Effect of cyproterone acetate on platelet aggregability, fibrinolytic activity and fibrinolytic capacity in normal men

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Abstract. Nine healthy men were treated with a daily dose of 5 or 10 mg of the anti-androgen cyproterone acetate. Platelet aggregability was increased in 6 of 9 men; fibrinolytic activity decreased in 7 of 7 and the fibrinolytic capacity decreased in 5 of 7 volunteers. We conclude that platelet aggregability, fibrinolytic activity and capacity may be modified by anti-androgen treatment and therefore attention should be paid to the coagulation parameters when cyproterone acetate is used.

Increased platelet responsiveness occurs in thromboembolic disease (Acheson et al. 1972) ischaemic heart disease (Gormsen et al. 1977) and after acute myocardial infarction (Zahavi & Dreyfuss 1969). In animal models testosterone promotes platelet aggregability (Johnson et al. 1977), experimental arterial thrombosis (Uzunova et al. 1978) and pulmonary platelet aggregates (Uzunova et al. 1977). No human studies have been done on platelet aggregation during androgen or anti-androgen treatment. We have therefore taken the opportunity of a male fertility control study to determine the effects of daily low doses of the anti-androgen cyproterone acetate on adenosine diphosphate (ADP) induced platelet aggregation and coagulation parameters in young healthy men.

Materials and Methods

Nine healthy men aged 25–35 years in a male anti-fertility study (a WHO multicenter trial) were given placebo tablets for 3 months followed by 6 months treatment with a daily oral dose of cyproterone acetate (5 or 10 mg). The criteria for entry into the study is described by Føgh et al. (1979). The treatment period was followed by a recovery phase of at least 6 months. Blood samples were drawn in the placebo period and after at least 6 weeks of treatment with cyproterone acetate and again in the recovery phase (8 weeks or more following cessation of treatment).

Platelet aggregation studies were performed on all volunteers while fibrinolytic activity and capacity were measured in all except two of the volunteers, because scheduling was not possible.

Platelet aggregation was studied in a Payton aggregometer (Payton No. 300) as earlier described (Gormsen et al. 1977). Aggregation was induced by ADP concentrations of 0.25, 0.50, 0.75, 1.0, 2.0 and 5.0 μM ADP final concentration. The results were recorded as the thresh-

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25
old concentration of ADP which produced an aggregation curve with a secondary wave and a maximal amplitude of 80% of the response of platelet poor plasma.

The fibrinolytic activity was estimated by determination of the spontaneous lysis time of a clot produced by the euglobulin fraction of plasma as described elsewhere (Andersen & Gormsen 1977). This method reflects the fibrinolytic activity produced by the endothelial cells; the normal range being 60–180 min. Fibrinolytic capacity was estimated by the euglobulin lysis time of plasma from a blood sample taken after compression of the upper arm for 5 min with a blood pressure between systolic and diastolic values. The fibrinolytic capacity is an index of the ability of the endothelial cells to increase fibrinolytic activity; the normal range is less than 60 min. The values were compared by the non-parametric Wilcoxon rank sum test at $P < 0.05$ except for the platelet aggregation where the Wilcoxon (1945) matched-paired sign rank test at $P < 0.05$ was used.

The serum testosterone was measured by a radioimmunoassay (Corker et al. 1978).

Results

In the nine volunteers to whom the anti-androgen drug cyproterone acetate was administered the platelet aggregability was increased in 6, unchanged in 2 and decreased in 1 subject ($0.02 < P < 0.05$, Fig. 1). The fibrinolytic activity decreased in 7 of 7, whereas fibrinolytic capacity was decreased in 5 volunteers, increased in one and unchanged in one ($0.02 < P < 0.05$, Table 1). One of the volunteers had pathological values during the placebo period.

Serum testosterone levels of the volunteers during treatment were decreased about 50% when compared to the levels measured in the placebo period (Føgh et al. 1979). Serum cholesterol and serum triglycerides were in the normal range during placebo, treatment and recovery phase.

Table 1.
Fibrinolytic activity and capacity in min in 7 normal male volunteers before, during and after treatment with cyproterone acetate.

<table>
<thead>
<tr>
<th>Volunteers</th>
<th>Placebo</th>
<th>Cyproterone acetate</th>
<th>Recovery</th>
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<tr>
<td></td>
<td>Fibrinolytic</td>
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<tr>
<td></td>
<td>Activity</td>
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<td>Activity</td>
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<tr>
<td>7</td>
<td>115</td>
<td>75</td>
<td>&gt;240</td>
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</table>

The fibrinolytic activity and capacity are measured in min.
Discussion

The increase in platelet aggregability found in 6 of 9 healthy men treated with the anti-androgen cyproterone acetate and the decrease in both fibrinolytic activity (7 or 7) and capacity (5 of 7) appears to be an undesirable trend. However, so many factors are involved in thromboembolic diseases that it is difficult to evaluate the data. No previous studies have been published on the effect of an anti-androgen on human platelet aggregation and fibrinolytic activity. However, a sex difference in fibrinolytic activity and responsiveness has been observed previously. Cash (1966) found a higher spontaneous fibrinolytic activity in women compared to men and a higher fibrinolytic responsiveness after exercise in women than in men. An anti-androgen would therefore be a speculative protective treatment. The observed increase in platelet aggregability after treatment with cyproterone acetate was unexpected. A possible explanation is that lower doses of cyproterone acetate act as a partial agonist or it could be a direct effect of cyproterone acetate on platelet aggregation; finally it could be due to the strong prostaglandinal effect of the compound. The decrease in fibrinolytic activity and capacity is in accord with the described increased activity after treatment with testosterone (Fearnley & Chakrabarti 1962). If thrombotic risk is related to increased platelet aggregability, as measured with ADP, and to decreased fibrinolytic activity and capacity then there may be an increased risk during treatment with low doses of cyproterone acetate.

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References


