Control of hidradenitis suppurativa in women using combined antiandrogen (cyproterone acetate) and oestrogen therapy

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SUMMARY

The effects of combined treatment with the antiandrogen, cyproterone acetate, and ethinyl oestradiol on four women with long-standing hidradenitis suppurativa have been investigated. The condition was controlled successfully in all patients with 100 mg/day cyproterone acetate using the reversed sequential regimen; lowering the antiandrogen to 50 mg/day caused deterioration. Before treatment, plasma testosterone levels were within the normal range, but plasma androstenedione values were raised and sex hormone binding globulin levels were low. On treatment, the androstenedione concentration fell and sex hormone-binding globulin values were raised. However, since these levels were unaltered by reducing the antiandrogen dosage, the main action of the therapy is probably that of the antiandrogen within the target cells.

Hidradenitis suppurativa, or apocrine acne, is thought to occur as a result of closure of the apocrine pore with subsequent bacterial infection (Shelley & Cahn, 1955); androgens have been implicated in its aetiology (see, for example, Brunsting, 1952).

Since acne, an androgen-dependent condition also involving pore occlusion and bacterial infection, responds to combined cyproterone acetate and oestrogen therapy (Neumann, Aydinlik & Lachnit-Fixson, 1984), we have investigated the effect of such treatment on four women with long-standing hidradenitis suppurativa. Although the antiandrogen is the most effective component of such treatment for hirsutism (Sawers, Randall & Iqbal, 1982), cyproterone acetate must be given to women of reproductive age in conjunction with oestrogen to ensure contraception so that the possible feminization of a male foetus is avoided.

METHODS

Patient histories
All four women had at least one child and none was hirsute.

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Patient 1. Aged 33 years at the start of treatment, this patient had had recurrent vulval and pubic abscesses for 5 years, particularly during the week before, and after, menstruation. Previous treatment had included antibiotics and radiotherapy.

Patient 2. Aged 39 years, this patient presented with a history of boils in the groin since childhood, and in the axilla for 13 years. A pilonidal sinus had been excised 10 years earlier and she had previously been prescribed numerous courses of antibiotics.

Patient 3. Aged 29 years, this patient had had lesions in the vulva and external auditory meatus since the age of 10 years. She had also developed severe facial acne over the previous 3 years. Her earlier treatment had included plastic surgery of the groin and 6 years on a contraceptive pill (Ovran).

Patient 4. Aged 24 years, this patient presented with pustules on the vulva which had persisted for 5 years, becoming increasingly painful in the 6 months before treatment commenced. She had taken a contraceptive pill (Ovranette), but had ceased this prior to attending the clinic.

Clinical protocol
Patients attended clinics at 28-day intervals where, in addition to clinical investigation, sebum production was measured by a modification of the method of Strauss and Pochi (1961) as previously described by Ebling and Randall (1985), and blood samples were taken for various hormonal measurements. The endocrine assays have been reported by Sawers, Randall & Iqbal (1982). At least two basal measurements were obtained before treatment commenced. Clinical improvement was assessed both subjectively from patients' observations and objectively by recording the severity and location of the condition assessed by the same clinician; photographs were also taken, both before and during treatment.

All patients started on the reversed sequential regimen of Hammerstein and Cupceancu (1969) with 100 mg of cyproterone acetate per day for 10 days and 50 μg of ethinyl oestradiol per day for 21 days. After 3–7 months, the oestrogen component was reduced to, and maintained at, 30 μg per day to reduce potential side-effects of oestrogen treatment; the cyproterone acetate was also reduced to 50 mg per day in all patients at some time during their therapy. The levels for individual patients were altered at different stages during their treatment for various clinical reasons.

RESULTS

Clinical results
All patients exhibited rapid objective clinical improvement and also reported a subjective impression of improvement after only one to two cycles of treatment. This improvement increased and was then maintained during therapy (Fig. 1). The facial acne in Patient 3 also improved rapidly.

When cyproterone acetate was reduced to 50 mg per day three patients showed worsening of their symptoms. Patient 1 also noted recrudescence during the parts of the cycle where cyproterone acetate was not taken; this patient also had two periods, of 3 and 4 months respectively, taking Eugynon 30 (i.e. oestrogen but no antiandrogen), but on both occasions her abscesses returned.
Patients 3 and 4 showed no recurrence after treatment had been discontinued for 14 and 5 months respectively, after 23 and 11 cycles of therapy. Patient 4 had shown recurrence previously during a 6-month withdrawal from treatment after an accident, when she had already completed eight cycles.

**Sebum production**

Sebum production in Patients 1 and 3 was initially high, but was rapidly reduced to normal female levels after one to two cycles of treatment and remained low (Fig. 2). The other women had normal sebum production rates both before, and during, therapy.
Endocrine data
Although plasma testosterone levels were within the normal range, values for androstenedione, the main circulating androgen in women, were high, except in Patient 3 who was taking a contraceptive pill (Table 1). The major plasma binding protein for sex steroids, sex hormone-binding globulin, was present in concentrations well below the normal female levels, except in Patient 3.

On treatment, plasma testosterone levels remained within the normal range, while androstenedione concentrations were reduced to around the upper limit of the normal range. Sex hormone-binding globulin levels were greatly increased to 100–240 nmol DHT bound per litre; levels in Patient 3 were also increased to about 200 nmol. This means that the ratio of testosterone:sex hormone-binding globulin was rapidly lowered.

There was no consistent effect on any of the endocrine parameters during alteration of the doses of either cyproterone acetate or oestrogen.

Side-effects
All four patients reported feeling depressed during treatment, but three had severely ill parents or suffered a bereavement during the period of study. One patient (Patient 2) withdrew from therapy after 13 months due to depression; this patient had a previous history of depression.

Patient 1 reported breast tenderness and Patient 3 became amenorrhoeic when treatment was discontinued. No consistent effects on weight were noted.
Control of hidradenitis suppurativa with cyproterone acetate and oestrogen

TABLE 1. Hormone levels in four women with hidradenitis suppurativa

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plasma hormones (nmol/l)</th>
<th>Sex hormone-binding globulin (nmol DHT/l)</th>
<th>Testosterone/sex hormone-binding globulin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Testosterone</td>
<td>Androstenedione</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.92</td>
<td>10.45</td>
<td>19.0</td>
</tr>
<tr>
<td>2</td>
<td>1.10</td>
<td>13.20</td>
<td>18.2</td>
</tr>
<tr>
<td>4</td>
<td>0.80</td>
<td>11.37</td>
<td>30.6</td>
</tr>
<tr>
<td>Mean</td>
<td>0.94</td>
<td>11.67</td>
<td>22.8</td>
</tr>
<tr>
<td>3*</td>
<td>0.48</td>
<td>5.47</td>
<td>59.0</td>
</tr>
<tr>
<td>Normal women</td>
<td>&lt;2.8</td>
<td>&lt;8.0</td>
<td>58.6 ± 1.01</td>
</tr>
<tr>
<td>Hirsute women</td>
<td>1.53 ± 0.46</td>
<td>11.09 ± 3.53</td>
<td>30.29 ± 14.41</td>
</tr>
</tbody>
</table>

Normal values – mean ± SD obtained from 59 women aged between 17 and 45 years (mean 31 years) and values for hirsute women (mean ± SD) from our parallel studies on 54 women with hirsutism. * Patient 3 was taking a contraceptive pill.

DISCUSSION

The combined cyproterone acetate (100 mg per day) and oestrogen treatment was very effective in controlling the long-standing hidradenitis suppurativa in all four patients. This confirmed our earlier report of a single patient (Ebling et al., 1980), which has since stimulated a larger study of women with hidradenitis suppurativa and their treatment with cyproterone acetate (Mortimer et al., 1986a,b). In two cases the improvement was maintained for several months after treatment had ceased.

The finding that plasma testosterone levels were within the normal range while androstenedione levels were raised contrasts with the raised testosterone levels reported by Mortimer et al. (1986a) in both hidradenitis suppurativa and hirsute patients; they did not measure androstenedione levels. Although this difference could be due to our much smaller number of subjects, the results of our large study of hirsute women also showed raised androstenedione and normal testosterone levels in accordance with other published data (Sawers, Randall & Iqbal, 1982). Sex hormone-binding globulin was below normal female levels, except in Patient 3. Exogenous oestrogen from the contraceptive pill is known to raise sex hormone-binding globulin concentration (Sawers, Randall & Iqbal, 1982). When sex hormone-binding globulin levels are low, it is generally believed that ‘free’ testosterone, i.e. that which is not bound to the carrier protein and is therefore more readily available to the cell, is increased. The ratio of testosterone to sex hormone-binding globulin can be used as an indicator of ‘free’ testosterone; in these patients, with the exception of Patient 3, the ratio was high, similar to hirsute patients (Table 1).

Although some side-effects were noted, these were tolerable to most patients. Depression is difficult to evaluate and in most of our patients coincided with traumatic events in their lives; the single patient who withdrew from treatment had a previous history of depression. The side-effects in patients taking combined cyroterone acetate and oestrogen therapy reported by other workers are similar to those of oral contraceptives containing 50 μg of ethinyl oestradiol (see review by Moltz, Schwartz & Hammerstein, 1982).

The possible sites of action of the treatment include: the competitive inhibition of the
androgen receptor by the antiandrogen in the target cells; decreased androgen production caused by negative feedback at the pituitary; and increased sex hormone-binding globulin levels, due to the oestrogen component, reducing the testosterone readily available to the cells. Although the circulating levels of androstenedione were lowered and those of sex hormone-binding globulin were raised, the main effect appears to be due to the local action of the cyproterone acetate in the skin, since the endocrine changes which occurred during treatment were not altered by reducing the antiandrogen dosage to 50 mg per day, but the patients' condition deteriorated. In addition, one patient, who was already taking a contraceptive pill prior to this therapy, showed only limited endocrine changes but dramatic clinical improvement of her facial acne and hidradenitis suppurativa.

These results lend support to the concept of hidradenitis suppurativa as an androgen-dependent disorder. They also suggest that androgen-dependent skin disorders, such as acne and hirsutism, are mainly caused by abnormal target organ responses to androgens, since our patients generally showed endocrine similarities to hirsute women before treatment, but were not hirsute.

Although combined cyproterone acetate and oestrogen therapy should not be used for women with a history of thromboembolic diseases because of the increased blood coagulability caused by oestrogens (Moltz, Schwartz & Hammerstein, 1982), the treatment seems highly appropriate for female patients with hidradenitis suppurativa. We have found that a dosage of 100 mg per day is necessary for full control of the condition.

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REFERENCES


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