EFFECT OF OESTROGEN AND TESTOSTERONE IMPLANTS ON PSYCHOLOGICAL DISORDERS IN THE CLIMACTERIC

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Summary In a double-blind trial oestradiol, oestradiol/testosterone, or placebo implants were assessed for their effects on psychological symptoms in women attending a menopause clinic. After two months, women receiving active treatment scored better than the placebo group on a self-rating scale of distress, on anxiety, and on depression ($p < 0.05$). Postmenopausal but not perimenopausal women improved after placebo, and at 4 months the scores in the three groups no longer differed significantly.

Introduction

ANXIETY, irritability, and depression arising in association with vasomotor and atrophic symptoms are common around the time of the menopause.[1,2] Although vasomotor and atrophic symptoms such as hot flushes, insomnia, and dyspareunia are generally attributed to hormonal changes and can be treated with oestrogen replacement therapy, there is disagreement about the frequency and aetiology of psychiatric disturbances. Do these symptoms respond to hormone treatment? Double-blind trials have shown the beneficial effects of oestrogen therapy on psychiatric disturbances,[3-6] but these studies have been criticised for their poor definition of menopausal status and the use of non-standardised psychological tests.[7]

Using a standardised method of psychiatric assessment we have quantified the effects of hormone replacement therapy against placebo in a well-defined population of women.

Patients and Methods

Trial Design

84 women referred to the clinic with menopausal symptoms were recruited into the trial after giving informed consent. Ethical approval was obtained from the ethical committee. Women with a contraindication to oestrogen replacement therapy were excluded. Plasma follicle stimulating hormone (FSH), luteinising hormone, and oestradiol were measured at entry to define menopausal status. Both perimenopausal and postmenopausal women were included. Perimenopausal women were defined as those with irregular menstruation, climacteric symptoms, and FSH values greater than 15 IU/l.[8] The postmenopausal group were women who had not menstruated for more than 6 months and in whom the FSH was more than 40 IU/l.

The women were randomly allocated in double-blind fashion into three implant groups—oestradiol 50 mg (E50), oestradiol 50 mg and testosterone 100 mg (E50/T100) (Organon), and placebo. Norethisterone 5 mg daily for 7 days each month was prescribed in all women, except 10 who had had a hysterectomy, to prevent endometrial hyperplasia.

Implantation was done by an independent doctor, as described by Thorn and Studd.[9] The women were seen every 2 months by the same doctor to assess response to treatment. The study was designed to last for 6 months but many women withdrew after 4 months because they felt that the effects of the implant were wearing off.

Rating Scales

Psychiatric symptoms were assessed with the short version of Kellner and Sheffield's self rating scale of distress (SRD30).[10] This standard questionnaire was designed to measure neurotic symptoms in patients participating in therapeutic trials and distinguishes between psychiatric and normal patients and between responses to drugs and placebo. The scale is scored from 0 to 90 and a result over 20 indicates psychiatric morbidity. The overall score can be broken down into four major subscales—anxiety, somatic disturbances, depression, and inadequacy. Full psychiatric assessment was made with the clinical interview schedule[11] in 35 patients to validate the SRD 30.

Statistical Analysis

Response to treatment was analysed longitudinally by Student's *t* test. Cross-sectional comparisons between the three treatment groups were made by analysis of variance.

Results

Drop-outs and Exclusions

Of the 84 women recruited 14 dropped out. 3 did not attend after implantation, all having had placebo implants. Of the 3 women who did not attend after their 2-month visit, 2 had been treated with E50/T100 and 1 with E50 implants. 8 women were withdrawn from the study before 4 months—1 because of acute cholecystitis (E50), 1 because of attempted suicide (E50/T100), and 6 because symptoms had not been alleviated (5 placebo; 1 E50). Of the remaining 70 women, 39 were perimenopausal and 31 were postmenopausal. 36 women needed a further implant at 4 months and therefore at 6 months numbers were too few for statistical analysis. There was no difference in duration of the implant in the three groups.

Baseline Characteristics

Before treatment there was no difference between the three groups in age, menopausal status, or the presence of a uterus (table I). Baseline SRD30 and subscale scores were all similar except for inadequacy which scored lower in the E50/T100 group (6·8, SD 4·2) ($p < 0.05$) than in the E50 (10·4, 4·9) and placebo groups (11·0, 4·8). Inadequacy was therefore not analysed further, though it was taken into account in the total SRD30 score.

Comparison of Methods of Scoring

The clinical interview schedule scores correlated highly with the SRD30 scores (Pearson correlation $r = 0.67$ and $r = 0.92$ at 0 and 2 months, respectively). The patients who had initial psychiatric interview were a representative subgroup of the total sample showing no difference in their baseline SRD30 scores or in response to treatment. Thus a therapeutic effect for assessment interview was excluded.

TABLE I—CHARACTERISTICS OF THE TREATMENT GROUPS (n = 70)

	Treatment groups		
	E50	E50/T100	Placebo
No	25	24	21
Mean age (yr)	46	50	48
Perimenopausal (no)	14	13	12
Postmenopausal (no)	11	11	9
Hysterectomy (no)	5	2	3

TABLE II—MEAN (SD) SCORES FOR PSYCHOLOGICAL ASSESSMENT

	Time from implant		
	0 mo	2 mo	4 mo
E50 group			
SRD30	40·8 (17·8)	24·1 (18·2)†	28·3 (21·9)
Anxiety	12·0 (5·7)	6·2 (5·3)*	8·2 (7·0)
Somatic disturbance	8·2 (4·2)	4·9 (3·8)	5·5 (4·8)
Depression	10·1 (5·1)	5·5 (5·0)†	7·0 (6·0)
E50/T100 group			
SRD30	32·1 (16·5)	14·1 (8·2)†	21·8 (20·6)
Anxiety	9·5 (5·3)	4·0 (2·7)*	6·2 (5·7)
Somatic disturbance	7·4 (4·8)	3·4 (2·7)	5·5 (5·0)
Depression	7·8 (4·8)	3·3 (2·3)†	5·0 (5·5)
Placebo group			
SRD30	42·1 (18·0)	31·8 (22·7)	26·5 (19·7)
Anxiety	11·7 (5·6)	9·0 (7·5)	7·6 (6·3)
Somatic disturbance	8·7 (4·2)	5·6 (4·3)	5·0 (4·1)
Depression	11·5 (6·2)	8·6 (6·5)	6·9 (5·8)

Significant difference between active over placebo groups: * = $p < 0.05$, † = $p < 0.01$.

Effect of Treatment on Psychological Scores

Table II shows the scores for psychological assessment in the treatment groups and the levels of significance between the active and placebo groups. There was a significant ($p < 0.001$) improvement over baseline in SRD30 and subscale scores at 2 months in the active treatment groups. Only somatic disturbance ($p < 0.01$) and depression ($p < 0.05$) were improved in the placebo group. Across-group comparison revealed significant differences, the two active treatment groups scoring less than the placebo group on the total SRD30, anxiety, and depression. At 4 months there was a significant improvement over baseline in SRD30 and subscale scores in all three treatment groups ($p < 0.05$ to $p < 0.001$ in the E50 and E50/T100 and $p < 0.01$ to $p < 0.001$ in the placebo groups). Comparison of the three treatment groups showed no difference. There was no difference in scores between the two active treatment groups at either 2 or 4 months.

Perimenopausal women.—Table III shows the scores for psychological assessment in this group. There was no significant improvement at 2 months in the placebo group. In the E50 and E50/T100 groups the SRD30 and the three subscale scores were significantly improved ($p < 0.01$ to $p < 0.001$). All scores for psychological disturbance were significantly lower in the two active treatment groups than in the placebo group. At 4 months the scores over baseline in the active treatment groups were higher than at 2 months, but with the exception of somatic disturbance in the E50/T100 group they were still significantly lower than baseline ($p < 0.05$ to $p < 0.01$). In the placebo group, however, the scores continued to improve and those for anxiety and somatic disturbance were significantly lower than baseline ($p < 0.05$). At this stage there was no significant difference between the scores of active treatment and placebo groups.

TABLE III—MEAN (SD) SCORES FOR PSYCHOLOGICAL ASSESSMENT IN PERIMENOPAUSAL PATIENTS

	Time from implant		
	0 mo	2 mo	4 mo
E50 group			
SRD30	41·9 (16·8)	22·4 (18·0)†	27·8 (19·4)
Anxiety	12·1 (4·7)	5·8 (5·0)†	8·2 (6·0)
Somatic disturbance	9·1 (7·6)	4·6 (3·8)*	5·6 (4·3)
Depression	10·3 (5·2)	5·1 (4·9)†	6·5 (5·3)
E50/T100 group			
SRD30	33·8 (17·3)	16·0 (9·6)†	27·0 (25·8)
Anxiety	10·1 (5·4)	4·8 (3·2)†	7·2 (7·2)
Somatic disturbance	7·6 (3·5)	3·5 (2·7)*	6·5 (5·8)
Depression	8·3 (5·5)	3·9 (2·9)†	6·6 (6·9)
Placebo group			
SRD30	47·1 (17·0)	41·3 (23·1)	34·2 (20·5)
Anxiety	13·2 (5·3)	12·3 (7·6)	9·6 (6·6)
Somatic disturbance	10·4 (3·9)	7·4 (4·6)	6·5 (4·6)
Depression	12·5 (6·4)	11·0 (6·6)	9·1 (4·5)

Significant difference between active over placebo groups: * = $p < 0.05$, † = $p < 0.01$.

TABLE IV—MEAN (SD) SCORES FOR PSYCHOLOGICAL ASSESSMENT IN POSTMENOPAUSAL PATIENTS

	Time		
	0 mo	2 mo	4 mo
E50 group			
SRD30	39·5 (19·6)	26·2 (19·1)	29·2 (25·8)
Anxiety	11·8 (7·1)	6·6 (5·9)	8·1 (8·5)
Somatic disturbance	7·0 (4·7)	5·2 (4·0)	5·5 (5·5)
Depression	9·6 (5·0)	6·0 (5·3)	7·6 (7·2)
E50/T100 group			
SRD30	30·0 (16·1)	11·9 (6·0)	15·7 (10·3)
Anxiety	8·7 (5·4)	3·2 (1·9)	4·8 (3·3)
Somatic disturbance	7·2 (5·6)	3·3 (2·8)	3·0 (1·4)
Depression	7·4 (4·0)	2·6 (1·3)	3·2 (2·4)
Placebo group			
SRD30	34·5 (18·0)	17·4 (13·1)	16·4 (13·8)
Anxiety	9·5 (5·6)	3·9 (3·5)	5·0 (5·0)
Somatic disturbance	6·1 (3·3)	3·0 (1·4)	3·0 (2·4)
Depression	9·4 (5·8)	5·0 (4·6)	4·1 (3·8)

Postmenopausal women.—Table IV shows the scores for psychological assessment in postmenopausal women. At 2 months there was a significant improvement ($p < 0.05$ to $p < 0.001$) in all three groups for the SRD30 score and its subscales, except for somatic disturbances in the E50 group and, more importantly, depression in the placebo group. Although at 2 months the placebo group did not seem to improve as much as the other two groups there was no significant difference between the three groups. At 4 months the SRD30 score was significantly improved only in the placebo group. In the E50/T100 group only the anxiety score and somatic disturbance were improved. There was no significant difference across the three groups.

Discussion

An unexpected finding of this study was the very high proportion of women (86%) with clinical psychiatric illness associated with climacteric symptoms (SRD30 over 20). Other reports have shown that 29% of women aged 40–55 in a general population sample[12] and 52% of women of a similar age referred to a gynaecology clinic (largely because of menstrual abnormalities)[13] had psychological disturbances.

No direct link between the menopause and depression has been established. The highest incidence of depression in middle life seems to arise in the few years before the cessation of periods.[14] This suggests that it is not low levels of oestrogen but changes in hormone concentration, such as arise in the cyclical depression of premenstrual syndrome[15] that predispose to depression during the menopause. There is evidence that women who are depressed are those who are most anxious about the menopause and attribute their low mood to it. Many of the women in our study blamed their

menopausal symptoms for their unhappiness; however, the large proportion with clinical depression suggests that the depression led to referral to a specialist menopause clinic in many cases.

Falling oestrogen levels may lead to low central nervous system neurotransmitter activity, either by reducing available tryptophan for serotonin synthesis or by reducing dopamine receptor sensitivity.[16] The physical symptoms of the menopause may cause a secondary depression in some susceptible women. Alternatively, the loss of reproductive potential may be seen as a loss of femininity and result in low self esteem.

The impressive placebo response in our patients may partly represent the self-limiting nature of depression and the therapeutic effect of 2-monthly visits to a sympathetic doctor. We have shown that psychological symptoms eventually improved irrespective of treatment regimen, although the response in the treated groups was more rapid—an important consideration in the management of the depressed patient.

Might norethisterone have influenced the results? This agent has been used for the the treatment of hot flushes[17] and therefore some of the improvement in the placebo group may have been due to the alleviation of this symptom; but norethisterone has side-effects that include irritability and depression.[18]

Perimenopausal women responded rapidly to active implants whereas the postmenopausal women improved on both active and placebo implants. There is epidemiological evidence that perimenopausal women have more psychological disturbances in conjunction with hot flushes than do postmenopausal women.[14] The perimenopausal women who have fluctuations in oestrogen levels seem to respond to a high dose of exogenous oestrogen that ablates their cycle. The decline of improvement at 4 months, particularly in perimenopausal women may be due to loss of efficacy of the implants.

Although the long-term benefits of implants on depression require further study, the initial response in perimenopausal women leads us to conclude that climacteric depression responds rapidly and well to hormone replacement therapy.

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References continued at foot of next column

Preliminary Communication

RAPID AND SAFE TERMINATION OF SUPRAVENTRICULAR TACHYCARDIA IN CHILDREN BY ADENOSINE

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Summary Adenosine (0·05–0·25 mg/kg intravenously) successfully terminated resistant supraventricular tachycardia (SVT) in three seriously ill newborn infants and one older child. Termination of tachycardia was achieved in each case within 20 s. Adenosine, unlike many other anti-arrhythmic agents, has no substantial negative inotropic effect under these circumstances and may become the drug of choice in haemodynamically compromised children with SVT. However, it has no value in prophylaxis against recurrent SVT.

INTRODUCTION

ADENOSINE, an endogenous purine nucleoside, is a potent anti-arrhythmic agent which impairs atrioventricular nodal conduction and thereby terminates re-entrant supraventricular tachycardias (SVT) that involve the atrioventricular node. Several clinical reports have suggested that adenosine is useful for the termination of both SVT induced during electrophysiological studies[1] and spontaneous SVT.[2,3] Since most episodes of SVT in children are due to atrioventricular re-entry, often involving an accessory pathway, adenosine ought to be appropriate for the treatment of such tachycardias. Adenosine triphosphate (ATP), which is rapidly degraded in vivo to adenosine, has previously been used to treat SVT in children, but it causes many side-effects.[4,5]

PATIENTS AND METHODS

All the children studied had recurrent SVT unresponsive to other agents (see table). Three were severely ill, in cardiac failure due to long-term spontaneously occurring SVT. The fourth patient (D) was admitted for an elective electrophysiological study.

Exclusion criteria were a history of asthma in relatives (adenosine has a weak bronchoconstrictor action when inhaled[6] but not when infused[7]) and concurrent treatment with dipyridamole, which potentiates the effect of exogenous intravenous adenosine.[8] No child

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