

A comparison of danazol and placebo in the treatment of adult idiopathic gynaecomastia: results of a prospective study in 55 patients

David J Jones FRCS

Consultant Surgeon

The Princess of Wales Royal Air Force Hospital, Ely, Cambridgeshire

Simon D Holt FRCS

Senior Registrar in Surgery

Peter Surtees FRCS

Senior Registrar in Surgery

The Princess Alexandra Royal Air Force Hospital, Wroughton, Wiltshire

David J Davison FRCS

Consultant Surgeon

Malcolm J Coptcoat FRCS

Registrar in Surgery

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In an attempt to define the efficacy of danazol in the treatment of idiopathic gynaecomastia, 55 patients were enrolled into a randomised double-blind comparison of danazol 200 mg twice daily for 3 months against placebo. The results of 52 patients were evaluated, three patients being excluded because of protocol violations. Danazol improved breast tenderness to a significantly greater degree than did placebo ($P=0.022$, danazol vs placebo) and was associated with statistically significant improvement in the degree of gynaecomastia and in its measured size ($P<0.05$). The intended management of patients who had received danazol was less likely to be surgery compared to the placebo group when assessed at the end of treatment (27% vs 50%). Minor side effects were common in both groups, but significant weight gain was noted in the danazol group alone.

If there is no urgent need for rapid resolution of gynaecomastia, danazol 200 mg twice daily can provide effective control of symptoms and may obviate the need for surgery.

Gynaecomastia is most commonly associated with puberty and may persist into adulthood. A large study of adolescent boys in 1961 (1) showed that 13.5% of 16-year-olds had gynaecomastia which persisted beyond

puberty, and in 7.7% the gynaecomastia had lasted for 3 years. Although the condition may also be secondary to malnutrition, primary testicular failure, secreting endocrine and non-endocrine tumours, thyrotoxicosis, Addison's disease, diabetes mellitus, liver disease and some drugs (oestrogens, digoxin, spironolactone, phenothiazines, methyl dopa, cimetidine), in many adults no cause is apparent.

Adult idiopathic gynaecomastia may cause pain, tenderness, fear and embarrassment in early adulthood. The armed forces have a large population of young men and in the period 1972–1987, over 1300 cases of gynaecomastia were admitted to military hospitals for surgical treatment. Many of these young men had requested treatment because of the psychological problems associated with their gynaecomastia and living in an all male environment.

Traditionally, surgery in the form of subcutaneous mastectomy has been the principal therapy, but potential complications such as haematoma, sepsis, scarring and altered nipple sensation as well as the need for time off work, hospital admission and general anaesthesia make this treatment less than ideal. More complex plastic reconstructive procedures may be necessary for patients with gross gynaecomastia (2).

Uncontrolled studies (3–7) have suggested that danazol (Winthrop) may have a role as an alternative to surgery.

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Correspondence to: Wing Commander D J Jones, The Princess of Wales Royal Air Force Hospital, Ely, Cambridgeshire

A double-blind, placebo controlled, randomised, two-centre study of the safety and efficacy of danazol in the treatment of adult idiopathic gynaecomastia was instituted.

Patients and methods

Between 1983 and 1987, patients presenting to two Royal Air Force Hospitals with adult idiopathic gynaecomastia were considered for enrolment into the study. Ethical approval had been obtained and informed consent was sought from all patients. Patients under 16 years of age or over 50 years old were excluded as were men under 45 kg or over 110 kg in weight. Patients with any possible underlying cause for gynaecomastia such as endocrine disorders, testicular tumours, drug-induced gynaecomastia or concurrent treatment with steroids or hormones were also excluded. Enrolled patients were allocated to receive either danazol 200 mg twice daily or matching placebo for 3 months.

Patients were seen initially and after 3 months' treatment, when history, examination, weight and blood pressure were recorded. The degree of gynaecomastia was noted as minimal, moderate, or marked by the clinician and calliper measurements made of the widest diameter of the lump. The callipers used were a micrometer type and proved accurate to within 1.0 mm both for repeated measurements by the same clinician and for measurements on the same patient by different clinicians. The presence of pain and tenderness was also recorded. Blood was taken for full blood count and liver function tests. Patients were seen at 2 and 6 weeks by their general practitioner in order to check for side effects. At the final visit the gynaecomastia was assessed by both clinician and patient. Any side effects were noted and intended future management was recorded. The need for surgery was based upon patient request and was dependent on symptoms or cosmetic appearance as perceived by the patient.

The enrolment characteristics of age, weight, duration of gynaecomastia, laboratory data, weight and blood pressure were analysed using Student's *t* test. Statistical analyses for the degree of breast pain, tenderness and calliper measurements were undertaken using the Wilcoxon Two Sample Test and the Wilcoxon Matched Pairs Test. The intended future management of patients was compared using the χ^2 test.

Results

Between 1984 and 1987, 55 patients were enrolled into the trial. Danazol was randomly allocated to 27 patients and placebo to 28 patients. Protocol violations led to the subsequent exclusion of three patients, one in the danazol group found to have Klinefelter's syndrome and two in the placebo group (one dispensed the wrong medication and one who left the RAF with no follow-up available). There were nine patients who withdrew

Table I. Breast tenderness at initial and final assessments

Tenderness	Initial		Final	
	Danazol (n = 26)	Placebo (n = 26)	Danazol (n = 26)	Placebo (n = 25†)
None	8	9	21	13
Mild	11	6	5	9
Moderate	7	10	0	3
Severe	0	1	0	0

* $P = 0.022$, danazol vs placebo

† One patient in the placebo group was not available for final review

during the study (five danazol and four placebo) for a variety of reasons including dyspepsia, nausea, muscle spasms, decreased libido, poor response, and service postings abroad. These reasons for withdrawal were equally divided between the two groups. All available information was included in the final analysis, as we took the pragmatic view that these patients would be part of a normal population and lack of compliance for a variety of reasons would always occur. Patients in the danazol group were older than the placebo group (mean 24.4 vs 20.8 years, $P = 0.0246$). Bilateral gynaecomastia was present in nine patients. Where present the results for the 'worst' breast were included in the analysis.

Of 15 patients complaining of breast pain at enrolment, five of six patients in the danazol group and six of nine patients in the placebo group had complete resolution by the end of the treatment. The details of 35 patients with breast tenderness are shown in Table I. Breast tenderness was significantly less severe statistically in the danazol group than in the placebo group at the end of treatment ($P = 0.022$). There was a significant improvement in the degree of gynaecomastia for those patients who received danazol ($P < 0.05$). No such improvement was seen in the placebo group (Table II).

There was a significant decrease in the mean diameter of the lump for the group of patients treated with danazol by the end of treatment (mean 3.70 cm to 2.86 cm, $P < 0.05$). There was some improvement in size in the placebo group (mean 4.13 cm to 3.34 cm, $P > 0.5$) but this was not statistically significant.

Table II. Degree of gynaecomastia at initial and final assessments

	Initial		Final	
	Danazol (n = 26)	Placebo (n = 26)	Danazol (n = 26)	Placebo (n = 25*)
Marked	2	4	4	2
Moderate	18	12	6	12
Minimal	6	10	10	8
None	—	—	6	3

* One patient in the placebo group was not available for final review

Intended future management

Of the patients receiving danazol, 27% subsequently requested surgery compared to 50% of patients in the placebo group at the end of the study.

Safety of treatment

Patients receiving danazol showed a significant increase in mean weight from 76.9 kg to 78.2 kg, five showing an increase of more than 3 kg. Patients in the placebo group showed no significant weight change; however, the only patient to complain of weight gain was in this group. There were no clinically significant changes in blood pressure in either group during treatment. Although there were minor variations in both groups in haemoglobin concentrations, AST, alkaline phosphatase and γ -GT levels, no clinically significant abnormalities were seen in any patient.

There were a number of side effects reported in both groups. None were clinically serious and there was no significant difference in the numbers reported by either group.

Discussion

Although there have been a number of studies investigating the efficacy of danazol in pubertal and adult gynaecomastia, this study is the first reported controlled trial to investigate the efficacy of danazol in adult idiopathic gynaecomastia. An uncontrolled study in 1979 (3) reported 17 patients with adult idiopathic gynaecomastia treated by danazol in whom marked or moderate regression was seen in 13. Further studies (4–6) on pubertal gynaecomastia found danazol of value in reducing the size of gynaecomastia in the majority of patients. More recently a study from Cardiff (7) reported on 15 adult patients treated with danazol of whom seven demonstrated an objective response.

Breast tenderness is common in gynaecomastia and danazol appears effective in reducing this symptom. It may also help reduce the degree of gynaecomastia (as perceived by the patient and clinician) and the size of the lump. Breast pain is uncommon in this group of patients and the numbers in the study are too small to draw conclusions regarding the efficacy of danazol in controlling this symptom.

The side effects reported were all minor. Weight gain was the most significant, but although a recognised side effect of treatment does not appear to be a cause for complaint in young men.

What then is the place of danazol in the treatment of adult idiopathic gynaecomastia? On the basis of this study, if there is no urgent need for rapid resolution of the condition, a therapeutic trial of danazol 200 mg twice daily may be effective and obviate the need for surgery. The reduced cost and morbidity related to the 1300 servicemen undergoing surgery between 1972 and 1987 in military hospitals would have been considerable, as it is often the size or cosmetic effect of the lump and its tenderness which lead these young men to request surgery.

In conclusion, danazol appears to be effective in reducing both the tenderness and size of adult idiopathic gynaecomastia and may reduce the subsequent need for surgery. It is important to exclude significant or serious underlying causes of gynaecomastia prior to treatment. Side effects are rarely of clinical consequence. Weight gain may occur but does not appear to be a problem if patients are warned that it may occur.

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