Danazol for benign breast disease

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Three groups of women with benign breast disease were treated with danazol for 3 to 6 months. Doses of 100 mg per day were given to 40 patients, 200 mg to 55, and 400 mg to 35. The age range of the patients was 20 to 48 years. The patients were rechecked at 6-month intervals over a period of 48 months. Most of them were seen four or more times after completion of therapy. Elimination of nodularity occurred in about two thirds; three experienced no improvement, and partial resolution was obtained in the remainder. Untoward effects were minimal or trivial. Danazol proved to be an excellent hormonal agent in the management of fibrocystic disease of the breast.
(AM. J. OBSTET. GYNECOL. 137:604, 1980.)

MANY HORMONES are involved in the process of mammary development, i.e., prolactin, growth hormone, insulin, cortisol, and sex steroids. In the adult, however, sex steroids play the dominant role. Most of the studies dealing with the role of hormones in mammary development have been done in rodents, for practical and obvious ethical reasons. In these species, the mammary glands develop along characteristically female lines only in the absence of circulating androgens during the period of breast differentiation. It is believed that inhibition of the mammary glands in male fetuses takes place about 36 to 48 hours after morphologic differentiation of the testes. Several experimental animal models have been used to study and confirm this phenomenon. The administration of inhibitors of fetal testosterone or the radiation of fetal testicles results in a feminized type of mammary development in male fetuses.[1, 2] These effects have also been demonstrated in in vitro experiments with the use of mouse mammary gland tissue. A case in point is the excellent breast development that occurs in individuals with the testicular feminization syndrome, despite an XY karyotype, because of an androgen insensitivity due to a defect of a cytoplasmic androgen-binding protein.[3] The lack of androgen bioactivity (despite normal concentrations of testosterone in the blood) plays an important role in the modulation of the growth and development of breast tissue. On the basis of this information, it is tempting to speculate how danazol induces the regressive changes in the breast so often observed after the administration of this steroid. It is of interest to note that Peters and co-workers[4] recently suggested that danazol may be useful in inducing a "medical oophorectomy" in patients with metastatic estrogen-sensitive breast cancer. Those authors showed that the administration of danazol resulted in regression of established mammary carcinoma in rats, thus producing a striking inhibition of carcinogenesis in those animals treated with dimethylbenzene anthracine, a well-known carcinogenic agent.

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Received for publication September 17, 1979.
Revised October 22, 1979.
Accepted October 30, 1979.

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Benign breast disease

Benign breast disease affects, more or less, almost all women sometime between adolescence and the menopause. Mazoplasia, adenosis, and fibrocystic disease are part of the panorama of progressive breast changes termed *mammary dysplasia*.[5] Although fibroadenomas and intraductal papillomas are usually benign, they are not included in this study on benign breast disease. The massive breast hypertrophy that occurs in adolescent girls is believed to be due to excessive responsiveness to endogenous estrogens. Fibrocystic disease, on the other hand, occurs for the greater part in ovulatory women, with the stromal, ductal, and acinar changes being the

0002-9378/80/130604+04$00.40/0

sult of an imbalance in the responses to estrogen and progesterone.

Mazoplasia. Mazoplasia affects women from 25 to 35 years of age and is clinically characterized by pain and swelling that extends to the axillary areas and is predominant during the premenstrual period. The histopathologic features are characterized by proliferation of the stroma and small numbers of lobules or acini.

Adenosis (Schimmelbusch's disease). Adenosis occurs in women during their thirties, and is manifested by multinodular mammary tissue, often associated with mastodynia (painful breasts). In this stage, there is epithelial hyperplasia of the ducts.

Cystic disease. Cystic disease may manifest as a single cyst (Cooper's disease) or multiple cysts (Reclus' disease). In most cases, it is an ill-defined entity that comprises such conditions as chronic cystic fibrosis, multiple adenosis, and mazoplasia, and affects women in their mid-forties.

Even though these types of breast disorders were recognized approximately one hundred years ago by various pioneers, such as Cooper, Brodie, Bloodgood, Reclus, and Schimmelbusch, the etiology and pathophysiologic features still remain unclear. Despite the original hypothesis of Taylor,[6] in 1936, who suggested possible hormonal role in the development and maintenance of benign breast disorders, the literature lacks conclusive data to correlate one with the other.

There is also a lack of uniformity concerning the management of benign breast disorders. Aside from aspiration of cysts, conservative surgical procedures on the breast are not the answer to the management of this hormone-dependent disorder. Different types of hormonal treatment have been proposed in the past, with varying results. This article reports some of our experiences with the use of danazol in the medical treatment of benign breast disorders. Danazol is an impeded androgen derived from 17-ethinyl testosterone, the first oral progestogen, known as ethisterone.

Material and methods

This study constitutes an evaluation of a series of 130 patients with fibrocystic disease who were treated for 3 to 6 months with either 100, 200, or 400 mg of danazol per day. The patients ranged in age from 20 to 48 years (Table I). Although fibrocystic disease is generally believed to be more common in the immediate premenopausal years, only 26% of our patients were in that age group (Table II). Fifty-three of them had had previous trials of hormonal therapy (Table III). The diagnosis was entertained if the patient had palpable nodosities. In most cases, pain and tenderness were also associated with nodularity. When indicated, xeromammography was performed to exclude malignancy. Patients were usually seen at 6-month intervals over a period of 48 months, and most of them were seen again at least four times. As an example, of the 55 patients receiving 200 mg/day, 55 were seen at 6 months, 55 at 12, 54 at 24, 47 at 36, and 24 at 48 months; a certain number unavoidably was lost to follow-up for a variety of reasons (Table IV).

During this period of observation, patients did not receive other therapy after completion of the course of danazol. Evaluation of efficacy was based on changes in symptoms that occurred after administration of the drug. Basically, the symptoms were pain, tenderness, and nodularity. The dosage employed was dependent on the severity of the disease. The lower dosages were used in the milder cases. Tables IV-VI express the re-

Table I. Distribution of patients by age

Age group (yr)	*No. of patients*
20-29	33
30-39	63
40-48	34
Total	130

Table II. Dosage and average duration of treatment with danazol for fibrocystic breast disease (90 to 180 days)

Dosage (mg)	*Average days*	*Total No. of patients*
100	129	40
200	131	55
400	150	35
Totals	136.6	130

Table III. Previous treatments for fibrocystic disease

Previous treatment	*No. of patients*
Estrogen-progestogen combination	22
Androgens	21
Progesterone	7
Progesterone, diuretics, vitamins	3
No previous treatment given	77
Total	130

Table IV. Evaluation of breast nodularity in 55 patients with benign cystic breast disease after 200-mg danazol therapy

	Evaluation after				
	6 mo.	*12 mo.*	*24 mo.*	*36 mo.*	*48 mo.*
Elimination	36	37	45	42	18
Partial resolution	19	18	9	5	6
Totals	55	55	54	47	24

Table V. Evaluation of breast nodularity in 35 patients with benign cystic breast disease after 400-mg danazol therapy

	Evaluation after				
	6 mo.	*12 mo.*	*24 mo.*	*36 mo.*	*48 mo.*
Elimination	28	28	25	20	19
Partial resolution	7	6	8	10	7
Unchanged	0	1	0	0	0
Totals	35	35	33	30	26

Table VI. Evaluation of breast nodularity in 40 patients with benign cystic breast disease after 100-mg danazol therapy

	Evaluation after				
	6 mo.	*12 mo.*	*24 mo.*	*36 mo.*	*48 mo.*
Elimination	26	25	26	27	7
Partial resolution	13	14	13	7	1
Unchanged	1	1	0	0	0
Totals	40	40	39	34	8

Table VII. Side effects during danazol therapy

Side effects	*No. of patients*
Muscle cramps	19
Acne	15
Oily hair	12
Hot flushes	4
Nervousness	4
Weight gain	3
Hairiness	2
Increased libido	4
Edema	4
None	63
Total	130

sults as recorded at the various follow-up periods. In the overall clinical evaluation, most of the 130 women were markedly improved, whereas the remainder showed partial alleviation. Danazol was particularly effective in the younger age group. Although there was return of some pain and tenderness in about one third of the patients, the fact that nodularity disappeared or was considerably reduced removed much of their anxiety and fear.

Danazol induced menstrual irregularities or amenorrhea and was dose related. The most frequent adverse reactions, considered either to be drug related or of uncertain relationship, were: muscle cramps (19); acne (15); oily hair (12); hot flushes (4); nervousness (4); gain in weight (3); hairiness (2); increased libido (4); edema (4). No side effects were reported in 63 cases (Table VII).

Patients who had the potential for conception were advised to start medication soon after the onset of the following menses. In this series, no patient conceived while on danazol; however, one patient with relative infertility (not part of this series) who began 100 mg of danazol immediately after the start of a scanty period was found to have been pregnant at the time. She took this dose for 98 days and was delivered at term of a normal female infant.

Comment

The beneficial effects of danazol in 10 patients with benign breast disease were first reported by Greenblatt and associates[7] in 1971. The effectiveness of danazol in this condition was confirmed by several investigators,[8–10] and by further reports from Greenblatt's group.[11, 12] In 1976, Lauersen and Wilson[8] reported that danazol in a daily dose of 400 mg resulted in marked objective and subjective improvement of symptoms in 87.5% of the patients with chronic cystic mastitis. A mild gain in weight was the major side effect of therapy. No significant changes in the concentrations of estrone, estradiol, follicle-stimulating hormone, luteinizing hormone, or progesterone were found in some patients evaluated before and during the administration of danazol.

Blackmore,[9] in 1977, collated the results obtained by several investigators on 260 patients with benign breast disease. Therapy with 200 to 400 mg daily for periods up to 6 months revealed that danazol caused a significant decrease in, or elimination of, breast pain and tenderness, and produced a decrease in, or disappearance of, nodular areas. Untoward effects were trivial, and blood chemistry profiles remained unchanged. The author suggested that a possible dose-response relationship may be established in order to obtain the minimal, clinically effective dose.

Also in 1977, Buckle[13] reported the effects of danazol on 14 patients with gynecomastia (11 adults and 3 adolescents). Approximately 70% of the patients showed marked regression of the gynecomastia, despite the variety of etiologies (thyrotoxicosis; spironolactone therapy; and idiopathic sexual precocity). A marked decrease in urinary follicle-stimulating hormone and little effect on the levels of luteinizing hormone were observed during therapy. There was also a reduction in the concentrations of testosterone. The effectiveness of the therapy and the lack of serious side effects led the author to conclude that danazol offers a useful treatment for gynecomastia.

Montgomery and associates,[10] in 1979, obtained relief of pain in 70% of patients treated with danazol for severe cyclic mastalgia. Levels of prolactin were within normal laboratory range in these patients before and

a therapy. Long-term administration of danazol does not affect the concentrations of prolactin in normally cycling and oophorectomized rhesus monkeys.[14] Thus, it is unlikely that the effects of danazol on patients with fibrocystic disease of the breast are mediated by prolactin.

The modus operandi of danazol therapy in benign breast disease remains uncertain, but two alternatives may be entertained to explain the mechanism of its effectiveness.

In doses of 100 mg or more per day, danazol usually prevents the mid-cycle surge of luteinizing hormone and is thus regarded as an antigonadotropin. In larger doses, danazol induces atrophy of the endometrium, regressive changes in the vaginal mucosa, and loss of ferning of cervical mucus, and often provokes hot flushes. All this suggests antiestrogen activity. Asch and associates[14] believe that danazol acts at a suprapituitary level since administration of luteinizing hormone–releasing hormone induces normal pituitary function during danazol therapy. On the other hand, danazol also acts directly at the gonadal level by inhibiting several enzymes involved in the steroidogenic process (17α-hydroxylase, 17-20 lyase, 3β-hydroxysteroid dehydrogenase, 17β-hydroxysteroid dehydrogenase, 21-hydroxylase, 11β-hydroxylase, and cytochrome P450).[15]

The direct and indirect inhibition of gonadal steroidogenesis induced by danazol creates a hormonal milieu similar to that of the postmenopausal period, in which (a) the absence of circulating steroid hormones results in regressive changes in the breast tissue, and (b) a direct action of danazol at the breast tissue level may be due to the blocking of estrogen and/or progesterone receptors.[16] Chamness, Asch and Pauerstein[3] have recently shown that danazol produces its effects by binding and translocating androgen, but not estrogen or progesterone receptors.

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