Effect of ethyloestrenol on fibrinolysis in the vessel wall

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Summary

Forty-nine patients with decreased fibrinolytic activity in the vessel walls or a decreased release mechanism, or both, were treated with ethyloestrenol for three to 17 months. Forty-five of the patients had had recurrent, phlebographically verified, deep venous thrombosis (DVT) and four had arterial thrombosis. Ethyloestrenol 8 mg/day was given to 31 patients and 4 mg/day was given to 12. The remaining six patients had been treated with a combination of phenformin and ethyloestrenol. The phenformin was withdrawn but they were kept on ethyloestrenol 8 mg/day. Another 15 patients with a normal fibrinolytic system—four with recurrent DVT and 11 with severe arteriosclerosis—were given ethyloestrenol 8 mg/day.

The spontaneous fibrinolytic activity, local fibrinolytic activity during standardised venous occlusion of the arms, and fibrinolytic activity of the vessel walls increased significantly after treatment with ethyloestrenol 8 mg/day for three months. No further increase occurred after three months, and ethyloestrenol 4 mg/day had no effect. No values rose significantly in the patients with a normal fibrinolytic system. One patient suffered a recurrence within three months of treatment, before the fibrinolytic system became normal. In one patient the fibrinolytic defect reappeared after 10 months in spite of continued treatment. Two of the three women of fertile age developed irregular cycles and intermenstrual bleeding, which disappeared when the treatment was withdrawn. No other side effects were observed.

Introduction

A defective fibrinolytic defence mechanism (decreased fibrinolytic activator activity in the vein walls or a defective release of fibrinolytic activator from the vein walls, or both) has been found in about 70% of patients with recurrent deep venous thrombosis (DVT) and no known predisposing condition.1 Fearley et al3 showed that phenformin (100 mg/day) combined with ethyloestrenol (8 mg/day) increased the spontaneous fibrinolytic activity of the blood. The same treatment was later
shown to increase the fibrinolytic activity in the vein walls when
given to healthy volunteers. Furthermore, when given to
patients with recurrent DVT and a defective fibrinolytic defence
mechanism treatment with phenformin and ethyloestrenol
increases the spontaneous fibrinolytic activity, the capacity to
release fibrinolytic activator during venous occlusion of the
arms, and the fibrinolytic activity of the vessel walls. Anabolic
steroids alone have also been shown to increase the venous
plasma fibrinolytic reserve of.

The side effects of phenformin are, however, serious, so the
effect on the fibrinolytic system of ethyloestrenol alone in doses of
8 mg/day or 4 mg/day was studied in 49 patients with recurrent
DVT.

Patients and methods

The 49 patients (34 men, 15 women) had either decreased fibrinolytic
activity in the vessel walls or a decreased release mechanism, or both.
Their ages ranged from 22 to 78 years (mean 51.3), and 10 were aged
under 40. None of the patients had any coexisting disease. Forty-five
of the patients had had phlebographically verified recurrent DVT
during the five years before the first examination (two to five thrombotic
episodes), and five also had had pulmonary embolism. The remaining
four patients had arterial thrombosis (thrombi were present in the
internal carotid artery or middle cerebral artery or the patients
suffered transient ischaemic attacks or peripheral arterial ischaemia).
On admission to the trial 10 of the patients were receiving dicoumarol
prophylactically, and this was continued until the fibrinolytic system
returned to normal. Six men had been treated with the combination
of phenformin and ethyloestrenol for one to four years.

The patients were examined on average three months after the end
of their last thrombotic episode. Each patient was examined on two
consecutive days and 21 were re-examined just before the beginning
of treatment to check that the defect was consistent. All patients were
then examined after three, six, and 10 to 17 months of treatment
(table I).

<table>
<thead>
<tr>
<th>TABLE I—Number of patients treated and followed up</th>
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<tr>
<td>Dose:</td>
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<td>No of patients</td>
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<td>1-7 months</td>
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*These patients had earlier received phenformin and ethyloestrenol together.

Thirty-one of the patients were given ethyloestrenol 8 mg/day, and
12 received 4 mg/day (table I). In six patients who had been on a
combination of phenformin and ethyloestrenol, phenformin was
withdrawn because of increased serum creatinine levels. Treatment
with ethyloestrenol continued in a dose of 8 mg/day. The patients
were followed up for recurrences of thrombosis and for side effects.
Fifteen patients (aged 35-82 years; mean 64.7 years) with a normal
fibrinolytic defence mechanism were also studied. Four had had
recurrent DVT (two to five episodes each) and the remaining 11 had
severe arteriosclerosis. These patients were given ethyloestrenol
8 mg/day and were re-examined after three, six, and 12 months.

Laboratory methods—The spontaneous fibrinolytic activity of
resuspended euglobulin precipitate of plasma was measured on
unheated fibrin plates* (normal range: 0-70 mm²). Venous occlusion
was performed as described. A sphygmomanometer cuff was placed around
each upper arm and inflated to a pressure between the systolic and
diastolic blood pressure for 20 minutes. Blood samples for determining the fibrinolytic activity of
resuspended euglobulin precipitate on fibrin plates were withdrawn
before the cuff was applied and again just before it was deflated. The
mean of the fibrinolytic activity in the samples withdrawn at the end
of occlusion from each arm was taken as a measure of the capacity of
releasing the fibrinolytic activators from the vessel wall. In 118
apparently healthy volunteers aged 18-50, the 5th percentile was
158 mm² (95% confidence interval 88-169 mm²).

Fibrinolytic activity in superficial hand veins—Biopsy specimens
excised from a superficial hand vein under local anaesthesia (0.5-
mepivacaine hydrochloride) were examined by Pandolfi's modification
of Todd's fibrinolysis autography technique.** The fibrinolytic
activity was expressed in arbitrary units. The median value found at
our laboratory in 70 healthy volunteers was 7.5 arbitrary units (range
6-10).

Fibrinogen concentrations were determined according to the
syneresis method of Nilsson and Olow (normal range: 2.0-4.0 g/l).

Statistical methods—The significance of differences was calculated
by Student's t test. The difference between the biopsy findings was,
however, analysed by Wilcoxon's sum rank test.

Results

The spontaneous fibrinolytic activity of circulating blood was
significantly increased after three months' treatment (P<0.001) and

![FIG 1—Spontaneous fibrinolytic activity (resuspended euglobulin
precipitate of plasma on unheated plates) during treatment with
ethyloestrenol 8 mg/day (●) and 4 mg/day (▲).]

![FIG 2—Local fibrinolytic activity during venous occlusion of arms
during treatment with ethyloestrenol 8 mg/day (●) and 4 mg/day (▲). Horizontal line indicates mean fibrinolytic activity of resuspended euglobulin precipitate on unheated fibrin plates of both arms.

| TABLE II—Number of patients with decreased fibrinolytic mechanism before
and after treatment with ethyloestrenol 8 mg/day or 4 mg/day |
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<tbody>
<tr>
<td>Dose</td>
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<tr>
<td>No of patients with decreased release capacity</td>
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<td>4 mg/day</td>
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| No of patients with decreased fibrinolytic activity in vessel
walls | 8 mg/day | 19/30 | 3/26 | 4/14 |
| 4 mg/day | 8/12 | 4/10 | 0/4 |
The fibrinolytic activity in the vessel walls was decreased (<6 arbitrary units) in 19 out of 30 patients before treatment with ethylestrenol 8 mg/day (fig 3). The mean level of the fibrinolytic activity rose significantly after three months' treatment (P < 0.001) and the mean remained at about 7 arbitrary units throughout the observation period. After three months' treatment three patients out of 26 examined still had a decreased vessel wall fibrinolytic activity, and after 10-17 months four out of 14 still showed a decreased level (<6 arbitrary units) (table II).

After treatment with 4 mg/day (fig 3) vessel wall activity did not increase significantly until after 10 to 15 months (P > 0.01). Before treatment eight out of 12 patients showed decreased activity in the vessel walls and four out of 10 showed decreased activity after three months' treatment (P > 0.05). After 10 to 15 months' treatment none of the four patients examined showed a decreased vessel wall activity (table II).

The patients who had earlier been treated with phenformin and ethylestrenol (8 mg/day) all had a normal fibrinolytic system when phenformin was withdrawn. During the subsequent treatment with only ethylestrenol (8 mg/day) they remained normal.

Spontaneous fibrinolytic activity, release capacity after venous occlusion, and fibrinolytic activity in the vessel walls did not increase significantly in patients with a normal fibrinolytic defence mechanism (table III). No significant changes of the fibrinogen were observed during treatment (P > 0.05).

One recurrence occurred within three months of treatment, when the fibrinolytic system was not yet normal. One patient developed suspected resistance. After three months' treatment both fibrinolytic activator activity in the vessel walls and release capacity became normal. At re-examination 11 and 16 months after the start of treatment a decreased vessel wall activity was found.

Side effects—Two of the three women of fertile age developed irregular menstrual bleeding and one of them also claimed to have put on weight. Because of these side effects the treatment was withdrawn, and the menstrual bleeding pattern returned to normal. No other side effects were observed.

Discussion
Prophylactic treatment with a combination of phenformin and ethylestrenol normalises the defective fibrinolytic system in patients with a decreased fibrinolytic activity in the vessel walls or a defective release capacity of fibrinolytic activators from the vessel walls, or both.4

Severe side effects, such as lactic acidosis, have, however, been reported during treatment with phenformin.10 11 One of the patients reported by Nilsson et al4 also developed this severe complication. Therefore it seemed reasonable to try treatment with the anabolic steroid ethylestrenol alone. In a dose of 8 mg/day ethylestrenol significantly increased the spontaneous fibrinolytic activity in the circulation and the release capacity of the fibrinolytic activators from the vessel walls after three months' treatment. Nevertheless, no increase occurred in patients who had a normal fibrinolytic system before treatment. The same was observed after combined treatment with ethylestrenol and phenformin. Ethylestrenol thus seems to influence specifically the defective mechanism and not only to induce an overall increase in synthesis of fibrinolytic activator and its release from the vessel wall. Most of the patients with a normal fibrinolytic system had severe arteriosclerosis, however, so the possibility that a damaged vessel wall might have contributed to the lack of response to treatment cannot be excluded. Also the fibrinolytic activity of the vessel walls increased significantly during three months' treatment, but after this initial increase no further increase was observed, which agrees with the findings after the combination therapy.4 The lower dose of 4 mg/day did not seem to be sufficient to affect the fibrinolytic system.

In four patients the fibrinolytic activity of the vessel walls did not respond to treatment with 8 mg/day. Only one patient developed a resistance to ethylestrenol.

No recurrence occurred in the patients with a fibrinolytic system that had returned to normal, which might suggest that the effective treatment that results in a normal fibrinolytic system is effective as thrombosis prophylaxis in patients with a fibrinolytic defect.

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References
10 Wise, P. H., et al., British Medical Journal, 1976, 1, 70.