Epsilon aminocaproic acid (EACA) myopathy

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Summary

Two female patients developed a severe, painful proximal myopathy after taking 18-30 g of epsilon-aminocaproic acid daily for 5 weeks. Marked elevations of serum aminotransferases, creatine kinase and aldolase levels were found and the first patient had electromyographic and muscle biopsy changes of an acute monophasic, necrotizing myopathy at the height of the illness. Resolution occurred in both cases on stopping the drug and the second patient had no electromyographic or muscle biopsy abnormalities 3 weeks later. Only 2 recognized cases of the condition have been reported previously but a review of the literature revealed several other possible examples.

Introduction

Epsilon aminocaproic acid (EACA) is an anti-fibrinolytic agent used in the management of certain haemorrhagic disorders (Martindale, 1977) and in the treatment of hereditary angioneurotic oedema (HAO) since it inhibits the C₁ component of complement (Korsan-Bengsten *et al.*, 1969). Mild side effects, such as diarrhoea, postural hypotension, dizziness, allergic reactions and dyspepsia are common. Less frequently, microthrombosis, venous thrombosis and pulmonary embolism can occur (Martindale, 1977). Myopathy has only rarely been described as a side effect of EACA therapy (Korsan-Bengsten *et al.*, 1969; Bennett, 1972) and the resulting clinical syndrome and pathological changes in muscle are poorly documented. Two cases are described which illustrate the clinical features of the condition and outline its pathological basis and natural history.

Case reports

Case 1

A 74-year-old woman had suffered sub-arachnoid haemorrhages (SAH), 29 years and 4 years previously, due to an inoperable aneurysm at the junction of the

internal carotid and posterior communicating arteries. She was admitted following a further ictus and was treated with 30 g of EACA daily in divided doses for 3 weeks, apparently without ill effect. Six weeks later, she suffered a further SAH and was treated with EACA as before. After 5 weeks on this regime she developed a progressive, painful proximal myopathy beginning in the muscles of the calves and pelvic girdle, subsequently extending to the upper arms and shoulders over a 2-week period. She had noticed a dark brown discoloration of her urine at the onset of these symptoms.

On examination she appeared ill but was afebrile. Marked muscle tenderness and weakness were present in the proximal muscles of both arms and legs and she was unable to lift her shoulders from the bed because of severe weakness of the muscles of the trunk and abdomen. The neck muscles were unaffected.

Investigations, course and management. Full blood count, differential white cell count and ESR were consistently normal. Thyroid function tests and serum proteins were within normal limits and no autoantibodies or viral antibodies were detected on screening. Her plasma K⁺ was reduced at 2.81 mmol/l but plasma urea, creatinine and other electrolytes were normal. Myoglobinuria was absent on admission but serum aspartate transaminase, creatine kinase (CK) and aldolase were markedly elevated at 625 i.u./l (normal <37 i.u./l), 4680 i.u./l (normal <50 i.u./l) and 122 i.u./l (normal <3 i.u./l) respectively (Fig. 1). Electromyographic examination of proximal muscles showed profuse spontaneous activity at rest, including true myotonic discharges and typical myopathic changes on voluntary contraction. A needle muscle biopsy taken from the left vastus lateralis muscle showed changes indicative of a severe, non-inflammatory necrotizing myopathy with active regeneration (Fig. 2).

The patient's total body potassium, calculated

FIG. 1. (a) Haematoxylin and eosin. Transverse section through muscle, Case 1. Active muscle necrosis, with infiltration of the fibres by macrophages, is occurring (N). Some fibres have associated satellite cells indicating regeneration (arrows). (b) NADH preparation. Necrotic fibres (N) have lost their staining properties whilst the actively regenerating cells (arrows) are darkly staining, indicating high metabolic activity.

from the $^{40}\text{K}^+$ content by whole body monitoring, was low at 27.57 mmol/kg (predicted level for body size 37.0 mmol/kg) at a time when her serum K^+

had risen to 2.95 mmol/l with oral potassium supplements. Hypokalaemia had been noted on previous admissions, although not consistently.

No cause had been found and urinary K⁺ excretion and plasma cortisol levels had been consistently normal.

The drug was withdrawn and her muscle pains and weakness resolved rapidly. Serum enzyme levels rapidly returned to normal (Fig. 1) and at follow-up 2 months later, the only clinical finding was a minimal proximal leg weakness.

Case 2

A 59-year-old woman suffered a sub-arachnoid haemorrhage but carotid angiography failed to demonstrate an aneurysm or other surgically treatable lesion. Vertebral angiography was not performed because of generalized arteriosclerosis and she was treated with EACA 18 g daily in divided doses. After 5 weeks of therapy, she developed pain and weakness in her right biceps and deltoid muscles and a more generalized proximal myopathy subsequently developed.

Investigations, course and management. Routine haematological screening, ESR, plasma electrolytes and liver function tests remained normal but there was a gross elevation of serum aspartate transaminase (480 i.u./l), creatine kinase (6500 i.u./l) and aldolase (180 i.u./l) (Fig. 1). Withdrawal of the drug resulted in a rapid fall in serum enzyme levels and clinical improvement within one week. After 3 weeks the patient was well and enzyme levels had returned to normal. Electromyography and open biopsy of the left biceps muscle at that time revealed no abnormality.

FIG. 2. Relationship between evolution of symptoms and serum enzyme levels during and after EACA therapy.

TABLE 1. Clinical, biochemical and histological features in reported cases of EACA myopathy

References	Subjects age (years)/sex	Diagnosis	Daily dose of EACA (g)	Duration of treatment before symptom (weeks)	CK i.u./l (normal < 50)	Biopsy
Korsan-Bengsten <i>et al.</i> , 1969	31/M	HAO	30	5	?	—
		HAO	30	7	?	Focal necrosis
Bennett, 1972	32/M	Ulcerative colitis	24	6	1360	—
Frank <i>et al.</i> , 1972	22/M	HAO	24	24 days*	?	—
	47/M	HAO	24	4 days*	141	—
Erill, Cabezas and Ausina, 1974	48/M	HAO	16-18	24	?	—
Shaw and Miller, 1974	?/F	'obstetric problem'	24	?	?	—
This report, 1978	74/F	SAH	30	5	4680	Severe necrotizing myopathy
	59/F	SAH	18	5	6500	Normal†

? Result unknown.

— Not performed.

HAO Hereditary angioneurotic oedema.

SAH Subarachnoid haemorrhage.

* Patients were treated for 7-8 months at a dose of 16 g/day before increasing dose to 24 g/day.

† Biopsy taken 3 weeks after stopping therapy with EACA.

Discussion

Only 2 reports of EACA myopathy have appeared previously (Korsan-Bengsten *et al.*, 1969; Bennett, 1972) but cases of painful proximal myopathy attributable to the drug have been mentioned by several other authors (Frank *et al.*, 1972; Erill, Cabezas and Ausina, 1974; Shaw and Miller, 1974). Table 1 illustrates the daily doses of drug administered and the length of time for which the drug was taken before symptoms developed in each case. The 2 cases described here illustrate the typical syndrome. Muscle pain and tenderness are usually the earliest symptoms, rapidly followed by weakness with widespread involvement of proximal and axial muscles, the neck muscles being unaffected. Myoglobinuria may occur, together with marked elevation of serum enzyme levels reflecting the severity of the myopathy. The present cases also illustrate the reversibility of the myopathy on withdrawing the drug.

The fact that symptoms only appear after 4–6 weeks of treatment with daily doses of 18–30 g suggests a cumulative dose-related effect. However, many patients have taken up to 32 g daily for long periods without developing a myopathy (Korsan-Bengsten *et al.*, 1969), raising the possibility of an

idiosyncratic reaction. The relevance of hypokalaemia in the development of the myopathy in Case 1 is conjectural. Hypokalaemia itself can cause muscle weakness and might therefore be a precipitatory factor but changes in K^+ level were not noted in any other case.

Acknowledgments

We wish to thank Dr C. Strang for allowing us to report the first case and Dr Peter Fawcett for performing and reporting the electromyographic studies.

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