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The management of persistent menopausal symptoms with oestradiol–testosterone implants: clinical, lipid and hormonal results

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Seventeen patients attending two menopause clinics were treated with combined subcutaneous implants of oestradiol (40 mg) and testosterone (100 mg), because oral oestrogens had not provided adequate symptomatic relief, particularly of decreased libido. There were significant improvements in libido, enjoyment of sex and tiredness ($P < 0.01$), and in lack of concentration ($P < 0.05$), but there was no significant change in flushes, sweats and depression. Based on an analogue scale, libido increased from a mean basal score of 13.5 to a maximum of 86.1 at 3 mth. Symptomatic improvement was maintained for 4–6 mth.

There were no significant changes in total serum cholesterol and triglycerides nor in cholesterol subfractions. When expressed as a percentage of the preimplant values, maximal changes in hormonal parameters were observed at 1 mth. Thus, follicle stimulating hormone (FSH) was 53% of basal, luteinising hormone (LH) 54%, oestradiol 186%, total testosterone 291%, and free testosterone 342%. Only 1 patient complained of hirsutism and weight gain.

We conclude that the hormonal implants provided substantial symptomatic relief, particularly of loss of libido, while causing rises to mid-follicular concentrations of oestradiol and maximal testosterone levels about three times normal, without significant effects on plasma lipids.

(Key words: Hormone implants, Clinical effects, Lipid effects, Hormonal effects, Loss of libido)

Introduction

Although the symptoms of oestrogen deficiency occurring during or after the peri-menopausal period usually respond well to oral oestrogens, loss of libido may persist despite relief of hot flushes and vaginal dryness. Absent libido in the female may create marital difficulties and loss of self-esteem. It has been reported that the symptoms respond well to testosterone administered by implant [1].

We undertook an open study to evaluate the effectiveness of combined oestradiol

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and testosterone implants in alleviating menopausal symptoms not responding to standard oral oestrogens. Evaluation included the assessment of symptomatic responses and the effects of the implants on serum gonadotrophins, oestradiol and total and free testosterone, as well as on serum lipids, measured at monthly intervals.

Patients and Methods

Seventeen patients attending two hospital menopause clinics and one private practice were selected for this pilot study because they complained of persistent symptoms, particularly loss of libido, despite therapy with conjugated equine oestrogens (Premarin), 1.25 mg daily, or oestradiol valerate (Progynova), 4 mg daily. Their mean age at menopause was 37.5 yr, range 28–50. Their mean age at the time of admission to the study was 42 yr (range 35–51). Ten had undergone hysterectomy and oophorectomy (at ages between 30 and 43 yr), one had undergone hysterectomy only (at age 40), and one oophorectomy only (at age 31), whilst 5 subjects had undergone spontaneous menopause (at ages 28, 39, 42, 42 and 50 yr).

Information was obtained regarding past history of breast disease, hirsutism, post-menopausal bleeding or depression and specific questions were asked regarding the presence of flushes, sweats, palpitations, headaches, dyspareunia, aches and pains and insomnia. Patients were asked to rate their lack of concentration, depression, inability to cope and tiredness on a scale of 0–100 with 100 representing complete freedom from these problems. They were asked to rate their libido on a scale of 0–100, their enjoyment of sex on a scale of 0–3, both scores being relative to their memory of experience in their 20s. They were asked whether they initiated sexual activity and to record the number of times per month when they experienced climax.

We performed a complete physical examination initially and took blood for measurement of gonadotrophins, oestradiol, total and free testosterone, cholesterol and its subfractions and triglycerides. Patients with contraindications to hormone therapy such as a past history of benign breast disease, thrombosis or recent postmenopausal bleeding were excluded.

We implanted pellets (Organon) of testosterone (100 mg) and oestradiol (40 mg) subcutaneously and requested patients to return at monthly intervals for symptomatic assessment, measurements of weight and blood pressure and assessment of the presence of acne, hirsutism, voice change or breast lumps. We took blood samples as at the initial visit. For patients with an intact uterus, we prescribed medroxyprogesterone (Provera), 10 mg daily for 10 days following each monthly visit.

Serum FSH, LH, oestradiol and testosterone were measured as described previously [2]. Free testosterone was measured by the method of Hammond et al. [3]. Serum cholesterol, triglycerides and high density lipoprotein cholesterol were measured by the methods of Allain et al. [4], Bucolo and David [5] and Allen et al. [6] performed on an Abbott ABA-100 Bichromatic analyser. Normal ranges were as follows:

- FSH (post-menopausal): 23–107 IU/l.
- LH (post-menopausal): 19–73 IU/l.
- Total testosterone (cycling women): 1–3 nmol/l.
- Testosterone – %free (cycling women): 63–93%.
- Derived absolute free testosterone: 6–28 pmol/l.
- Oestradiol:
  - Early follicular phase, 150–500 pmol/l.
  - Late follicular phase, 500–1200 pmol/l.
  - Post-menopausal women, < 10–150 pmol/l.
- Serum cholesterol: < 6.5 mmol/l.
- Triglycerides: < 2.0 mmol/l.
- High density lipoprotein cholesterol: > 1.20 mmol/l.

Results

Table I shows the percentage of subjects with various symptoms at the time of implantation and at each monthly visit thereafter. Oral oestrogen therapy had been maintained until the time of implantation and the symptoms were therefore those

TABLE I

PERCENTAGE OF PATIENTS (TOTAL NUMBER ASSESSED IN PARENTHESES) WITH VARIOUS SYMPTOMS BEFORE AND AFTER HORMONE IMPLANTATION.

Symptom	Mth after implant					
	0	1	3	4	5	6
	Percent of patients (total number assessed)					
Flushes	41 (17)	29 (17)	24 (17)	19 (16)	40 (15)	47 (15)	50 (16)
Sweats	35 (17)	24 (17)	29 (17)	13 * (16)	27 (15)	40 (15)	38 (16)
Lack of concentration	41 (17)	29 (17)	12 ** (17)	19 ** (16)	40 (15)	27 (15)	29 (14)
Tiredness	71 (17)	59 (17)	35 *** (17)	44 * (16)	60 (15)	60 (15)	66 (15)
Depression	50 (14)	50 (14)	43 (14)	31 (13)	46 (13)	25 (12)	54 (13)
Absent or reduced libido	94 (17)	82 (17)	70 (17)	43 *** (14)	73 (15)	80 (15)	80 (15)
Absent or reduced enjoyment of sex	100 (16)	69 (16)	47 (15)	29 *** (14)	43 (14)	54 (13)	60 (15)
Zero climax	50 (16)	31 (16)	13 (15)	0 *** (14)	14 (14)	8 (13)	38 (13)
No initiation of sex	88 (16)	75 (16)	27 (15)	21 *** (14)	57 (14)	62 (13)	57 (14)

Analysis of variance; * $P < 0.10$; ** $P < 0.05$; *** $P < 0.01$.

persisting despite adequate oral oestrogen dosage. Symptoms initially present included hot flushes, sweats, lack of concentration, tiredness, depression, absent or markedly diminished libido, diminished sexual enjoyment, absence of climax at love making and no initiation of sex. Three subjects had a past history of depression and were excluded from the analysis of this symptom's response to implantation. One patient who had no partner was excluded from the analysis of sexual enjoyment, initiation of sex and number of climaxes. A total of 5 subjects was not included in the analysis for sexual enjoyment, initiation of sex or climaxes per month for the visits at 2, 4 and 5 mth following implantation because at that time they had no relationship and no intercourse. Two subjects were not included in the analysis of libido, enjoyment, initiation of sex or number of climaxes at the 3rd month because of personal problems or illness leading to a lack of sexual interest and of intercourse. Two thirds of the subjects reported a complete absence of libido. Fifty-six percent of the patients rated their enjoyment of sex as nil and 12% initiated sexual activity with their partner. Two thirds of patients had not experienced orgasm for at least several months whilst one third reported climax occurring between 2 and 10 times per month. As shown in the table, there was a tendency for all symptoms to improve with the lowest percentages of patients being symptomatic 3–4 mth following insertion of the implants. Statistically, highly significant improvements ($P < 0.01$) were found for tiredness, absent or reduced libido, absent or reduced enjoyment of sex, absence of climax and failure to initiate sex. The mean baseline analogue score for libido was 13.5 rising to 76.5 at 2 mth and 86.1 at 3 mth following the implant. At 6 mth, levels had fallen to 53.3. Similar changes occurred in the scores for enjoyment of sex. There was also improvement in lack of concentration ($P < 0.05$) but no statistically significant changes occurred in flushes, sweats or depression. Weight and blood pressure showed no significant changes throughout the period of observation.

Table II shows the mean levels of serum FSH, LH, oestradiol, total and free testosterone, cholesterol, triglycerides and high density lipoprotein cholesterol. FSH

TABLE II

MEAN HORMONAL AND LIPID VALUES.

Months of study	Measured variables (±SD)							
	FSH (IU/l)	LH (IU/l)	E_2 (pmol/l)	T (nmol/l)	Free T (pmol/l)	Chol (mmol/l)	HDLC (mmol/l)	TG (mmol/l)
0	23.0 ±13.6	24.6 ±13.9	344 ±229	2.3 ±1.2	20.0 ±16.9	5.8 ±1.0	1.7 ±0.4	1.5 ±1.0
1	12.3 ±7.0	13.2 ±10.7	640 ±198	6.7 ±3.2	68.4 ±25.7	5.6 ±1.0	1.6 ±0.6	1.4 ±0.9
3	15.9 ±11.8	14.5 ±12.8	450 ±196	4.2 ±1.8	43.8 ±15.4	6.0 ±1.3	1.6 ±0.4	1.5 ±0.6
5	15.6 ±8.6	18.9 ±12.0	476 ±277	2.5 ±1.2	20.0 ±12.0	5.8 ±1.1	1.7 ±0.4	1.2 ±0.4

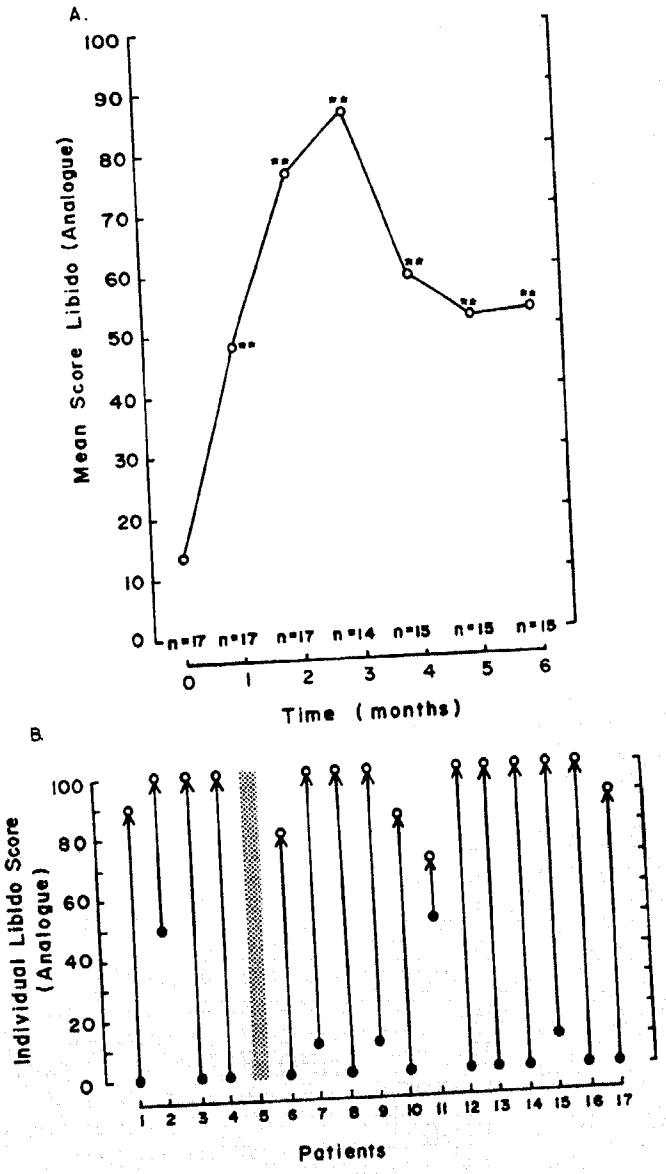

Fig. 1. A. Mean self-rating of libido (on an analogue scale) before and after the implantation of testosterone and oestradiol. Numbers of subjects at each point are shown just above the scale for the abscissa. ** Score significantly different from that at time 0 ($P < 0.01$). B. The initial self-rating of libido (●) and highest rating (○) following testosterone-oestradiol implantation. The score of 0 indicates complete absence of libido and the rating of 100 represents an optimal level of libido. The hatched column represents a patient who had no partner and was excluded from the analysis.

was maximally suppressed at 1 mth to 53% of the preimplant value, whilst LH was maximally suppressed at 2 mth to 50% of baseline. Both gonadotrophins then rose steadily to reach preimplant values at 6 mth. Plasma oestradiol peaked at 1 mth reaching a mean of 640 pmol/l compared with a preimplant value of 344. The latter is somewhat higher than expected in post-menopausal women probably because of preceding oral oestrogen therapy. The values then slowly fell but remained in the midfollicular range with a mean value of 493 pmol/l at 6 mth. Plasma total and free

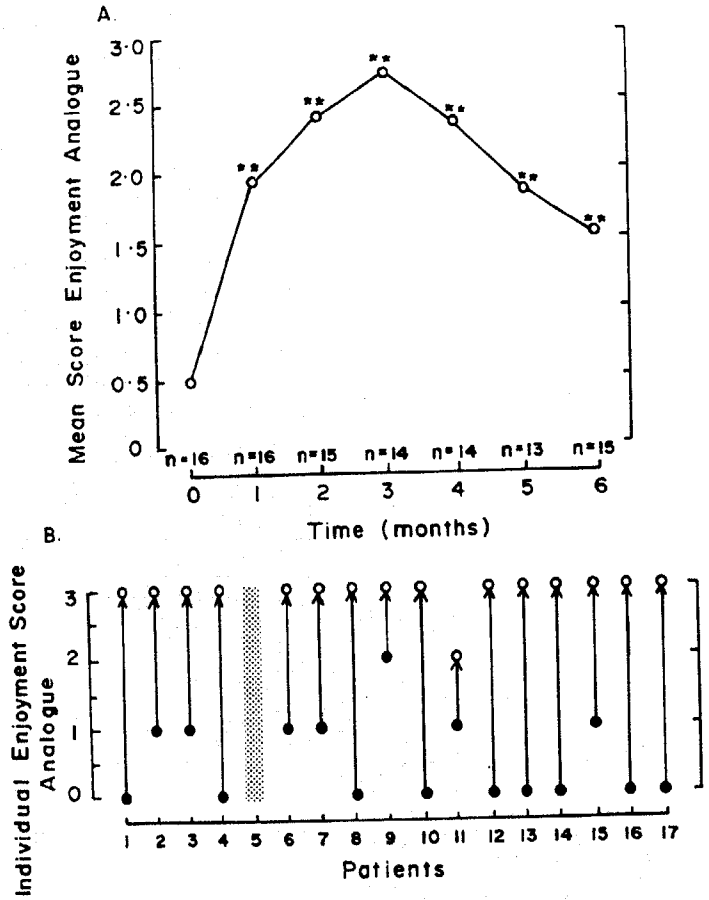

Fig. 2. A. Numerical representation of level of sexual enjoyment based on a self-rating scale of 0 to 3, 3 representing optimal level as recalled during the subject's 20s. The mean number of subjects at each point is given just above the scale for the abscissa. ** Score significantly different from that at time 0 ($P < 0.01$). B. Individual scores for enjoyment of sex. The initial level (●) and the optimal level achieved following implantation of oestradiol and testosterone (○) are shown. The number of subjects at each point is shown just above the abscissa. The hatched column represents a patient who had no partner and was excluded from the analysis.

testosterone rose and fell in parallel, peaking 1 mth after the implant and remaining slightly elevated above the upper limit of normal at 6 mth with total testosterone being 3.9 nmol/l at that time. The mean peak value was 6.7 nmol/l. No significant changes were seen in the serum lipids.

Side effects

Side effects following hormone implants were minimal. One patient complained of the development of very mild hirsutism and weight gain and one singer complained of alteration of her voice range. The patient who developed increased hair growth withdrew from the study at 4 mth. One patient failed to attend two visits because she was unable to take time off from a new job.

Discussion

Symptoms of sexual dysfunction commonly occur after the menopause [7], and are particularly frequent among women attending menopausal clinics [8]. The efficacy of oestrogen replacement therapy in improving loss of libido is controversial [9–11], but several reports attest to the efficacy of hormone implants containing both oestradiol and testosterone [1,12], although a recent study [13] suggested that the combined implants were no more effective than oestradiol implanted alone. However, there was no indication in the latter report whether the patients had been given oral oestrogen prior to their admission to the study.

The present open study was designed to assess whether combined hormonal implants would relieve the symptoms of decreased sexuality which were persistent after an adequate period of oral oestrogen replacement in conventional dosage. We found that the combined implants produced a striking improvement in libido and sexual enjoyment, with less striking but significant improvement in the remaining symptoms. Maximal symptomatic improvement was noted two to four months following implantation, whilst maximal hormonal changes were found after one month. Symptoms returned despite maintenance of plasma oestradiol concentrations in the mid-follicular range, and testosterone values at or above the upper limit of normal. The recurrence of symptoms at pre-menopausal oestradiol concentrations has been noted by others [12], and is not readily explicable: it suggests that symptoms are related to therapy rather than absolute hormone concentrations.

The side effects noted in the present study were minor and infrequent: of particular note was the low frequency of masculinising complications, as has been noted previously [12] although our period of follow-up was relatively short. The lack of change in serum lipids was reassuring, as the possibility of an increase in risk factors for atherosclerotic vascular disease is a major consideration of the choice of hormone replacement therapy. We cannot, however, conclude that testosterone will not promote atherosclerosis on the basis of this data.

In conclusion, our open, pilot study shows that combined hormone implants are highly effective in relieving loss of libido which does not respond to conventional

oral oestrogen therapy. Whether testosterone is required for this effect will require a controlled study which we are undertaking.

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