Myoglobinuria following epsilon-aminocaproic acid (EACA) therapy

Case report

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Myoglobinuria developed in a patient with subarachnoid hemorrhage treated with a course of 1.43 kg of epsilon-aminocaproic acid (EACA) given over 41 days. Review of eight other cases with a variety of medical disorders shows that this effect occurs after at least 4 weeks of taking doses of a minimum of 24 gm EACA per day. The effect seems to be reversible if discovered early. This side-effect should provide impetus for restricting the duration of EACA therapy to periods under 28 days, in doses no higher than 24 gm/day.

KEY WORDS • myoglobinuria • epsilon-aminocaproic acid therapy • subarachnoid hemorrhage • Amicar

EPISILON-AMINOCAPROIC acid (EACA) is an antifibrinolytic agent used to prevent bleeding in hereditary angioneurotic edema, and to prevent rebleeding in subarachnoid hemorrhage. Undesirable effects of its usage are nausea, diarrhea, rash, and thrombotic events. An uncommon side-effect is weakness with myoglobinuria after prolonged intake at high doses. We report here a case in which this effect was unusually severe, and compare it with other known cases in the literature.

Case Report

This 51-year-old Oriental woman was admitted to the hospital in April, 1979, with headache and a stiff neck. Computerized tomography (CT) scan of the head demonstrated blood around the basal cisterns, and arteriography showed spasm of the right internal carotid and right posterior cerebral arteries. No aneurysm was demonstrated. Therapy with EACA (Amicar) was begun at an intravenous dose of 38 gm/day. Repeat arteriography 2 weeks later was normal. The EACA was continued intravenously for 28 days, then given orally at 24 to 36 gm/day for 12 more days. The patient’s blood pressure was controlled with hydralazine and methyldopa, and she received intermittent steroid treatment for cerebral edema.

After 36 days of EACA therapy, dark urine was noted. The next day, the patient slid from a chair and was too weak to stand. Arteriography again exhibited no aneurysm or spasm. Diphoresis, rapidly progressive weakness of the proximal muscles, darkening urine, high temperatures, and a rising pulse were noted over the next 3 days. The drug was discontinued after 41 days of therapy and, because of weakness and shallow respirations, she was transferred to the intensive care unit.

At physical examination, the patient was febrile (38.3°C) with a pulse of 112 per minute. She could not swallow, sit, or lift her head from the pillow, and was able to move only her wrists, fingers, ankles, and toes. Her voice was soft and had a nasal quality. Respirations were shallow, but there was no cyanosis, and the results of cardiovascular examination were normal. The thigh muscles were tender, but were without fasciculations or muscle swelling. The gag reflex was diminished and, except for that of the brachioradialis, the deep tendon reflexes were absent. Results of a sensory examination were normal. The hematocrit was 33%; the white blood cell (WBC) count, 42,000/cu mm. The creatinine phosphokinase (CPK) level was 1544 IU (normal 0 to 70 IU), with no myocardial fraction detected. Urinalysis showed 4+ hemoglobin, but no red cells were seen. Immunochromic testing confirmed the presence of
TABLE 1

Summary of reported cases of myoglobinuria with epsilon-aminocaproic acid therapy*

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Disease</th>
<th>Duration of Treatment (days)</th>
<th>Total Dose (kg)</th>
<th>Dose (gm/day)</th>
<th>Max CPK (IU)</th>
<th>CPK Time to Normal</th>
<th>Clinical Findings</th>
<th>Time to Recover</th>
<th>Biopsy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett, 1972</td>
<td>1</td>
<td>22, M</td>
<td>HANE</td>
<td></td>
<td>18-24</td>
<td></td>
<td>141 hours</td>
<td>easily tired, aches, cramps</td>
<td>hours</td>
<td>1 wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>24, F</td>
<td>HANE</td>
<td></td>
<td>16-24</td>
<td>30</td>
<td>24</td>
<td>profound weakness</td>
<td>hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>30, F</td>
<td>HANE</td>
<td></td>
<td>0.72</td>
<td></td>
<td>24</td>
<td>extreme weakness, myoglobinuria</td>
<td>1 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geronemus, et al., 1974</td>
<td>4†</td>
<td>31, M</td>
<td>HANE</td>
<td></td>
<td>35</td>
<td>1.05</td>
<td>30</td>
<td>profound weakness</td>
<td>2 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>49</td>
<td>1.47</td>
<td>30</td>
<td>myoglobinuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nibbelink, et al., 1975</td>
<td>5</td>
<td>24, F</td>
<td>HANE</td>
<td></td>
<td>28</td>
<td>0.672</td>
<td>24</td>
<td>unable to climb stairs, tender muscles, myoglobinuria</td>
<td>3 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post, et al., 1977</td>
<td>6</td>
<td>32, M</td>
<td>UC</td>
<td></td>
<td>63</td>
<td>1.57</td>
<td>24</td>
<td>weakness at 49 days, no effect on rechallenge at 16 days, myopathic changes on EMG</td>
<td></td>
<td></td>
<td>myopathic changes</td>
</tr>
<tr>
<td>MacKay, et al., 1978</td>
<td>7</td>
<td>44, M</td>
<td>SAH</td>
<td></td>
<td>44</td>
<td>1.75</td>
<td>36</td>
<td>proximal weakness, myoglobinuria, myalgia, myoglobinuria</td>
<td>3 wks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>64, F</td>
<td>SAH</td>
<td></td>
<td>14</td>
<td>2.02</td>
<td>36</td>
<td>1000</td>
<td>2 wks</td>
<td></td>
<td>myoglobinuria</td>
</tr>
<tr>
<td>Brodkin, 1980</td>
<td>9</td>
<td>52, F</td>
<td>SAH</td>
<td></td>
<td>56</td>
<td>1.43</td>
<td>36</td>
<td>1500</td>
<td>2 mos</td>
<td></td>
<td>degeneration of both fiber types, little inflammation, variable fiber &amp; shape</td>
</tr>
</tbody>
</table>

*CPK = creatinine phosphokinase; HANE = hereditary angioneurotic edema; UC = ulcerative colitis; SAH = subarachnoid hemorrhage; EMG = electromyography.
†There were two separate treatment episodes in this case.

Myoglobin in the urine. An electromyogram showed evidence of inflammatory myopathy, and a muscle biopsy showed marked atrophy and vacuolation of both fiber types, with little inflammatory response and no evidence of thrombosis in the vessels.

The patient recovered slowly; after 1 week she could swallow, raise her head, and move her arms, the left more than the right. A CT scan 1 week after discontinuing EACA showed a left thalamic and internal capsule infarct not present on the earlier studies. After 2 weeks, she could sit upright; after 4 weeks, she could push herself in a wheelchair. At 6 weeks, she could walk with assistance. All this time the left side was stronger than the right. Her WBC count fell to normal; the myoglobin in the urine disappeared 2 weeks after discontinuation of EACA, and her CPK level was normal 2 months later.

Discussion

Epsilon-aminocaproic acid (EACA) (C,H,N,O) is an acid of low molecular weight (119) that resembles lysine. The EACA is rapidly absorbed after oral and intravenous administration, and is excreted 60% to 90% unmetabolized at approximately 75% of the glomerular filtration rate. The drug acts by inhibiting both plasminogen and plasmin, which are agents active in promoting clot lysis. The level needed to inhibit plasminogen, 13 mg/100 ml, is achieved at a dose of 24 gm/day in a patient with normal renal function. Therefore, use of the drug at this dosage may be useful in preventing dissolution of already formed clots. Geronemus and associates found that they needed 1 to 4 days of doses at 36 gm/day to raise the streptokinase clot lysis time from normal at 3 hours to a presumed therapeutic level of 16 hours. However, once this level was achieved, many patients required only 24 gm/day to maintain this level of lysis inhibition.

The drug seems to be well tolerated, with diarrhea and rash being the most common side-effects. In 1969, Korsan-Bengsten, et al., reported a severe case of weakness and myoglobinuria in a man with hereditary angioneurotic edema, who took 30 gm of EACA per day. In 1972, Frank, et al., reported weakness and elevation of CPK in three of five patients with this condition. Since then, there have been incidental and detailed reports of myoglobinuria in patients taking EACA. These reported cases are summarized in Table 1, where a cluster of cases around a total dose...
of 1.5 kg and a treatment duration of 4 to 8 weeks can be noted. Most of the authors commented on the rapid onset of symptoms. No cases of myoglobinuria were reported when the dose of EACA was below 24 gm/day, and all reported cases involved doses of at least 24 gm/day for longer than 28 days.

An allergic mechanism through which EACA attacks muscle is unlikely, since rechallenging affected patients (Cases 1, 2, 3, 4, and 6, Table 1) did not lead to recurrent symptoms. Nor is thrombosis a probable cause, since in our case and in Case 4, Table 1, muscle biopsy showed no signs of small-vessel thrombosis or muscle infarction. Frank, et al., suggested that EACA might damage muscle by acting as a lysine analog, but no one has yet used lysine to treat or protect patients exposed to long-term EACA therapy.

The most common indication for high-dose treatment with EACA is in cases of subarachnoid hemorrhage, to prevent rebleeding. The literature supports its use during the first 2 weeks after such a hemorrhage. No study supports its use beyond 2 weeks from the initial bleeding. Most studies do not attempt to use varied doses while measuring the effect of EACA on clot lysis. Thus, the optimum duration of treatment and the optimum dosage are not known. Doses of EACA higher than 24 gm/day for longer than 4 weeks can produce myoglobinuria, and lower doses may also be toxic. MacKay, et al., suggested that patients undergo serial CPK tests and that they be observed for weakness during prolonged treatment. The observation of Geronemus, et al., that after an initial EACA dose of 36 gm/day the dose may be lowered deserves the attention of physicians prescribing this drug. Given the severity of the weakness in our patient and in some of the reported cases, clinicians should be hesitant about using EACA for longer than 3 weeks without data to support its use for that period of time. Some measure of EACA activity, such as the streptokinase clot lysis time, should also be used as a guide for determining the lowest effective dosage.

References


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