
<td>leg &amp; abdominal muscle weakness</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frank, et al., 1972</td>
<td>47, F</td>
<td>30, F</td>
<td>16</td>
<td>10</td>
<td>141</td>
<td>10</td>
<td>normal</td>
<td>profound generalized weakness</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gilligan, 1974</td>
<td>48, M</td>
<td>84</td>
<td>16</td>
<td>1300</td>
<td>1100</td>
<td>17</td>
<td>15</td>
<td>leg weakness climbing stairs</td>
<td>severe muscle weakness</td>
<td>-</td>
<td>-</td>
<td>focal hyaline necrosis with regeneration</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shav &amp; Miller, 1974</td>
<td>23, F</td>
<td>90</td>
<td>10</td>
<td>900</td>
<td>750</td>
<td>15</td>
<td>40</td>
<td>normal</td>
<td>severe weakness</td>
<td>fatigue</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rizza, et al., 1976</td>
<td>44, M</td>
<td>56</td>
<td>36</td>
<td>1500</td>
<td>1050</td>
<td>1000</td>
<td>18</td>
<td>48</td>
<td>generalized proximal extremities, abdominal &amp; truncal weakness</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mackay, et al., 1978</td>
<td>64, F</td>
<td>55</td>
<td>36</td>
<td>2000</td>
<td>750</td>
<td>1250</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>Lane, et al., 1979</td>
<td>74, F</td>
<td>35</td>
<td>30</td>
<td>1100</td>
<td>4680</td>
<td>140</td>
<td>10</td>
<td>generalized proximal extremities, abdominal &amp; truncal weakness</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Brit, et al., 1980</td>
<td>59, F</td>
<td>35</td>
<td>18</td>
<td>600</td>
<td>6500</td>
<td>21</td>
<td>21</td>
<td>normal</td>
<td>severe noninflammatory necrotizing myopathy with active regeneration</td>
<td>normal after recovery</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biawa, et al., 1980</td>
<td>20, F</td>
<td>35</td>
<td>12</td>
<td>400</td>
<td>58,235</td>
<td>1592</td>
<td>529</td>
<td>24</td>
<td>70</td>
<td>massive necrosis; no vascular thrombosis</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Brodkin, 1980</td>
<td>51, F</td>
<td>41</td>
<td>38</td>
<td>1600</td>
<td>1544</td>
<td>56</td>
<td>42</td>
<td>atrophy &amp; vacuolization; no vascular thrombosis or inflammation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kennard, et al., 1980</td>
<td>36, F</td>
<td>52</td>
<td>24</td>
<td>1200</td>
<td>6000</td>
<td>36</td>
<td>56</td>
<td>proximal legs &amp; truncal weakness</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td></td>
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<tr>
<td>Brown, et al., 1982</td>
<td>72, F</td>
<td>22</td>
<td>30</td>
<td>900</td>
<td>29,800</td>
<td>1027</td>
<td>627</td>
<td>415</td>
<td>46</td>
<td>26</td>
<td>44</td>
<td>proximal arm followed by leg &amp; truncal weakness</td>
<td>+</td>
<td>necrotic fibers, all at same stage of necrosis; no inflammatory infiltrate</td>
<td>-</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>41</td>
<td>48</td>
<td>26</td>
<td>1200</td>
<td>16,029</td>
<td>150</td>
<td>578</td>
<td>1148</td>
<td>50</td>
<td>45</td>
<td>45</td>
<td>4/16</td>
<td>9/16</td>
<td>3/16</td>
<td>6/16</td>
<td>5/19</td>
<td>3/19</td>
</tr>
</tbody>
</table>

* Of the 19 cases, presenting symptoms were fully described in only 16. EACA = epsilon-aminocaproic acid; CPK = creatine phosphokinase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; LDH = lactate dehydrogenase; and ESR = erythrocyte sedimentation rate; - = no information available; = absent; + = present.

† The patient in this report underwent two separate courses of therapy, both resulting in myopathy.
EACA-induced myopathy

A review of these cases reveals that EACA toxicity appears after a cumulative dose. The mean duration of therapy before onset of symptoms was 48 days (range 28 to 90 days). The mean total dose of EACA was 1200 gm (range 400 to 2000 gm). The mean daily dose was 26 gm/day (range 10 to 38 gm/day). The syndrome has occurred only in adults, with a mean age of onset of 41 years (range 20 to 74 years). There was a female predominance (13 of 18 patients, or 72% of cases). The three patients developing acute tubular necrosis were female.

Mean time until clinical resolution of symptoms was 45 days after discontinuation of EACA (range 18 to 85 days). Presenting symptoms were myalgia, muscle tenderness, and weakness. The symptoms were adequately described in 16 cases. Of these, the presenting symptoms were pain and/or tenderness in three (19%); pain, tenderness, and weakness in nine (57%); and weakness without pain in three (19%). In five cases (31%), there was a component of calf pain or swelling; however, this was always associated with other symptoms. The pattern of muscle weakness was primarily proximal or truncal: in four of 13 cases (30%), the weakness was manifested only in the lower extremities (by difficulty in walking or climbing stairs), and in the other nine cases (70%), the presentation was of generalized muscular weakness or fatigue. In two of these, there was also a respiratory function impairment.

Levels of CPK, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and lactate dehydrogenase (LDH) were generally elevated, CPK often dramatically. The mean CPK level was 16,029 IU (range 141 to 58,235 IU). Mean SGOT was 1150 IU (range 1000 to 1592 IU). Mean SGPT was 578 IU (range 529 to 627 IU). Mean LDH was 1148 IU (range 415 to 2443 IU). The mean duration of CPK elevation, after discontinuation of EACA, was 30 days (range 10 to 56 days). Erythrocyte sedimentation rate (ESR) was elevated in seven of nine cases (78%); the mean ESR, when it was noted to be elevated, was 45 mm/hr.

Myoglobinuria was positively identified in five of the 19 cases (26%), and acute tubular necrosis was present in three (16%). The mean EACA dose leading to myoglobinuria was 1000 gm (range 400 to 1600 gm), with the daily dose ranging from 10 to 38 gm/day. The mean EACA dose leading to acute tubular necrosis was 900 gm. Each time acute tubular necrosis was present, it was clinically reversible, as was the proximal myopathy, both clinically and histologically.

Muscle biopsy at the onset of symptoms consistently demonstrated a necrotizing myopathy, with random distribution of degenerating and regenerating myofibers that exhibited sparse or absent inflammatory infiltrates. In our case, the finding of fibers at the same state of necrosis was consistent with a single toxic insult. In two cases, repeat muscle studies were obtained after clinical recovery and revealed no residual damage.

In the first reported case, Korsan-Bengsten, et al., suggested that the myopathy associated with EACA was secondary to induced intravascular coagulation; however, they noted no intravascular thrombi in their biopsy specimen. They concluded that the muscle necrosis was a result of ischemia. In 1973, Gilligan noted that his own patient and the patient reported by Korsan-Bengsten, et al., both had several allergies, and that the EACA myopathy may be of allergic etiology. However, allergies have not been seen in other patients.

Frank, et al., suggested that EACA acts as a lysine analogue and affects the integrity of the sarcolemma. They reported a patient who was treated with lysine hydrochloride for 1 week before restarting EACA, which had been previously discontinued because of the onset of severe weakness. No toxicity resulted. There have been no further trials of lysine, and this case is not sufficiently well documented to allow any conclusions to be drawn.

Mackay, et al., reported two cases in 1978. They pointed out that the onset of myopathy was delayed, that the course was progressive as long as EACA was continued (at least at the same dose), and that the myopathy resolved several weeks after discontinuation of the drug.

Elevation of SGOT occurred in 15% of patients with muscular dystrophy and in 25% of patients with polymyositis, and increased with myoglobinuria. In company with LDH, aldolase, and SGPT, SGOT is a component of muscle cells. There is no reason to suspect an associated focal hepatitis, as was suggested by Mackay, et al. Alkaline phosphatase has never been found to be significantly elevated in any of these cases.

There are other examples of delayed myopathy of toxic etiology with findings similar to EACA myopathy. The SGOT, SGPT, and CPK are elevated in other toxic myopathies. Clofibrate, a fatty acid ester, can cause liver injury in cases of rhabdomyolysis. There is, however, hepatomegaly and tenderness on physical examination, as well as muscle tenderness. Myofiber necrosis and Type II fiber atrophy are found in the myopathy associated with chronic alcohol abuse.

Britt, et al., recorded a case with renal failure, myoglobinuria, and the highest associated CPK level (58,235 IU) among the 19 cases of this entity (including our own), yet the lowest total EACA dose (420 gm). Subendocardial injury was suggested by the presence on the electrocardiogram of ST depression and T-wave inversion. These authors postulated direct myocardial toxicity as a component of the spectrum of injury. In our case, myocardial infarction, recent or organized, was not found at autopsy. Charytan and Purtilo reported a case of renal failure following an intravenous dose of EACA, leading to diffuse glo-
merular capillary thrombosis. No renal biopsies have, however, been performed on any of these cases of EACA myopathy and renal failure. Their patient did not have myopathy, and the lesion was probably of different etiology.

The cases presented by Britt, et al,7 and Gilligan16 demonstrated that myoglobinuria may develop even in cases where the daily dose was less than 24 gm/day. Their patients received 12 and 10 gm/day, respectively. The course of therapy seems always to have been prolonged, however; it was not less than 28 days in any case.

References

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