PAPERS AND ORIGINALS

Idiopathic recurrent superficial thrombophlebitis: treatment with fibrinolytic enhancement

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Summary

Sixteen patients with idiopathic recurrent superficial thrombophlebitis were shown to have a defect of blood and tissue fibrinolytic activity. After six months' treatment with stanozolol their mean dilute blood clot lysis time and plasma fibrinogen fell significantly and the mean fibrin plate lysis area increased. Attacks of thrombophlebitis stopped completely in 13 patients, though five patients later suffered recurrences and phenformin had to be added to their treatment. Fibrinolytic enhancement with stanozolol seems to be effective in this previously intractable condition, and regular blood studies will indicate which patients also need phenformin.

Introduction

Idiopathic recurrent superficial thrombophlebitis (IRST) is a rare, painful, and intractable condition that does not respond to treatment with anticoagulants. Until recently there was little that could be done for patients with IRST other than administer palliative treatment for each attack. In 1975 Nilsson[1] reported that some of these patients had reduced blood and tissue fibrinolytic activity and responded favourably to fibrinolytic enhancement with a combination of ethyloestrenol and phenformin.

We therefore investigated the fibrinolytic status of 16 patients with IRST and assessed the effect of treatment with stanozolol.

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Patients and methods

Sixteen men aged 26 to 61 (mean 43 years) were investigated. On average they had had one severe attack of superficial thrombophlebitis every eight weeks (range 1-24) for a mean time of 7·7 years (range 4-20). They had all had episodes of phlebitis in the legs and seven had also had attacks in the arms. Phlebographic evidence of previous deep vein thrombosis was present in five. Eleven patients had been treated with anticoagulants with minimal benefit, and nine were still being treated in this way when they were investigated.

Apart from IRST, no patient had any other abnormality detectable by clinical examination, blood count, chest radiograph, intravenous pyelography, or barium meal examination. The pyelogram and barium meal examination were performed to exclude a carcinoma. The duration of the symptoms and the wellbeing of the patients also made an occult carcinoma most unlikely. No patient had any evidence of arterial disease.

Forty-eight healthy ambulant volunteers provided blood samples for the control studies.

The patients were assessed before treatment, every month during the first four months of treatment, and then every two months.

They attended the clinic between 0930 and 1130 after taking a standard light breakfast. A 15-ml sample of blood was removed from an antecubital vein, without venous congestion, for measuring the dilute blood clot lysis time (DBCLT),[2] fibrin plate lysis area (FPLA),[3 4] and plasma fibrinogen concentration.[5] At the initial visit vein wall fibrinolytic activity was measured on a short segment of vein removed from the dorsum of one hand using 1% plain lignocaine and a minimum of trauma.[4 6]

After the initial assessment all patients were given stanozolol 5 mg twice a day by mouth. As stanozolol is an anabolic steroid, full blood counts and liver function tests were performed at each visit. The patients were asked to record the severity, duration, and site of their attacks of thrombophlebitis. They were also asked to note any side effects of the treatment. The results were analysed using Student's *t* test.

Results

Pretreatment fibrinolytic activity—The patients' mean values for DBCLT, FPLA, plasma fibrinogen, and vein wall activity were significantly different from those of the normal volunteers (table I). DBCLT, FPLA, and plasma fibrinogen concentrations were measured in all 16 patients, and all three were abnormal in 13 patients; in two further patients two of the investigations gave abnormal results.

TABLE I—*Mean blood and tissue fibrinolytic activity and plasma fibrinogen concentration in 16 patients with IRST compared with values in 48 normal ambulant subjects*

Test	Patients with IRST	Normal ambulant subjects	Significance of difference (*t* test)
DBCLT (min)	608	256	P<0·0001
FPLA (mm²)	240	453	P<0·0001
Plasma fibrinogen (g/l) ..	4·13	2·75	P<0·0001
Vein wall activity (arbitrary units)	11·6 (14 patients)	24 (17 controls)	P<0·009

One patient showed only decreased fibrinolytic activity in his hand vein biopsy specimen. A decreased fibrinolytic activity of the hand vein biopsy was found in 13 of the 14 patients in whom this investigation was carried out successfully.

Fibrinolytic activity after six months' treatment with stanozolol—After our initial investigations four of the 16 patients were followed up in other hospitals because they lived far from London. The results of their blood tests after six months' treatment were not included in our analysis as variations in the methods used by different laboratories would have invalidated the statistical comparisons. Table II shows the effect on blood fibrinolytic activity of six months' treatment in the 12 patients we reinvestigated. The blood fibrinolytic activity of all patients improved. There was a significant reduction in the DBCLT and plasma fibrinogen concentration and a significant increase in the FPLA. The vein wall fibrinolytic activity was not measured after treatment because we did not think that it was ethically justifiable to ask the patient to undergo another minor operation.

TABLE II—*Effect of six months' treatment with stanozolol on mean blood fibrinolytic activity and plasma fibrinogen levels of 12 patients with idiopathic recurrent superficial thrombophlebitis*

Test	Before treatment	After treatment	Significance of difference (*t* test)
DBCLT (min)	578	172	P<0·003
FPLA (mm²)	247	409	P<0·01
Plasma fibrinogen (g/l) ..	3·40	2·97	P<0·03

Effect of six months' treatment on symptoms—All the patients felt better by a mean time of six weeks (range 2 to 24) after the start of treatment because they had noticed a decrease in the severity and frequency of their attacks. After six months' treatment the attacks of thrombophlebitis had stopped completely in 13 of the 16 patients. In the remaining three patients it took 32, 40, and 52 weeks of treatment to control the attacks. Treatment had lasted a mean of 19 weeks (range 4-52) before the attacks stopped. All the patients who were taking anticoagulants at the beginning of the trial had this treatment stopped within three months of starting the stanozolol.

Recurrent attacks during treatment with stanozolol—Eleven patients have had no recurrence of their thrombophlebitis for a mean time of 12·5 months (range 3-24) while taking stanozolol alone. After a mean treatment time of 12 months (range 8-15) attacks of thrombophlebitis recurred in five patients. They had experienced complete relief of their symptoms for 4·4 months. Recurrence of symptoms was associated with a decrease in the blood fibrinolytic activity and a rise in the fibrinogen level. When phenformin (one time-release capsule a day) was added to the treatment the phlebitis stopped after a mean time of 10·8 weeks (range 4-32), the blood fibrinolytic activity improved, and the plasma fibrinogen concentration fell. These five patients had no further recurrence of their symptoms while taking both drugs.

Side effects of stanozolol—The side effects of stanozolol were minor. Nausea, tiredness, slight ankle oedema, and muscular cramps occurred in a few patients for a short time in the early stages of treatment. Seven patients gained an average of 3·2 kg in weight, but only one was troubled by a persistent increase in weight. Four patients developed symptoms of migraine during the initial period of treatment. All four had suffered from migraine in the past. Their headaches were controlled by clonidine hydrochloride and after about three months they required no further treatment. No patients showed any changes in their liver function values. One patient had an increase in his packed cell volume after three months' treatment, but his blood count returned to normal after the drug was stopped.

Discussion

All but one of these 16 patients with IRST had an abnormality in at least two of the indices of fibrinolytic activity, and in none was fibrinolytic activity completely normal. When Nilsson described the effect of ethyloestrenol and phenformin on 10 patients with IRST she implied that some had a normal fibrinolytic activity. The consistency of our findings may rest on our selection of patients with a long history and indisputable diagnosis.

We chose to use stanozolol to enhance fibrinolytic activity[7] rather than a combination of ethyloestrenol and phenformin because it is simpler for the patient to take and likely to have fewer side effects. The stanozolol improved the patients' blood fibrinolytic activity and controlled their symptoms in 19 weeks. Eleven patients remained asymptomatic while taking stanozolol alone, but, after an initial improvement, another five developed recurrent attacks, which were controlled by adding phenformin to their treatment. This suggests that in some patients stanozolol alone will not maintain the enhanced fibrinolytic activity for long. By regularly measuring DBCLT, FPLA, and fibrinogen levels, however, it is possible to detect that the stanozolol is becoming less effective and so give the patient phenformin as well before the thrombotic incidents recur. Regular blood studies are worth while if they prevent most patients from having to take a second drug.

We suggest that fibrinolytic enhancement is the treatment of choice for IRST because no other form of treatment has been shown to reduce the frequency of attacks and because all the evidence suggests that this disease is caused by a primary defect of blood and tissue fibrinolysis. In most cases stanozolol seems to be the drug of choice, as it is effective when used alone and has few side effects. If the symptoms relapse during treatment they can be brought under control by adding phenformin.

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