PAPERS AND ORIGINALS

Treatment of Raynaud's phenomenon by fibrinolytic enhancement

P E M JARRETT, M MORLAND, N L BROWSE

British Medical Journal, 1978, 2, 523-525

Summary and conclusions

Twenty patients with advanced Raynaud's phenomenon, in 14 of whom it was secondary to scleroderma, were treated with stanozolol, an anabolic steroid that enhances natural fibrinolysis. All showed an increase in hand blood flow and a reduction in symptoms during treatment. This response may have been caused by the lysis of fibrin deposited in the digital arteries and the reduction of plasma viscosity.

Stanozolol is a useful addition to the treatment of patients with advanced Raynaud's phenomenon who have trophic changes.

Introduction

Many patients with idiopathic or scleroderma-associated Raynaud's phenomenon have reduced blood fibrinolytic activity as measured by the euglobulin lysis time,¹ and many with idiopathic Raynaud's phenomenon have raised plasma fibrinogen concentrations and increased blood viscosity.² The small digital arteries and arterioles of patients with severe idiopathic or scleroderma-associated Raynaud's phenomenon show intimal proliferation and thrombosis,³ and in scleroderma there may be fibrin deposits in the lumen of the digital capillaries.⁴

We thought that enhancing blood fibrinolytic activity in patients with Raynaud's phenomenon might improve the hand blood flow, either by reducing fibrinogen concentrations and thus blood viscosity or by increasing the lysis of any fibrin that

was deposited in the small vessels and reducing the number of minor thromboses. Before beginning a clinical trial of the effect of fibrinolytic enhancement in such patients we measured the blood fibrinolytic activity and plasma fibrinogen concentrations in 50 patients with idiopathic or scleroderma-associated Raynaud's phenomenon. Twenty of these patients then entered the trial, in which the effect of fibrinolytic enhancement with the anabolic steroid stanozolol was assessed by measuring hand blood flow, skin temperature, and grip strength.

Patients and methods

Blood fibrinolytic activity and plasma fibrinogen concentrations were measured in 24 patients with idiopathic and 26 with scleroderma-associated Raynaud's phenomenon. Those with idiopathic disease (seven men and 17 women) had a mean age of 49 years (range 21-76) and had had their symptoms for a mean of 10.4 years (range 1-49). The patients with scleroderma (four men and 22 women) had a mean age of 53.2 years (range 28-76) and had had their symptoms for a mean of 9.7 years (range 1-40).

Twenty of these 50 patients had advanced disease and were admitted to the clinical trial: six—all women—had idiopathic Raynaud's phenomenon, and 14—2 men and 12 women—had scleroderma. The six women with idiopathic disease had a mean age of 60.8 years (range 38-76) and a mean duration of symptoms of 17.7 years (range 6-49). The 14 patients with scleroderma had a mean age of 51.6 years (range 28-76) and a mean duration of symptoms of 9.3 years (range 1-23). All 20 patients had undergone cervical sympathectomy more than 12 months before the trial, and all had severe bilateral disease with trophic changes and symptoms such as pain and recurrent infection in the fingertips.

Forty-eight ambulant volunteers acted as controls for the blood investigations.

Blood tests were carried out on all patients and volunteers between 0830 and 1030 after a standard, light, non-fatty breakfast. Fibrinolytic activity was measured by the dilute blood clot lysis time (DBCLT)⁵ and fibrin plate lysis area (FPLA).^{6,7} Plasma fibrinogen was measured by the clot weight method of Ingram.⁸ Blood flow in the left hand was measured by venous occlusion plethysmography after the lightly clad, recumbent patient had rested for half an hour in a quiet thermal laboratory maintained at $23 \pm 0.5^\circ\text{C}$ and 50-60% humidity. The temperature of the water in the plethysmograph was 35°C .

Skin temperature was measured at the same time as the blood flow with thermocouples applied to the middle of the palm and centre of

St Thomas's Hospital Medical School, London SE1 7EH

P E M JARRETT, FRCS, consultant surgeon (now at Kingston Hospital, Kingston-upon-Thames, Surrey)

M MORLAND, BSC, research assistant, department of surgery

N L BROWSE, MD, FRCS, professor of vascular surgery

the pulp of the index finger of the right hand. The thermocouples were attached and insulated by adherent pads of foam rubber 1-cm thick $\times$ 1.5 $\times$ 1.5 cm. Temperatures were plotted automatically every 10 seconds by a Honeywell multichannel recorder. Resting skin temperature was taken as the reading obtained when the print-out had been steady for 15 minutes.

Grip strength was measured with a mechanical grip meter (Downes sprung-metal goniometer). Both hands were tested three times, and the mean of six readings (three from each hand) was taken as the grip strength.

The patients were asked to note the frequency and severity of their attacks of vasospasm and the number and site of infections occurring in their fingers and hands.

All results were analysed with Student's *t* test and, when indicated, a paired *t* test.

Trial design—The 20 patients studied entered the trial sequentially between June and November 1976 to obviate any effect of seasonal changes on blood flow. All were given stanozolol (Stromba), which enhances fibrinolytic activity,⁹ in a dose of 5 mg twice daily by mouth for three months. Treatment was then stopped for three months, and then a second course of stanozolol in the same dosage was given for a further three months. Blood fibrinolytic activity, plasma fibrinogen concentrations, hand blood flow, and palm and index-finger temperatures were measured before entering the trial, at the end of the first three months of treatment, after three months without stanozolol (with the addition of the grip strength measurements), and after the second three months of treatment. As stanozolol is an anabolic steroid, liver function tests were carried out at each visit.

Results

FIBRINOLYTIC ACTIVITY AND FIBRINOGEN CONCENTRATIONS

Table I shows the mean DBCLT, FPLA, and plasma fibrinogen concentrations in all 24 patients with idiopathic Raynaud's phenomenon, the 26 patients with scleroderma, and the 48 normal ambulant volunteers. Compared with the healthy volunteers both groups of patients had significantly reduced fibrinolytic activity as shown by a prolonged DBCLT and a reduced FPLA ($P=0.009$ and $P=0.004$ respectively in the idiopathic cases, and $P=0.0003$ and $P=0.05$ respectively in those with scleroderma). Plasma fibrinogen concentrations were significantly higher in both the patients with idiopathic Raynaud's phenomenon and those with scleroderma ($P=0.001$ and $P=0.0001$ respectively).

TABLE I—Mean ($\pm$ SE of mean) fibrinolytic activity (DBCLT and FPLA) and fibrinogen concentrations in patients with idiopathic Raynaud's phenomenon and scleroderma compared with normal ambulant volunteers

	No of subjects	DBCLT (min)	FPLA (mm ²)	Fibrinogen (g/l)
Normal ambulant volunteers	48	256 $\pm$ 18	453 $\pm$ 37	2.75 $\pm$ 0.072
Patients with idiopathic Raynaud's phenomenon	24	376 $\pm$ 53*	323 $\pm$ 49*	3.79 $\pm$ 0.16*
Patients with scleroderma-associated Raynaud's phenomenon	26	473 $\pm$ 72*	335 $\pm$ 43*	4.25 $\pm$ 0.19*

DBCLT = Dilute blood clot lysis time. FPLA = Fibrin plate lysis area.
*Comparison with normal volunteers: $P<0.05$ (Student's *t* test).

EFFECT OF STANOZOLOL

Four of the 20 patients who entered the trial failed to complete the first three months of treatment for reasons unrelated to the drug. One of these was included in the 12 patients who completed the second three months of treatment. After one month without treatment one patient insisted on restarting her tablets and was thus excluded from the second three months of the trial.

Hand blood flow (table II)—Before treatment the mean blood flow in the left hand was 5.3 ml/min/dl tissue (range 1.13–13), and after three months of stanozolol this had risen to 10.9 ml/min/dl (range 3.9–26). This 106% increase was significant ($P<0.005$; paired *t* test). After three months without stanozolol the mean hand blood flow had fallen to 8.7 ml/min/dl (range 3.6–17.2)—that is, above the level

TABLE II—Mean ($\pm$ SE of mean) effect of stanozolol on hand blood flow in patients with idiopathic and scleroderma-associated Raynaud's phenomenon

	Pretreatment	After 3 months' stanozolol	After 3 months' no treatment	After second 3 months' stanozolol
No of patients	16	16	12	12
Blood flow (ml/min/dl tissue)	5.3 $\pm$ 0.73	10.9 $\pm$ 1.7*	8.7 $\pm$ 1.27	14.2 $\pm$ 2.3*

*Comparison with previous value shown: $P<0.05$ (Student's *t* test).

recorded before entry to the trial. There was no significant difference ($P>0.05$) between the blood flow after the three months without stanozolol. After the second three months of treatment there was a further 63% increase in mean hand blood flow to 14.2 ml/min/dl tissue (range 6.35–28.22). This was a significant improvement on the flow measured just before the second course of treatment ($P<0.05$) but was not significantly different from the flow recorded at the end of the first three months of treatment ($P>0.05$).

Plasma fibrinogen concentrations (table III)—After three months of stanozolol treatment the mean plasma fibrinogen concentration had fallen from 3.9 (range 2.59–5.53) to 2.8 (range 1.73–4.59) g/l ($P=0.0004$). After three months with no treatment the mean concentration had risen to 3.7 (range 2.25–5.19) g/l ($P<0.02$). The second three months of treatment reduced the mean fibrinogen concentration to 3.2 (range 1.97–4.79) g/l, which differed significantly from the value recorded at the beginning of the second course ($P=0.04$).

DBCLT (table III)—There were significant changes in the DBCLT after each course of treatment. The change from a mean of 428 min (range 90–1130) to a mean of 178 min (range 105–345) after the first course was highly significant ($P=0.003$). The change from a mean of 489 min (range 140–1440) to a mean of 184 min (range 110–330) during the second course was just significant ($P=0.04$). In the intervening three months without treatment the mean DBCLT rose significantly to pretreatment values.

FPLA (table III)—There was no significant change in the FPLA after the first course of treatment ($P>0.05$). Some of these measurements, however, were plagued by troubles with the pH meters and we doubt the accuracy of these results. The problems were solved by the time the second course of treatment began, and the results showed an increase in mean lytic area on the fibrin plate from 343 mm² (range 100–715) to 448 mm² (range 120–915). This increase was significant when assessed by the paired *t* test ($P>0.05$).

Palm and index-finger temperatures (table IV)—There were

TABLE III—Mean ($\pm$ SE of mean) effect of stanozolol on fibrinolytic activity (DBCLT and FPLA) and plasma fibrinogen concentrations in patients with idiopathic and scleroderma-associated Raynaud's phenomenon

	No of patients	DBCLT (min)	FPLA (mm ²)	Fibrinogen (g/l)
Pretreatment	16	428 $\pm$ 74	374 $\pm$ 48	3.92 $\pm$ 0.21
After 3 months' stanozolol	16	178 $\pm$ 20*	384 $\pm$ 57	2.78 $\pm$ 0.19*
After 3 months' no treatment	12	489 $\pm$ 128*	343 $\pm$ 54	3.73 $\pm$ 0.23*
After second 3 months' stanozolol	12	184 $\pm$ 22*	448 $\pm$ 82*	3.17 $\pm$ 0.25*

DBCLT = Dilute blood clot lysis time. FPLA = Fibrin plate lysis area.
*Comparison with previous value shown: $P<0.05$ (Student's *t* test).

TABLE IV—Mean ($\pm$ SE of mean) effect of stanozolol on palm and index-finger temperatures in patients with idiopathic and scleroderma-associated Raynaud's phenomenon

	No of patients	Palm temperature (°C)	Index-finger temperature (°C)	Grip strength (kg)
Pretreatment	16	30 $\pm$ 0.94	27.3 $\pm$ 1.2	
After 3 months' stanozolol	16	33.2 $\pm$ 0.6*	31.3 $\pm$ 1.02*	
After 3 months' no treatment	12	31.1 $\pm$ 1.1*	29.3 $\pm$ 1.33*	69.2
After second 3 months' stanozolol	12	33.9 $\pm$ 0.5*	32.8 $\pm$ 0.7*	84.7*

*Comparison with previous value shown: $P<0.05$ (Student's *t* test).

significant increases in the mean palm temperature after each course of treatment, rising from 30° (range 25-34.4) to 33.2°C (range 29.1-36.15) after the first course ($P=0.006$) and from 31.1° (range 25.1-35.8) to 33.9°C (range 31.3-35.9) after the second course ($P<0.02$). The mean temperature of the index finger also increased significantly, from 27.3° (range 22.9-34.25) to 31.3°C (range 24.4-35.4) after the first course of treatment ($P<0.02$) and from 29.3° (range 22.4-35.4) to 32.8°C (range 28.5-35.7) after the second course ($P<0.03$).

Grip strength—The mean grip strength before the second course of treatment was 69.2 kg (range 10.5-192); after treatment it was 84.7 kg (range 12.5-200). This change was significant when assessed by the paired t test ($P=0.00005$).

Subjective changes—Some 80% of the patients (13 of the 16 completing the first course of treatment, and 10 of the 12 completing the second course) stated that their hands were improved by each course of stanozolol. They said that the Raynaud's attacks were less frequent, of shorter duration, and less severe during treatment and that their hands felt warmer between attacks.

Side effects of treatment—During treatment four patients felt tired and had minor fluid retention. This latter complication was easily controlled with chlorothiazide diuretics. Two patients had amenorrhoea, one complained of acne, and another, older woman complained of slight facial hirsutism. One patient had an increase in serum aspartate aminotransferase during the second three months of treatment, which fell rapidly to normal after stopping treatment. There was no other alteration in routine liver function values in this or any other patient. No appreciable change in haemoglobin concentration or packed cell volume was recorded during treatment.

Discussion

We confirmed the findings of others^{1,2,7} of raised plasma fibrinogen concentrations and decreased blood fibrinolytic activity in patients with idiopathic and scleroderma-associated Raynaud's phenomenon. It therefore seemed logical to investigate the effect of a drug that reduces plasma fibrinogen and increases blood fibrinolysis in these diseases.

Patients with longstanding severe Raynaud's phenomenon with trophic changes in the fingers in whom sympathectomy and vasodilator drugs have failed to halt the progress of the disease are fortunately rare. We therefore decided against a double-blind cross-over trial and chose to make blind objective measurements of hand blood flow and blood fibrinolysis during two three-month periods of treatment set three months apart to compensate for any effect on hand blood flow of the prevailing weather.

The number of patients studied does not permit valid statistical comparison of the results between the patients with idiopathic disease and those with scleroderma, but when analysed as a whole the results show that stanozolol caused a highly significant increase in hand blood flow. This increase apparently persisted to a varying degree for at least three months after stopping treatment, despite the plasma fibrinogen concentrations and blood fibrinolytic activity having returned to their abnormal pretreatment values. The second course of treatment raised the hand blood flow to a level greater than that seen after the first course of treatment, and again there was a significant reduction in plasma fibrinogen and DBCLT.

The persistent improvement in blood flow after treatment in association with the return to abnormal plasma fibrinogen concentrations suggests that stanozolol did not operate solely through the reduction of plasma fibrinogen and the concomitant decrease of blood viscosity. A possible alternative or additional mode of action is that stanozolol reduced the deposition of intravascular fibrin and increased the rate of lysis of pre-existing fibrin clots. The changes in palm and index-finger temperatures were similar to and confirmed the validity of the hand blood flow measurement.

Some patients noticed that their hands were stronger after taking the drug and said they could perform some activities that they had not been able to do for some time. This prompted us to measure grip strength in the second period of treatment. The patients' observations were confirmed by the objective finding of a significantly improved grip strength.

A multitude of drugs^{3,10} have been used to treat severe Raynaud's phenomenon but there is no accepted regimen because no drug has been found to be particularly effective. Our results suggest that fibrinolytic enhancement by stanozolol should be considered in patients with advanced disease *when all other methods have failed*. Although this drug maintains its effect for a long period,⁹ it should be used with caution and control because of occasional side effects. As the fibrinolytic enhancement persists for one to two months after stopping treatment we give intermittent three-month courses separated by periods of one or two months. This minimises side effects—though does not eliminate the need for regular liver function tests and haemoglobin and packed cell volume measurements—and allows treatment to be timed to coincide with periods of cold weather.

Our results suggest that stanozolol should be considered when treating patients with advanced Raynaud's phenomenon when other, more conventional methods have failed. The mode of action of the drug is not clear, but we postulate that the improvement in hand blood flow is secondary to the increased blood fibrinolytic activity caused by the drug, which initiates the removal of both intravascular and perivascular fibrin.

We are grateful for the support of the British Heart Foundation and Winthrop-Sterling Ltd.

References

- Cunliffe, W J, and Menon, I S, *British Journal of Dermatology*, 1969, **81**, 220.
- Pringle, R, et al, *Lancet*, 1965, **1**, 1086.
- Birstingl, M, *Postgraduate Medical Journal*, 1971, **47**, 297.
- Norton, W L, *Laboratory Investigation*, 1970, **22**, 301.
- Fearnley, G R, et al, *Clinical Science*, 1957, **16**, 645.
- Astrup, T, and Mulletz, S, *Archives of Biochemistry and Biophysics*, 1952, **40**, 346.
- Browse, N L, et al, *British Medical Journal*, 1977, **1**, 478.
- Ingram, G I C, *Journal of Biochemistry*, 1952, **51**, 583.
- Davidson, J F, et al, *British Journal of Haematology*, 1972, **22**, 543.
- de Takats, G, and Fowler, E F, *Journal of the American Medical Association*, 1962, **179**, 99.

(Accepted 19 June 1978)

ONE HUNDRED YEARS AGO A man came to me with a swelling, about the size of a hen's egg, in the right submaxillary region, which had been gradually increasing for some weeks past, and was extremely tender. It appeared to be a sac tolerably, but not tensely, filled with fluid. I examined the mouth, and found one of the lower molars on that side much decayed, the gum around it swollen, and the aperture of an abscess in the gum just below it; but could trace no connection between this and the swelling under the jaw, to which I returned. On again examining, I detected, loose in the cavity, a small hard substance, which suddenly eluded my grasp and could be felt no longer. Returning to the mouth and looking under the tongue, I saw the aperture of Wharton's duct gaping open widely; and, passing a pair of forceps just within it, I managed to get hold of a calculus about half an inch long and one-eighth of an inch in diameter, the withdrawal of which allowed the escape of a quantity of milky fluid, which diminished somewhat the size of the swelling. I introduced an ordinary probe its whole length down the duct into the cavity; its withdrawal was followed by another gush of fluid. The swelling, though considerably smaller, was still tender. Giving the man a wash for the mouth, I told him to call in two days. On his again coming, the swelling had almost entirely disappeared, and was no longer tender. The aperture of the duct still continued very open, and there was still a little oozing of milky fluid from it. I again passed a probe, but could not introduce it so far as before. I drew the before mentioned offending tooth, and the patient went away. I have seen him since; the swelling has quite gone, and he has had no more trouble.

The calculus appears to have formed in the duct, causing the accumulation of fluid behind it, and consequent dilatation of the duct, which allowed the body to fall back into the cavity so formed. I must, during my manipulation, have squeezed the cyst, propelling the calculus, together with some fluid, again into the duct towards the aperture, thus allowing its removal. (*British Medical Journal*, 1878.)