A double-blind controlled cross-over trial of cyproterone acetate in females with hidradenitis suppurativa

P.S. MORTIMER, R.P.R. DAWBER, MARY A. GALES* AND R.A. MOORE*

Department of Dermatology, The Slade Hospital, Oxford and *Department of Clinical Biochemistry, Radcliffe Infirmary, Oxford, U.K.

Accepted for publication 21 February 1986

SUMMARY

In order to examine whether anti-androgen therapy was effective in hidradenitis suppurativa (HS), ethinyloestradiol 50 μg/cyproterone acetate 50 mg in a reverse sequential regimen was compared with ethinyloestradiol 50 μg/norgestrel 500 μg (Eugynon 50) in 24 female patients. Both treatments produced substantial improvement in disease activity. Seven patients cleared and have remained free of disease for 18 months, five patients improved, four remained unchanged, while two deteriorated. Cyproterone acetate was not clinically significantly more effective than E50, and both gave a similar reduction in free androgen index. Anti-androgen therapy appears to be beneficial in the treatment of hidradenitis suppurativa.

Hidradenitis suppurativa (HS) is a chronic inflammatory disorder of apocrine gland-bearing skin in which deep-seated abscesses and multiple draining sinuses develop (Hurley, 1979). Although infection undoubtedly contributes to the disease (Leach et al., 1979; Hight et al., 1980), the primary event is considered to be poral occlusion (Shelley & Cahn, 1955), with the pathogenesis being similar to that of acne vulgaris. As in acne, androgen action is necessary for the development of HS and significantly elevated plasma testosterone levels have been demonstrated in a group of females with HS (Mortimer et al., 1986).

Cyproterone acetate is of proven benefit in the treatment of acne vulgaris (Fanta, 1980) and hirsutes (Hammerstein, 1979), and, anecdotally, has been shown to be of benefit in HS (Ebling et al., 1979). In view of the similarities between HS and acne vulgaris, a trial of anti-androgen therapy for HS was undertaken. We report here a double-blind, within-patient, controlled trial of ethinyloestradiol 50 μg and cyproterone acetate 50 mg, compared with ethinyloestradiol 50 μg and norgestrel 500 μg (Eugynon 50) in the treatment of HS in 24 female patients, and on the response of circulating androgens to such treatment.

Correspondence: Dr P.S. Mortimer, Department of Dermatology, The Slade Hospital, Headington, Oxford OX3 7JH, U.K.
Clinical trial

Patients. Twenty-four females (age range 20–44 years; median 27) with HS were entered into the trial. The diagnosis of HS was based on clinical criteria (Mortimer et al., 1986): recurrent boils in apocrine-bearing sites for more than 3 months, presence of comedones in apocrine skin or retroauricular sites and exacerbation of disease pre-menstrually. Disease severity varied from moderate to severe with one to several apocrine sites involved. Duration of disease varied from 6 months to 27 years (median 5 years), with the age of onset ranging from 11 to 43 years (median 18 years). Five patients had axillary disease, six genito-crural involvement, and 11 had both regions affected. Other sites exhibiting HS were mons pubes (1 patient), pre-sternum (1 patient), retro-auricular area (1 patient) and labia majora (1 patient). Patients were considered suitable for the trial if they had no medical contra-indications to hormonal therapy and had HS of at least 6 months’ duration. Ethical approval was obtained from the Central Oxford Research Ethics Committee and informed consent was obtained from each patient. Patients were advised to use alternative means of contraception during the trial.

Trial design.

Two treatments were compared in a double-blind cross-over study:

(i) (CPA): ethinyloestradiol 50 μg/cyproterone acetate 50 mg (CPA) in a reverse sequential regimen, where ethinyloestradiol was given on days 5–25 of each menstrual cycle and CPA on days 5–14 of each menstrual cycle (day 1 of the first cycle being the first day of menstrual bleeding).

(ii) (E50): ethinyloestradiol 50 μg/norgestrel 500 μg (Eugynon 50, Schering) given daily on days 5–25 of each menstrual cycle (day 1 of the first cycle being the first day of menstrual bleeding).

Patients were allocated to two groups, matched for age and duration of disease. Group A received CPA followed by E50 and Group B received E50 followed by CPA.

The treatments were given sequentially for a total of 12 months with cross-over at six months. All other medication was stopped at least one month prior to commencing the trial. No other treatment, other than topical antiseptics, was allowed during the trial.

Objective clinical assessment proved difficult owing to the natural fluctuation of the disease activity of HS. Methods using photography, weight of discharge, and spot or boil counting proved unsatisfactory. A system of assessment by the patient over the treatment period as a whole was devised. Three sites, right axilla, left axilla, and the ano-genital region, were assessed independently using three parameters: frequency of lumps and boils, quantity of discharge and pain and discomfort.

Objective assessment was made by one observer (P.S.M.) on the basis of the clinical appearances after each treatment as judged by the number of inflamed and non-inflamed nodules, the degree of induration and tenderness, and the presence of draining sinuses. Comedones, while often found, were not considered an indicator of disease activity. Using a pre-treatment baseline as the reference point, changes in disease activity were scored as clear (+3), much improved (+2), improved (+1), unaltered (0), worse (–1), much worse (–2). Each parameter was scored and an overall global assessment of the response to treatment was based on the sum of the scores for each parameter.

Disease severity was rated by the patients using visual analogue scales, based on an unmarked
10 cm line, at the end of each treatment period, representing 'worst it has ever been' at one end to 'completely healed' at the other.

Patients were reviewed every 3 months unless problems demanded more frequent visits.

_androgen assessment_
In an effort to see whether any treatment response was related to alteration in circulating androgens, each patient had blood taken before and on completion of, each 6 month treatment period. Samples were analysed for total testosterone (T), sex hormone binding globulin (SHBG) (measured using a Farmos SHBG-IRMA Kit), dehydroepiandrosterone sulphate (DHEA-S), and prolactin. A Wilcoxon matched pairs signed ranks test was used to compare changes in hormone levels.

## RESULTS

### Clinical trial
Eighteen patients completed the trial. Four patients were withdrawn because of treatment side-effects, and two patients because of exacerbation of the disease. Of those completing the trial, 10 patients were in Group A (sequence CPA:E50) and eight patients in Group B (sequence E50:CPA).

Of the 18 patients completing the trial, eight reported minor side-effects while taking E50 and five while taking CPA. E50 produced a variety of non-specific side-effects, while CPA more consistently caused symptoms of weight gain, headaches and breast soreness.

The drop out rate, while relatively high (6 out of 24), was related in four cases to drug intolerance (two to CPA; and two to E50), and in only two cases, to treatment failure.

Objective assessment alone provided insufficient evidence of improvement or deterioration of the disease owing to the fact that the surface appearances in HS frequently belie the events occurring deep down at the base of the apocrine glands. Several conspicuous superficial pustules often proved trivial to the patient, whereas the hidden deep seated solitary abscess with little surface change resulted in severe pain and toxicity. In addition, the natural history of the condition was periods of relative inactivity punctuated by severe exacerbations with one or multiple ‘boil’ developments. Therefore, an accurate assessment could only be made with knowledge of the frequency and severity of boils and abscesses as judged by the patient. This information was included in the global assessment.

![Figure 1](attachment:image.png)

**Figure 1.** Cumulative scores for each patient with each treatment. ■ CPA; □ E50; — no change; withdrawn.
FIGURE 2. Patients' assessment of disease severity rated on visual analogue scales after each treatment.
• E50; ○ CPA. Bars represent mean ± SD.

TABLE 1. Response of circulating androgens to each treatment (mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Total testosterone (T)</th>
<th>Sex hormone binding globulin (SHBG)</th>
<th>Free androgen index T/SHBG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>nmol/l</td>
<td>nmol/l</td>
</tr>
<tr>
<td>Baseline</td>
<td>17</td>
<td>2.12 (±0.26)</td>
<td>50 (±6.7)</td>
</tr>
<tr>
<td>Cyproterone acetate (CPA)</td>
<td>13</td>
<td>1.46 (±0.25)**</td>
<td>159 (±31.6)**</td>
</tr>
<tr>
<td>Norgestrel (E50)</td>
<td>16</td>
<td>0.95 (±0.16)**</td>
<td>69.7 (±8.3)*</td>
</tr>
</tbody>
</table>

Comparison with baseline: *P<0.05; **P<0.01.

The results showed no clinically significant differences between the two treatments as judged by both the disease activity scores (Fig. 1) and visual analogue scales, but there was a striking improvement compared with the baseline with both treatments during the course of the trial; cumulative scores for the first and the second 6 months were +9 in Group A and +4 in Group B.

Five patients improved, four remained the same, two deteriorated. However, most importantly, seven patients cleared, having had continuously troublesome disease for up to 20 years (median 5 years).

The visual analogue scales gave very similar results to the cumulative scores (Fig. 2).

Hormone data
Treatment with E50 produced a significant reduction in the plasma testosterone (P<0.01)
Cyproterone acetate in hidradenitis suppurativa

(Table 1). CPA also reduced the plasma testosterone ($P < 0.01$). However, E50 reduced plasma testosterone significantly more than did CPA ($P < 0.05$).

Treatment with E50 produced a significant increase in SHBG ($P < 0.05$), but this was not as large as that produced by CPA ($P < 0.01$). CPA increased SHBG significantly more than did E50 ($P < 0.01$).

T/SHBG ratio (free androgen index) was reduced below the baseline values with both treatments ($P < 0.01$). There was no statistically significant difference in T/SHBG ratio between the two groups at the end of treatment.

**DISCUSSION**

The improvement in the majority of patients by the end of the trial suggested that both E50 and CPA were beneficial in treating HS, and the equal reduction of active circulating androgens in both groups supported this. While an unconscious willingness on the part of both observer and patient to see improvement must be borne in mind, this cannot possibly explain the clearance in seven patients, nor the striking improvement in another five. When choosing a suitable placebo in a double-blind trial with CPA, an alternative hormonal preparation had to be considered and to use less than 50 μg ethinylestradiol with high dose CPA would have been inappropriate. E50 is anti-androgenic, as circulating androgen levels demonstrated, and this therefore minimized or negated the demonstration of any anti-androgenic benefit from CPA.

Androgens are only one aspect of a multifactorial aetiology in HS (Hurley, 1979; Shelley & Cahn, 1955). Infection plays a significant role in established disease but is probably not of primary importance in the pathogenesis of the disease. Anti-androgen therapy alone was less effective in those cases complicated by infection with pathogenic bacteria, e.g. *Staph. aureus*. Conversely, it was noticeable that all patients who cleared had negative bacteriology (bacteriological study was not part of the protocol and therefore not performed in all patients). Chronicity of disease was not a reason for lack of response to treatment, although, in general, patients with more extensive disease in terms of fibrosis or scarring, open cavities and deep seated loculated abscesses, fared less well.

HS patients are a heterogeneous group endocrinologically, many possessing other features of cutaneous virilism, e.g. hirsutes, and acne vulgaris with or without elevated circulating androgens (Mortimer et al., 1986). As with acne, severity of HS does not seem to correlate with abnormalities in circulating androgens, nor does treatment response seem to relate to any reduction in male hormone levels. Such parameters are therefore only a crude indicator of an androgenic abnormality, which probably exists within the tissues of the target organ, in this case the apocrine gland.

There is evidence to support the view that HS is an androgen-dependent condition and benefits from anti-androgen therapy. The similarities between acne vulgaris and HS in their basic pathogenesis, and tendency to co-exist support this. However, HS differs from acne in site and its complication by infection. Anti-androgen therapy is of most benefit in disease not complicated by pathogenic bacteria and therefore may ultimately be most useful in combination with other therapies, e.g. antibiotics, or after surgery to prevent relapse. In general, HS is only recognized at a moderately advanced stage, and therefore to secure adequate control of the disease, early diagnosis and prompt treatment is crucial.

**ACKNOWLEDGMENT**

We thank Schering Chemicals Ltd for financial support and for supply and packaging of tablets,
Dr Karen Johnson for help with the preparation of the manuscript, Dr C. Guerrier for referral of patients, and Anne E. Wiles, Consultant Statistician, for statistical advice.

REFERENCES


This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.