Clinical Aspects of the Use of Gamma Linolenic Acid in Systemic Sclerosis

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Systemic sclerosis is a multi system disorder, for which there is no satisfactory treatment. Theoretically, dietary supplementation with essential fatty acids may lead to an increase in their derivatives, the vasoactive prostaglandins, which benefit the acute and chronic ischaemic lesions of this disease.

We assessed the value of concentrated essential fatty acids in patients with systemic sclerosis, concentrating particularly on vascular symptoms and objective tests of vascular reactivity. Twenty-five patients with systemic sclerosis were randomised to receive concentrated essential fatty acids or placebo, for 6 months in a double-blind parallel group study. There was no significant difference between the active and placebo groups in terms of maximum blood flow after warming, minimum blood flow after cooling or the recovery time after cooling. There were no significant differences between the groups in the other parameters measured.

Dietary essential fatty acids have no role in the treatment of vascular symptoms in established systemic sclerosis. *Key words: prostaglandins; vascular reactivity; laser Doppler flowmetry.*

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Systemic sclerosis is a multi system disorder, characterised by the association of connective tissue fibrosis and vascular abnormalities. It is thought to be the result of endothelial cell damage, which in turn produces vascular occlusion and tissue ischaemia (1,2). At present there is no satisfactory treatment for systemic sclerosis (3). Raynaud's phenomenon can be treated with vasodilators, but in general they are less useful in patients with systemic sclerosis. Naturally occurring arachidonic acid derivatives, particularly prostacyclin and prostaglandin E1, have been shown through their vasodilatory and antiplatelet effects to help acute and chronic ischaemic lesions in this disease (4,5). They are not currently available as oral preparations for routine use in clinical practice.

Evening primrose oil (EPO) contains large quantities of essential fatty acids (EFAs) including approximately 8% gamma linolenic acid (GLA), which is the precursor of the vasoactive prostaglandin derivatives (6). In theory, reduced vascular reactivity (7), platelet aggregation (8) and inflammation (9) might be expected as a result of dietary supplementation with GLA. A study of the use of EPO in Raynaud's phenomenon of mixed aetiologies suggested there may be some benefit (10) from this form of treatment. We have assessed the value of concentrated EFA, containing gamma linolenic acid, on clinical aspects of systemic sclerosis over a 6-month period, concentrating particularly on vascular symptoms and objective tests of vascular reactivity.

PATIENTS AND METHODS

Twenty-five patients with well characterised systemic sclerosis (based on the American Rheumatism Association criteria (11)) were included in the study. They were randomised (by Scotia) to receive either oral EPO or placebo for 6 months in a double-blind parallel group study. Patients with severe inter current illnesses, those with epilepsy, those on phenothiazines, anticoagulants and lithium, and females who were pregnant or actively trying to conceive were excluded from the study. A full history, including a drug history, and a clinical examination were performed. Twenty-two women and 3 men entered the study; they were aged between 19–78 years and had a 1–22-year history of systemic sclerosis. Sixteen women and 2 men had limited type systemic sclerosis, and 6 women and one man had diffuse type systemic sclerosis (15). Thirteen patients were in the active group and 12 in the placebo group.

RESULTS

There were no significant differences between the groups at baseline. Patients were entered into the study between January and June and final readings were therefore made from July to December. Fourteen patients were on medication deemed essential, which remained unchanged throughout the trial, with two exceptions, both of these on placebo: one patient was initially on hydroxychloroquine and one took nifedipine for 1 week. The following were unchanged: 5 patients were on non-steroidal anti-inflammatory drugs, 5 were on oral prednisolone, 2 took nifedipine, one penicillamine, one transderm nitro patches, one oxpentifylline and one naftidrofuryl. Twenty-one out of 25 patients completed the trial. Two withdrew from the active arm before the 3-month assessment, one due to diarrhoea, one was lost to follow-up. Two withdrew from the placebo group: one patient found the capsules too large to swallow, the other was lost to follow-up.

Patients randomised to active treatment took an EFA preparation, containing concentrated EPO and marine fish oil, 6 capsules daily (3 capsules bd after meals) which contained 1620 mg GLA (Scotia), or 6 identical placebo capsules (500 mg sunflower oil and 5 mg vitamin E) daily for 6 months. Sunflower oil capsules were chosen as the placebo because they were identical in appearance to the active (EFA) treatment capsules but they do not contain significant amounts of GLA. Each capsule of the EFA preparation contained 270 mg GLA as the free fatty acid and as the lithium salt, 45 mg eicosapentaenoic acid as the free fatty acid, 7.5 mg docosahexaenoic as the free fatty acid, 5 mg lithium ion and antioxidants (5.0 mg natural vitamin E, 0.25 mg ascorbyl palmitate and 0.10 mg citric acid). The medication was introduced as two capsules daily and was increased stepwise every 2 to 3 days until the full dose was reached. Compliance was assessed by asking the patients to return their capsules at each visit. Additional pre-treatment medication was discontinued if possible but essential medication was continued throughout the trial. All subjects were assessed by objective measures of blood flow pre-treatment, and at 3 and 6 months. Each assessment took place in a constant temperature room at $23 \pm 1.6°C$. The patient rested quietly for at least 20 min before baseline observations were made. Assessments were performed by the same observer

at each visit. The presence and number of cutaneous ulcers of the hands were recorded. Laser Doppler blood flow (Perimed Pfld, using maximum flux recording) at the palmar aspect of the distal phalanx of a finger of the right hand was recorded. Either the index or middle finger was used, and the same finger was used at each visit. The blood flow was recorded accurately to a previously described protocol (12). Measurements were made at baseline, secondly after warming (immersion of the subjects right hand in a water bath set at 37°C for 10 min) and thirdly, during and after cooling (the patient's right hand was placed in a clear perspex box for 10 min, into which air was blown through crushed ice; this gave an approximate temperature of 17°C at the finger tips). Laser Doppler flowmetry was recorded at zero, then at 2-min intervals until baseline levels were achieved or for 25 min (which ever was the shorter). Laser Doppler flowmetry is a reliable tool for measuring clinically relevant changes (13,14).

A 5-point scale was used to record the patient's subjective symptom assessment, at 0, 3 and 6 months (1 = much worse, 2 = worse, 3 = no change, 4 = better, 5 = much better). Each subject was given a diary to complete weekly; this documented any attacks of Raynaud's, how long they lasted, where they occurred (indoors or outside) over a 24-h period during that week. Finally the extent of cutaneous sclerosis was recorded on a 0–3-point scale at six sites: hands, arms, trunk, legs, feet and face.

Statistical evaluation of the results was performed by the Kruskal Wallace test, on the change in the measured variables over the study period. These trial numbers gave a power of 80% at an α of 0.05.

Blood flow studies

Blood flow as measured by laser Doppler flowmetry had a wide range. The maximum blood flow after warming and minimum blood flow after cooling at each respective visit were compared in each patient. The changes in blood flows after 6 months' treatment were not significantly different.

Nor was the time to return to baseline after cooling significantly different between the active and placebo groups at 6 months.

Cutaneous ulceration

Cutaneous ulcers of the hands were present initially in 5 of the actively treated patients and 6 placebo-treated patients. At 6 months 3 patients in the active treatment group and 6 patients in the placebo group had ulcers.

The median number of ulcers per patient fell from 1 (interquantile range 0–3) at baseline to 0 (0–2) at 6 months in the active group, and from 1 (0–2) at baseline to 0 (0–1) at 6 months in the placebo group.

Two patients in the active treatment group had healing of their ulcers during the 6-month trial period. No actively treated patient developed ulceration during the trial. One patient in the placebo-treated group developed ulcers during the 6-month period. There was no significant change between the groups in terms of the number of ulcers the patients had. Forty-eight percent of patients either had no ulcers or experienced no change in the number of ulcers throughout the study period.

Subjective assessments

The patients' subjective views were similar at 3 and 6 months. Patients in the active group had a mean score of 3.5 (range 3–5) at 3 months and 3.1 (range 1–5) at 6 months. In the placebo group the figures were 2.9 (range 1–4) and 3.1 (range 2–4), respectively. At 6 months, 15 patients (60%) (8 in the active group and 7 in the placebo) felt no difference. There was no significant difference between the groups.

Twenty-four patients returned their diaries. The number and duration of attacks, in both groups, declined but there was no significant difference between the two groups.

Cutaneous sclerosis

Predictably the extent of cutaneous sclerosis was not significantly altered in any patient over the 6 months. Mild improvements and deteriorations were noted in both groups. The median score was 4 (interquantile range 1–6) at baseline and 3 (1–7) at 6 months in the active group and 3 (1–6) at baseline and 2 (1–3) at 6 months in the placebo group. No significant differences were elicited between the groups.

Adverse events

There were no unpredicted side-effects. Gastrointestinal problems were the main symptoms related to active therapy; 3 patients had nausea and indigestion, 3 had diarrhoea and this necessitated withdrawal from the trial in one. In the placebo group one patient complained of indigestion, one had a transient headache and one a brief rash. The headache and rash were thought to be coincidental.

Compliance

This group of well-motivated patients had good compliance, as assessed by checking their returned capsules and by the incidence of adverse events.

DISCUSSION

EFAs, as EPO, are used in a wide variety of conditions – from atopic eczema to pre-menstrual tension and mastalgia – with differing degrees of success.

Theoretically, dietary supplementation with EFA should improve the acute and chronic ischaemic lesions which are part of systemic sclerosis, through production of vasoactive prostaglandin derivatives (5,6). Disappointingly in this study, there was no evidence of clinical benefit to these patients with systemic sclerosis from dietary supplementation with concentrated fatty acids. Vascular symptoms and consequences of vascular pathology were equally uninfluenced. Not surprisingly, we were also unable to demonstrate any effect on cutaneous sclerosis.

Other studies have shown limited clinical benefit. Belch et al. (10) looked at the effect of EPO in patients with Raynaud's phenomenon. They found no significant improvement in blood flow, as measured by hand temperatures and cold challenge plethysmography, in agreement with our findings. However, 6 of 11 patients in their EPO group reported subjective improvement compared with 2 of 9 in the control group. They also noted that the placebo group had significantly longer and more frequent attacks of Raynaud's, as assessed by diaries which the patients completed daily. There was no significant difference between our two groups in terms of frequency or duration of attacks of Raynaud's. The earlier study only lasted

8 weeks compared to 6 months for ours; this may account for some of the differences in results.

Patients in our trial were allowed to continue their regular medication, if it was regarded as essential. Several patients were taking drugs known to effect the vascular system, mainly in the group that received placebo. This is unlikely to have influenced the results, since neither group demonstrated significant improvements in either objective or subjective measures of change, and they showed similar vascular measurements at the outset of the study. The numbers in this trial were not large. It is possible that a small significant effect would have been detected by a larger study. However, it remains most likely that essential fatty acids have at best a very limited role in the treatment of vascular symptoms in established systemic sclerosis. Their role in early disease was not investigated.

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