PAPERS AND SHORT REPORTS

Acne: double blind clinical and laboratory trial of tetracycline, oestrogen-cyproterone acetate, and combined treatment

R GREENWOOD, L BRUMMITT, B BURKE, W J CUNLIFFE

Abstract

Since the recent introduction of a drug regimen containing 2 mg of the antiandrogen cyproterone acetate and 50 µg ethinyl-oestradiol (Diane; oestrogen-cyproterone acetate) several uncontrolled reports have extolled the benefits of this drug. Double blind studies, however, are lacking. Sixty two patients with moderate or moderately severe acne were therefore included in a double blind trial of treatment for six months comparing tetracycline alone, oestrogen-cyproterone acetate alone, and a combination of these agents. Sebum excretion rates and bacterial counts were measured before, during, and after treatment, at the same time as a clinical assessment was made.

At six months the acne (as assessed by overall grade) had improved by 68% in the antibiotic treated group and by 74% in the oestrogen-cyproterone treated group. The group given a combination of both agents improved by 82%, which was significantly better ($p < 0.025$) than the improvement in the tetracycline treated patients. No significant difference was found between the groups given oestrogen-cyproterone alone and the combined treatment. The sebum excretion rate was suppressed by 25% in the patients in both groups receiving oestrogen-cyproterone but not in the group given antibiotics alone.

Oestrogen-cyproterone acetate is as effective as antibiotics in treating acne in women, and adding antibiotics offers no advantage over using oestrogen-cyproterone on its own, although in this study the combination was more effective than tetracycline alone at six months.

Introduction

Interest in the hormonal treatment of acne in women has been present since the sebaceous gland was found to be sensitive to androgens.¹ Oestrogens have been used effectively to treat acne but the dose required causes unacceptable side effects.² Plainly, the ideal hormonal treatment would be one that affected only the skin, but no successful topical hormonal treatment is yet available. Oral and topical antiandrogenic treatments have been tried since Neumann and Elger first reported the effect of cyproterone acetate on mouse sebaceous glands.³ In addition to being antiandrogenic, cyproterone acetate is progestogenic, such that in combination with oestrogen it provides contraceptive cover on a par with conventional combined oral contraceptives and has been used extensively in Europe. In the treatment of acne and related conditions it was given initially as the so called reverse sequential regimen of Hammerstein and Cupceancu,⁴ when 50-200 mg cyproterone acetate daily for 10 days of the menstrual cycle was combined with 40-60 µg ethinyl-oestradiol given daily for 21 days of the cycle. More recently a preparation containing 2 mg cyproterone acetate and 50 µg ethinyl-oestradiol (Diane) has been introduced as useful for the treatment of acne in women.^{5,6} In particular it is not known how this treatment compares with antibiotic treatment of acne. We set up a study to examine this point. Furthermore, as a combination treatment of the oestrogen-cyproterone preparation and antibiotics may be seen as possibly superior to a single entity this was compared as well. Women who had already tried antibiotics for their acne were chosen for a double blind randomised study. Oestrogen-cyproterone and antibiotic treatment influence different aetiological factors of acne and so the effect on sebum excretion and surface bacteria was assessed.

Patients and methods

We recruited 92 women aged 16-30 years with acne. All were referred from their general practitioners and they thereby represented a normal population with acne. Most had had low dose antibiotic treatment. A separate observer allocated the patients at random to one of the following three treatment groups. Treatment was for six months.

Group 1 received the oestrogen-cyproterone preparation for 21 days out of 28 with tetracycline 500 mg twice daily continuously (combination treatment).

Leeds Foundation for Dermatological Research, Department of Dermatology, The General Infirmary, Leeds LS1 3EX

R GREENWOOD, MA, MRCP, consultant dermatologist

L BRUMMITT, BSC, research associate

B BURKE, MB, CHB, clinical assistant

W J CUNLIFFE, MD, FRCP, consultant dermatologist

Correspondence to: Dr Cunliffe.

Group 2 received oestrogen-cyproterone for 21 days out of 28 plus placebo tetracycline taken twice daily continuously.

Group 3 received placebo oestrogen-cyproterone for 21 days out of 28 and tetracycline 500 mg twice daily continuously.

Whether receiving placebo or active tetracycline the patients were told to take the antibiotic half an hour before food with a sip of water to maximise absorption.⁷ No topical treatment was given.

Patients were assessed at an initial baseline visit, then every two months for six months. A final assessment was made two months after stopping treatment. Each patient was observed clinically by one observer. Clinical evaluation comprised grading and counting of lesions.⁸ The sebum excretion rate was measured at each visit by the gravimetric technique.^{9,10} Micro-organisms on the surface of the right cheek of 57 patients (22 in group 1, 18 in group 2, 17 in group 3) were sampled using the scrub technique of Williamson and Kligman.¹¹ Diluted samples were spread on either reinforced clostridial medium (Oxoid) containing 6µg furazolidone (Eaton Laboratories) per ml for propionibacteria or blood agar base (Oxoid) for micrococcaeae. Aerobic plates were incubated for 48 hours at 37°C and anaerobic cultures for seven days in a cold catalyst anaerobic jar (atmosphere 10% carbon dioxide, 90% hydrogen) at 37°C. Counts were expressed as log₁₀ colony forming units per cm² skin.

The numbers of patients dropping out and the reasons for doing so were analysed by χ^2 and Fisher's exact tests. Paired *t* tests were used to compare variation in the weights of the rather small number of patients (48 out of 92) who had their weight recorded at both the first and fourth visits.

Sebum excretion rates and the clinical assessments of lesions were compared within groups between visits by paired *t* tests and the results converted to percentage for display. For comparison between groups the Wilcoxon test and the Kruskal-Wallis one way analysis of variance were used.

Rises and falls were also considered, since an apparent lack of change in a mean or median may be the result of large variations in counterbalancing directions, and this was done using the sign test.

Results

The numbers recruited for the three groups starting the trial were uneven because of an error of randomisation. The difference, however, was not statistically significant and had no biasing effect on the results.

Attendance failures and side effects—Thirty patients dropped out of the trial, about equal numbers dropping out of each treatment group (Table).

Reasons for patients dropping out of trial

	Combination treatment	Oestrogen-cyproterone alone	Tetracycline alone
Lack of compliance	4	2	5
Lack of efficacy	2	—	1
Wished to become pregnant	1	—	2
Sebum excretion rate measurements too time consuming	1	5	1
Side effects:			
Chest pain	1	—	—
Headaches	1	—	—
Menstrual irregularity	1	—	—
Breast tenderness	1	—	—
Increased blood pressure	—	1	—
Dysmenorrhoea	—	1	—
Total	12	9	9

The commonest reason for exclusion from the final results was lack of compliance (*n* = 11). Seven failed because of the time consuming nature of the measurements of sebum excretion rate. Side effects were common but usually minor. One patient taking the oestrogen-cyproterone preparation developed mild but definite hypertension necessitating withdrawal; the blood pressure had returned to normal two months after stopping the drug. There was a small but significant weight gain in both oestrogen-cyproterone treated groups.

Grades of acne and lesion counts—All three treatment groups showed a gradual improvement in facial grade and total acne grade (figs 1 and 2). This overall improvement was reflected in a significant reduction in non-inflamed and inflamed lesions. The reduction was significant at all points compared with baseline. At the end of six months the improvement in lesion counts varied between 51% and 80% (figs 3 and 4). There were only two significant differences among the treatment groups after six months. The combined

treatment (Diane plus tetracycline) produced significantly greater improvement than did tetracycline alone, both for overall grade (fig 2; *p* < 0.025) and for inflamed lesions (fig 4; *p* < 0.001). Oestrogen-cyproterone alone was not significantly different from either of the two treatments.

Sebum excretion rate (fig 5)—Surprisingly, the antibiotic treated group showed an increase of the order of 7-13% in the sebum excretion rate, this being significant only at the end of the second month. Both oestrogen-cyproterone treated groups showed a significant reduction in sebum excretion at two, four, and six months. Maximum suppression of 26.9% in the group given the oestrogen-cyproterone preparation alone was seen by four months, and the combined treatment produced suppression of 23.7% at six months. The effects of both hormonal regimens were significantly different from that of tetracycline alone (*p* < 0.001), and at two months patients given oestrogen-cyproterone alone showed greater suppression of their sebum excretion than that achieved by the combined treatment (*p* < 0.05).

Bacteriology—None of the treatments caused a significant reduction in the density of micrococcaeae on cheek skin. Both antibiotic regimens achieved a significant reduction in counts of propionibacteria of the order of 1 log cycle, but there was no significant difference between these treatments in the reductions caused (fig 6).

Relapse data—Although not part of the original protocol, we followed up where possible those patients who could attend two months after stopping treatment. We were able to investigate 20 (80%) of the 25 patients given the combined treatments, 14 (67%) of the 21 given the oestrogen-cyproterone preparation alone, and 9 (56%) of the 16 given the antibiotic. Counts of inflamed and non-inflamed lesions showed no change; the improved overall grade was maintained in the hormonal treatment groups but the tetracycline group showed a relapse of their acne (fig 1). Intergroup analyses showed that the antibiotic treated group fared significantly less well than patients given the combined regimen (*p* < 0.005); on the face improvement was maintained best by both the combined treatment group (*p* < 0.001) and the group given the oestrogen-cyproterone preparation alone (*p* < 0.025) (fig 1). The sebum excretion rate returned towards pretreatment values after both regimens of oestrogen-cyproterone (fig 5).

Discussion

This study confirmed several predicted results. It showed the benefit of tetracycline alone and of the oestrogen-cyproterone preparation alone. There are few studies showing long term benefit of oral tetracycline taken over six months.¹² Most are of shorter duration, usually three or four months or less. This study showed that with tetracycline continuing improvement was seen at two, four, and six months as assessed by the overall grades. Spot counts suggested that a steady state of improvement occurred between four and six months, but the discrepancy between grade and counts may be explained by the observation that inflamed acne lesions show various intensities of inflammation.⁸ In this study we did not distinguish between the more active inflamed and less active inflamed lesions. Clinical studies with oestrogen-cyproterone preparation using less refined assessment techniques have shown that improvement is maintained over a six month treatment period,⁶ and our findings support this. As with tetracycline alone, oestrogen-cyproterone acetate produced a maintained improvement over the second, fourth, and sixth months. There have been no other studies to show whether adding antibiotics brings greater benefit. Both drugs work in acne through different mechanisms. Oestrogen-cyproterone reduces the sebum excretion rate¹³; antibiotics can affect the function of *Propionibacterium acnes*¹⁴ and probably affect the host inflammatory mechanisms. It seemed likely that there may be synergism between the oestrogen-cyproterone preparation and tetracycline. This study, however, showed limited clinical benefit of the drug combination.

Our study produced a few unexpected results. The tetracycline treated group showed an overall increase of the sebum excretion rate of the order of 7-13%, just reaching significance at two months. Other studies have failed to show an effect of antibiotics on sebum excretion.¹⁵ Our observation was unlikely to be a technical error since the patients started the treatment at different points in time and other studies carried out concurrently did not give any unusual results. The effect of another antimicrobial agent, benzoyl peroxide, on the sebum excretion rate is controversial¹⁶⁻¹⁷ but in our laboratory we find that it increases the rate by 22%.¹⁸ We do not

FIG 1—Effect of three treatments on facial grade. Values indicate original acne score in arbitrary units. Compared with baseline: ** $p < 0.01$; *** $p < 0.001$.

FIG 2—Effect of three treatments on total grade. Values indicate original acne score in arbitrary units. Compared with baseline: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; † $p < 0.025$.

FIG 3—Effect of three treatments on non-inflamed lesions. Compared with baseline: * $p < 0.05$; ** $p < 0.01$.

FIG 4—Effect of three treatments on inflamed lesions. Compared with baseline: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

FIG 5—Effect of three treatments on sebum excretion rate (SER). Compared with baseline: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

FIG 6—Effect of three treatments on skin surface ($\log_{10}$) counts of propionibacteria. Bars are SEM.

think that this is a primary effect on sebaceous gland function and suggest that benzoyl peroxide, by reducing ductal cornification,¹⁹ may affect sebum outflow.²⁰ Since tetracycline also reduces non-inflamed lesions an effect on sebum outflow may explain the increase in sebum excretion. These observations may be relevant in understanding the effect of the oestrogen-cyproterone preparation and of the combined treatment on sebum excretion rates. Both regimens of oestrogen-cyproterone reduced the sebum excretion rate by 25% at six months, but at two months the reduction with the combined treatment was significantly less than with the oestrogen-cyproterone preparation alone. The reduced sebosuppressive effect of the combined treatment may be due to at least two mechanisms. If the antibiotic increases sebum excretion by improving ductal outflow then this will modify the sebosuppressive effect of oestrogen-cyproterone. An alternative explanation is a possible drugs interaction. Oral contraceptive steroids undergo enterohepatic circulation,²¹ which may contribute to their normal function. Antibiotics may, by affecting the gut bacterial flora, reduce the enterohepatic circulation and so reduce the amounts of

cyproterone acetate or ethinyloestradiol, or both, available to act on the sebaceous gland.

The mechanism of sebum suppression by oestrogen-cyproterone is uncertain. There is no evidence to suggest whether it is the ethinyloestradiol or the cyproterone acetate which reduces the sebum excretion rate. Ethinyloestradiol in a dose of 60 μg by itself has been shown to reduce the sebum excretion rate by 20%.² Oral contraceptives containing 50 μg ethinyloestradiol will reduce the rate by 34%²² and might therefore be expected to ameliorate acne to a similar extent as the oestrogen-cyproterone preparation. Cyproterone acetate given to men in a daily dose of 25 mg reduces the sebum excretion rate by 17%.²³ Cyproterone acetate without oestrogen has not been given to women with an intact uterus because of its strong progestogenic action, which would be likely to result in menstrual irregularities, but it seems that 2 mg cyproterone acetate is unlikely to reduce sebum excretion by the amounts seen in our study. It is suggested that oestrogen in combination with cyproterone does have some benefit by suppressing sebum. Nevertheless, suppression of the sebum excretion rate by 25% is unlikely to explain the entire clinical benefits of the hormone treatment. There is indirect evidence that ductal cornification is under hormonal control,²⁰ and as oestrogen-cyproterone significantly reduces non-inflamed lesions it is likely that it must reduce ductal cornification; whether this is a direct or indirect effect is uncertain. In our study, although antibiotics did significantly reduce the counts of propionibacteria, the oestrogen-cyproterone preparation alone had no such effect and so an indirect effect of this agent on bacteria in reducing comedogenesis is most unlikely.

There are also few clinical or laboratory studies reporting events after stopping treatment. With the exception of isotretinoin²⁴⁻²⁵ all acne treatments fail adequately to maintain improvement once they are stopped. In our study follow up was for only two months. Assessment of total and facial grades indicated that both hormonal treatment groups fared better than the group given the antibiotic alone.

Side effects occurred in all groups and, although responsible for some withdrawals, they were not a serious problem for the patients. Side effects were not significantly more common in the hormonal treatment groups and were those classically seen with hormonal treatment or antibiotics. Drop out rates did not differ significantly among the groups. Another criticism of our study is that we did not give any of our patients topical agents. There is no published evidence on whether topical treatment is required in conjunction with oral treatment. Since beginning this study, however, we have shown that at six months oral antibiotics produce a 59% improvement of the acne compared with 72% when oral treatment is combined with topical benzoyl peroxide. We do not know whether the beneficial effect of oestrogen-cyproterone would be improved by the concomitant application of benzoyl peroxide. Work is, however, currently underway to investigate this.

We conclude that this preparation of oestrogen 50 μg and cyproterone acetate 2 mg is at least as effective as high dose (1 g daily) antibiotics. Nevertheless, the second month after the end of a six month course the group of patients who had taken antibiotics alone relapsed at a greater rate than those who had taken oestrogen-cyproterone alone. Combining the two treatments failed to yield any significant benefit over oestrogen-cyproterone alone but did produce a greater improvement than tetracycline alone, and it is unlikely that such a complicated dual regimen will be of any value in practical terms. The government recommendations for this preparation of oestrogen and cyproterone acetate are that it may be used in women with severe acne recalcitrant to long term antibiotics. Based on this study, however, in which we have shown an unquestionable benefit of the drug similar to that of oral antibiotics, we suggest that it should be tried in the following groups of patients: (a) those whose oral contraception is jeopardised by antibiotic induced diarrhoea, and (b) those whose acne has been improved by conventional treatment but shows no sign of further improvement after three to six months.

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Reassessment of inflammation of airways in chronic bronchitis

J BRENDAN M MULLEN, JOANNE L WRIGHT, BARRY R WIGGS, PETER D PARE, JAMES C HOGG

Abstract

The term chronic bronchitis has been criticised because it is associated with hypersecretion of mucus rather than bronchial inflammation. This study was designed to establish the presence or absence of clinical chronic bronchitis and measure pulmonary function in 45 patients about to undergo resection of the lung. The condition in the cartilaginous and small airways and the severity of the emphysema were then measured in the resected specimen. The results from 20 patients who had clinical chronic bronchitis were compared with those in 25 patients who did not. The data show that patients with chronic bronchitis had greater inflammation (a) on mucosal surfaces ($p < 0.05$) of all bronchi larger than 2 mm luminal diameter and (b) around glands ($p < 0.005$) and gland ducts ($p < 0.05$) in bronchi larger than 4 mm diameter. A variable degree of inflammation was present in the submucosa of smaller bronchi. The groups had equivalent proportions of mucous glands and Reid's indices in central airways, and no differences were noted in measurements of pulmonary function, condition of small airways, or emphysema.

These data show that the term chronic bronchitis is justified by inflammation of cartilaginous airways and suggest that this abnormality may be the cause of the chronic productive cough.

Introduction

The Ciba Guest symposium of 1959 defined chronic bronchitis as "the condition of subjects with chronic or recurrent excessive mucus secretion in the bronchial tree."¹ As the diagnostic criterion is clinical the relation of hypersecretion of mucus to a condition in the airways in chronic bronchitis has been a source of controversy. Reid described an index of bronchial gland enlargement which she thought correlated with the amount of sputum produced.² Subsequent studies showed that this index was normally distributed without a clear separation between the bronchitic and non-bronchitic groups.³⁻⁶ Although chronic bronchitis implies inflammation, the absence of documented inflammation of airways in these cases has recently led to objection to the term bronchitis.⁷

The common association of chronic bronchitis and the chronic limitation of airflow led early workers to assume that hypersecretion of mucus resulted in the limitation of airflow.^{8,9} Recent epidemiological studies, however, have suggested that chronic bronchitis and chronic limitation of airflow should be considered as separate entities rather than as manifestations of a single disease.¹⁰⁻¹³ The site of increased airway resistance in patients with chronic limitation of airflow has been shown to be the small conducting airways,¹⁴ where the obstruction appears to be due to an inflammatory process.¹⁵⁻²⁰ This study examines the nature of the condition in the central airways in patients with chronic bronchitis and determines its relation to the condition in the peripheral airways.

Patients and methods

We studied 45 patients admitted to this hospital for resection of an upper lobe ($n=40$) or lung ($n=5$) for, in most cases, bronchial carcinoma. Informed consent was obtained in all cases. A modified questionnaire by the British Medical Research Council was used to assess their exposure to cigarettes, cough, and history of sputum. To examine the differences in condition of airways and function of lungs between patients with chronic bronchitis and those without the patients were divided into two groups:

University of British Columbia Pulmonary Research Laboratory, St Paul's Hospital, Vancouver, British Columbia, Canada V6Z 1Y6

J BRENDAN M MULLEN, MD, FRCP(C), pathologist
JOANNE L WRIGHT, MD, FRCP(C), pathologist
BARRY R WIGGS, BSC, statistician
PETER D PARE, MD, FRCP(C), physician
JAMES C HOGG, MD, professor of pathology

Correspondence and requests for reprints to: Dr Hogg.