Ann. rheum. Dis. (1966), **25**. 175.

FAILURE OF ϵ-AMINOCAPROIC ACID IN THE TREATMENT OF SCLERODERMA

BY

A. P. HALL AND J. T. SCOTT
Department of Medicine, Postgraduate Medical School, London

In recent years ϵ-aminocaproic acid (EACA) has been introduced to clinical medicine as an antifibrinolytic agent (Sherry, Fletcher, Alkjaersig, and Sawyer, 1959) and has been used in the treatment of a variety of haemorrhagic disorders (Sweeney, 1965).

Rotstein, Gilbert, and Estrin (1963) commented favourably on its therapeutic effect in progressive systemic sclerosis (scleroderma) and later (Rotstein, Reiss, Lauriello, and Bourel, 1965) reported that 21 of 33 cases showed a fair to excellent response. Its beneficial effect was attributed to the hypothesis that the pathological changes in scleroderma were caused by breakdown products of fibrinolysis, which was inhibited by EACA.

The value of therapy in scleroderma is difficult to assess because of the variable course which the disease can run. It therefore seemed desirable to obtain further information about the new drug. This paper presents briefly our experience with EACA in eight patients. Six had classical scleroderma; one (Case 4) had dermatomyositis with calcinosis and sclerodactyly; and one (Case 8) had Werner's syndrome with sclerodermatous changes developing in the legs.

Methods of Assessment

Symptoms were carefully recorded before, during, and after therapy. Objective changes were noted, supplemented when indicated by clinical photography.

Strength of grip was tested with a standardized rubber bag attached to a mercury sphygmomanometer, filled with air to an initial pressure of 20 mm. Hg. A mean of three readings was taken at the same time of day. Passive stiffness of one or other second metacarpophalangeal joint and volume of one hand were measured by methods previously described (Scott, 1960). Reactive hyperaemia was also measured in the arm (Pickering, 1933). In patients with Raynaud's phenomenon, serial recordings of digital skin temperature during a period of reflex heating of the trunk were made before and after the intravenous phase of treatment.

Administration of EACA

For intravenous use 250 ml. 0·1 g./ml. solution (containing 25 g. EACA) were added to a bottle containing 300 ml. normal saline. Up to 50 g. EACA daily were given by infusion.

For oral use patients took either the granules containing 50 per cent. EACA, a syrup containing 0·2 g./ml., or (because the latter was usually unpalatable) an aqueous mixture of the same strength. Dosage schemes for every patient are shown in the Table (overleaf).

Patients Studied and Results of Treatment

The patients studied, together with the individual dosage of EACA and results of the treatment, are summarized in the Table, which shows that EACA did not appear to alter the natural progress of the disease in any patient. In view of the negative results, details of the assessment criteria outlined above are not given.

Discussion

In their first communication of the use of EACA in scleroderma, Rotstein and others (1963) gave their patients 210 g. of the drug intravenously over 7 days followed by 32 g. daily orally (sometimes later reduced to 16 g. daily). They reported that, in the patients who responded to therapy, the sclerodermatous skin became softer, oedema disappeared, pigmentation lessened, joints became more mobile, and Raynaud's phenomenon improved. The same group (Rotstein and others, 1965) reported that the patients who responded to the treatment were those showing the progressive stage of the disease, *i.e.*, oedema of the interstitial tissue and early fragmentation of the collagen and elastic fibres, whereas those who did not respond showed hyalinization of the interstitial tissue. They suggested that the action of the drug was anti-inflammatory, anti-allergic, diuretic, or a combination of these.

Although our experience is smaller than that of

TABLE
PARTICULARS OF

Patient No.	Age (yrs)	Sex	Clinical Details	Investigations	E.S.R. (mm./hr) (Westergren)
1	64	F	Raynaud's phenomenon and stiffness of extremities 3 yrs Scleroderma involving hands and feet	Barium swallow normal Electrocardiogram normal	8
2	24	F	Raynaud's phenomenon 2 yrs Thickened and pigmented skin upper limbs 1 yr Flexion contractures elbows 6 mths	Electrocardiogram: inverted T waves Electromyogram: myopathy R. deltoid Skin biopsy: Scleroderma	5
3	22	F	Tight skin on face and hands 12 yrs Raynaud's phenomenon 5 yrs Recurrent ulceration and healing of finger tips, 1 yr	*X* ray hands: bone resorption from terminal phalanges Brachial arteriogram: organic occlusion digital arteries	23
4	22	F	Acute polyarthritis with oedema lower legs and 50lb. weight loss in 1949 Features of chronic dermatomyositis and scleroderma with calcinotic nodules of fingers	*X* ray hands: bone resorption from terminal phalanges and calcinotic nodules	10
5	57	M	Raynaud's phenomenon and pigmentation skin 2 yrs Pulmonary infections and dysphagia 1 yr Extensive scleroderma of skin	Electrocardiogram: intraventricular conduction defect Chest *x* ray: cardiomegaly, interstitial fibrosis	20
6	67	M	Raynaud's phenomenon 15 yrs Dyspnoea 4 yrs Diarrhoea 1 yr Extensive scleroderma of skin	Skin biopsy: scleroderma Other investigations confirmed involvement of heart, kidneys, and small intestine	22
7	53	F	Fatigue and muscular aching 4 yrs Stiffness of extremities with Raynaud's phenomenon and oedema 2 yrs Tendon crepitus 1 yr	Skin biopsy: scleroderma	15
8	45	F	Greying of hair at age 16 Bilateral lens cataracts removed at age 28 Appearance of premature senility with muscle wasting and tight shiny skin on legs	Werner's syndrome diagnosed This patient was reported by Illis (1962)	34

Rotstein and his colleagues, we were unable to detect any improvement specifically associated with the drug in seven patients with scleroderma and one patient with dermatomyositis. The results were so unimpressive that a further trial was not undertaken.

We cannot say that EACA possesses no therapeutic action in scleroderma but, if it has any at all, this must be very slight or apparent in a small proportion of patients only. We doubt if it is, in fact, of any clinical use in this condition and statements of its beneficial effect should be treated with reserve unless substantiated by properly-controlled trials.

No serious toxic effects were encountered using these large doses, a fact which may be of interest to clinicians using EACA in the treatment of haemorrhagic diseases. None of our patients had any disorder of clotting as far as we know, but they were not investigated from this aspect. Case 1 had a transient episode of impaired colour vision and urticaria on the fourth day of infusion. The oedema in Case 7 increased during infusion. The only other adverse effects have been nausea and diarrhoea during oral therapy in seven of the eight patients, severe enough in Case 7 to make us discontinue the drug.

Other forms of treatment in scleroderma have been recently reviewed (Bywaters and Scott, 1965). Steroid hormones may suppress the more acute inflammatory manifestations of the disease, but nothing is known which will alter its variable course.

Summary

ϵ-aminocaproic acid was not found to be of any definite benefit in seven patients with scleroderma and in one patient with dermatomyositis.

We are indebted to Professor E. G. L. Bywaters, who suggested this study, and to KABI Pharmaceuticals for supplying the various preparations of EACA.

REFERENCES

Bywaters, E. G. L., and Scott, J. T. (1965). "Progress in Clinical Rheumatology", edited by A. St. J. Dixon, p. 142. Churchill, London.

EIGHT CASES

EACA Dosage	Toxic Effects	Follow-up
155g. intravenously over 3½ days, then 15g. orally daily for 6 mths	At end of infusion transient impairment of colour vision and urticaria	Gradual deterioration in scleroderma during drug treatment
15g. daily orally for 5 mths	Nausea	General symptoms were improving before treatment started Flexion contractures improved both on and off therapy
220g. intravenously over 4 days, then 15g. orally for 10 mths	Nausea on oral therapy	No obvious improvement associated with drug
40g. intravenously over 2 days, then 15g. orally for 3 mths	Syncope during infusion (probably unrelated to therapy) Nausea and diarrhoea on oral therapy	No improvement in condition of skin nor in calcinotic nodules
300g. intravenously over 6 days, than 45g. orally daily till death 6 wks later from pulmonary fibrosis	Nausea and diarrhoea on oral therapy	Rapid deterioration before and during treatment uninfluenced by therapy
15g. orally daily for 3 mths	Nausea	Slow progression of clinical features during treatment
195g. intravenously over 4 days, then 30g. orally for 1 wk	Oedema increased during intravenous therapy Oral therapy caused nausea and diarrhoea and drug was discontinued	Clinical course unaffected by treatment
6g. orally daily for 3 mths (maximum tolerated dose)	Nausea when higher dosage attempted	No change in skin on legs

Illis, L. (1962). *Postgrad. med. J.*, **38**, 286.

Pickering, G. W. (1933). *Brit. med. J.*, **2**, 1106.

Rotstein, J., Gilbert, M., and Estrin, I. (1963). *J. Amer. med. Ass.*, **184**, 517 (letter).

——, Reiss, F., Lauriello, A., and Bourel, M. (1965). *Arthr. and Rheum.*, **8**, 465 (Abstract).

Scott, J. T. (1960). *Ann. rheum. Dis.*, **19**, 361.

Sherry, S., Fletcher, A. P., Alkjaersig, N., and Sawyer, W. D. (1959). *Trans. Ass. Amer. Phycns.*, **72**, 62.

Sweeney, W. M. (1965). *Amer. J. med. Sci.*, **249**, 576.

L'échec de l'acide ε-aminocaproïque dans le traitement de la sclérodermie

RÉSUMÉ

Le traitement par l'acide ε-aminocaproïque n'apporta aucun avantage défini à sept malades atteints de sclérodermie et à un malade atteint de dermatomyosite.

El fracaso del ácido ε-aminocaproico en el tratamiento de la esclerodermia

SUMARIO

El ácido ε-aminocaproico trajo poco beneficio definitivo a siete enfermos con esclerodermia y a uno con dermatomiositis.