Effect of ethyloestrenol on fibrinolysis in the vessel wall

U HEDNER, I M NILSSON, S ISACSON

British Medical Journal, 1976, 2, 729-731

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 The phenformin was withdrawn but they were kept on ethyloestrenol 8 mg/day.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women of fertile age developed irregular cycles and intermenstrual bleeding, which disappeared when the treatment was withdrawn.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. Fearnley et al. 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.

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 ethyloestrenol1 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 1).

Thirty-one of the patients were given ethyloestrenol 8 mg/day, and 12 received 4 mg/day (table 1). 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 plates1 (normal range: 0-70 mm²).

Venous occlusion was performed as described. A sphygmonanometer 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 Olow1 (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

---

**TABLE 1—Number of patients treated and followed up**

<table>
<thead>
<tr>
<th>Dose:</th>
<th>8 mg/day</th>
<th>4 mg/day</th>
<th>8 mg/day*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>31</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>No of patients examined at:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>29</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>10-17 months</td>
<td>15</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

*These patients had earlier received phenformin and ethyloestrenol together.

---

**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 2—Number of patients with decreased fibrinolytic mechanism before and after treatment with ethyloestrenol 8 mg/day or 4 mg/day**

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Before treatment</th>
<th>At 3 months</th>
<th>At 10-17 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients with decreased release capacity</td>
<td>8 mg/day</td>
<td>18/31</td>
<td>4/29</td>
<td>2/15</td>
</tr>
<tr>
<td></td>
<td>4 mg/day</td>
<td>8/12</td>
<td>7/10</td>
<td>2/4</td>
</tr>
<tr>
<td>No of patients with decreased fibrinolytic activity in vessel walls</td>
<td>8 mg/day</td>
<td>10/30</td>
<td>3/26</td>
<td>4/14</td>
</tr>
<tr>
<td></td>
<td>4 mg/day</td>
<td>8/12</td>
<td>4/10</td>
<td>0/4</td>
</tr>
</tbody>
</table>
persisted at about the same level throughout treatment on both doses of ethyloestrenol (fig 1). After 10-17 months' treatment the further increase was hardly significant (P < 0.02).

The release capacity of fibrinolytic activators from the vessel walls, measured as the local fibrinolytic activity observed after venous occlusion, is given in fig 2. In 18 out of 31 patients the release capacity was defective before treatment (< 158 mm³). After three months' treatment with ethyloestrenol 8 mg/day only four patients still had a decreased release capacity and after 10-17 months' treatment only two of the 15 examined patients had a decreased release capacity (fig 2; table II). After three months' treatment with ethyloestrenol 8 mg/day a significant increase (P < 0.01) was obtained. No further increase was seen (P > 0.05) during treatment. No significant increase occurred in any of the 15 patients who had a normal release capacity before the treatment (see table III). No significant increase in the fibrinolytic capacity was observed after treatment with 4 mg/day over three to 17 months (table II).

![Table III](image)

<table>
<thead>
<tr>
<th>Table III—Effect of ethyloestrenol 8 mg/day in patients with normal fibrinolytic systems before treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Spontaneous fibrinolytic activity (mm³)</td>
</tr>
<tr>
<td>Release capacity (mm³)</td>
</tr>
<tr>
<td>Fibrinolytic activity in vessel walls (arbitrary units)</td>
</tr>
</tbody>
</table>

The fibrinolytic activity in the vessel walls was decreased (< 6 arbitrary units) in 19 out of 30 patients before treatment with ethyloestrenol 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 ethyloestrenol (8 mg/day) all had a normal fibrinolytic system when phenformin was withdrawn. During the subsequent treatment with only ethyloestrenol (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 ethyloestrenol 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. One of the patients reported by Nilsson et al. also developed this severe complication. Therefore it seemed reasonable to try treatment with the anabolic steroid ethyloestrenol alone. In a dose of 8 mg/day ethyloestrenol 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 ethyloestrenol and phenformin. Ethyloestrenol 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. 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 ethyloestrenol.

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.

This work was supported by grants from the Swedish Medical Research Council (B76-19X-00087-12B) and the Medical Faculty, University of Lund.

References

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