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SHORT COMMUNICATION

Low dose 25 mg oestradiol implants and 1 mg norethisterone as continuous combined hormone therapy: a prospective study

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The anxiety regarding no-bleed regimens is that breakthrough bleeding and endometrial hyperplasia may occur. We aimed to demonstrate that 25 mg oestradiol implants can be adequately opposed by a low dose of progestogen protecting against osteoporosis. Twenty-two patients were recruited to the study. The mean age was 62 years and body mass index of 26.5. Median oestradiol rose from 77 pmol/L at baseline to 275 pmol/L at one year. Median endometrial thickness remained unchanged at 4 mm and only two women withdrew with bleeding problems. There was one case of proliferative endometrium at one year—all others samples were either atrophic or secretory. Lumbar bone density (L2–L4) rose significantly from 0.939 to 0.992 g/cm^2 (+5.6%, $P = 0.005$) and the total femoral density rose from 0.872 to 0.890 g/cm^2 (+2.1%). Bone formation markers increased significantly (serum type 1 procollagen C terminal peptide, P1CP = 112–114, $P = 0.0376$) and bone resorption fell (serum type 1 collagen C terminal telopeptide, 1CTP = 3.0–2.9, $P = 0.2863$). E25 implants and low dose progestogen appear to avoid endometrial hyperplasia and bleeding problems while increasing bone density.

Introduction

Many postmenopausal women with an intact uterus would rather avoid bleeding when using hormone replacement therapy (HRT). The anxiety regarding no-bleed regimens is that breakthrough bleeding and endometrial hyperplasia may occur, particularly if the woman has high oestradiol levels when starting treatment.

Studies have already shown that the 25 mg dosage oestradiol implant is effective for control of climacteric symptoms with favourable metabolic effects[1]. It has also been shown that significant increases in bone density can be achieved with this dosage[2].

The primary outcome measure of this study was to demonstrate the endometrial safety of 25 mg oestradiol implants when used in a continuous combined regimen with low dose progestogen. Secondary outcome measures included hormonal parameters, biochemical bone markers and dual energy X-ray absorptiometry (DEXA) bone densitometry.

Methods

Following ethics approval for the study and signed consent, 22 postmenopausal women with greater than 12 months of amenorrhoea were recruited from the menopause clinic at The Chelsea and Westminster Hospital. Symptoms were assessed for a month at baseline using a prospective menstrual and menopausal symptom diary. Hormonal analysis consisted of follicle-stimulating hormone and oestradiol estimation. Transvaginal ultrasound scanning was carried out for endometrial thickness and Pipelle de Cornier sampling of endometrium was performed to determine histology.

Patients were treated with 25 mg oestradiol crystalline implants (Organon Laboratories, Cambridge), which were inserted every six months either in the lower abdomen or in the upper thigh areas. One tablet per day of 1 mg norethisterone (Primolut N, Upjohn Laboratories) was taken from the day of implantation continuously. Patients were advised that should they wish to discontinue the oestradiol implants they would have to continue with the progestogen for a minimum of one year in order to prevent endometrial hyperplasia from unopposed oestrogenic action. Compliance with the norethisterone was ensured by asking patients to return any unused tablets every six months.

Skeletal assessment was carried out using a Hologic 1000 bone densitometer with dual energy X-ray absorptiometry by a radiologist. Daily calibration of the system was carried out with a spine phantom and the variation coefficient was found to be 0.5%. Bone density data were

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compared with an untreated age and body mass index (BMI) matched historical control group of postmenopausal women who had been recruited from the same unit.

Serum was also taken for biochemical bone markers and immediately stored at −20 before analysis at the Department of Chemical Pathology at Charing Cross Hospital under Good Laboratory Practice. Bone formation was assessed using kits for P1CP (serum type 1 procollagen C terminal peptide) and resorption by 1CTP (serum type 1 collagen C terminal telopeptide).

Data were non-parametric and are therefore expressed as medians with ranges. Comparisons are made using the Wilcoxon test for related pairs and Mann–Whitney for unrelated data (comparison to control group data).

Results

Twenty-two women were recruited to the study with a mean age of 62 years (range 50–71) and a body mass index of 26.5 (range 20.2–34.1). The median age of menopause was 51 (range 40–53). At one year, 12 patients were completely amenorrhoeic and 7 patients had occasional spotting. Two women withdrew after less than six months due to breakthrough bleeding and one due to mastalgia.

Median oestradiol levels rose from 77 pmol/L at baseline to 275 pmol/L at one year. The median endometrial thickness remained unchanged at 4 mm at baseline and one year (Table 1).

In 12 women in which samples were obtainable, there was one case of a weakly proliferative endometrium at one year. Nine samples were atrophic and two were secretory. There were no cases of endometrial hyperplasia. In all the cases in which a sample was not obtainable, the double endometrial thickness was less than 4 mm and so it was not felt necessary to proceed with dilatation and curettage under general anaesthetic.

Median lumbar bone density (L2–L4) rose significantly from 0.939 to 0.992 g/cm^2 (+5.6%, $P = 0.005$) and total femoral density rose from 0.872 to 0.890 g/cm^2 (+2.1%) as did the respective age matched scores (Z score: lumbar spine +8.5% and total femur +5%) at one year compared with baseline (Table 1).

The results were compared with a historical, age and BMI matched control group of 14 postmenopausal women from our unit who had elected not to receive treatment for one year. The lumbar spine density in this group declined by 1.34% and the total femoral density declined by 0.48%. The changes in bone density between the treatment and no-treatment groups were significant ($P < 0.01$).

Markers of bone turnover indicated a significant increase in bone formation as assessed by P1CP and a significant decrease in bone resorption as assessed by serum 1CTP (Table 1).

Discussion

This is a novel report of usage of low dose 25 mg oestradiol implants and continuous 1 mg norethisterone as continuous combined HRT. Satisfaction rates were high, there were beneficial effects on the skeleton and endometrial safety was good. The dropout rate was low: 2/22 (9%) due to irregular bleeding and 1/22 (4%) due to mastalgia. These women declined a second implant at six-month follow up. The low dropout rate may reflect the acceptability of having the oestrogenic component in a low dose implanted formulation that avoids first pass metabolic effects and produces physiologic (midfollicular phase) oestradiol levels.

Initial bleeding problems are a recognised phenomenon with continuous combined preparations[3] but did not deter the majority of patients in our study from persisting with the treatment after six months. The majority of ongoing patients were amenorrhoeic 12/19(63%) and the rest had only occasional spotting 7/19(37%). Although the gonadomimetic tibolone is associated with a low incidence of breakthrough bleeding (15–17%) in the first few months, patients who continue on continuous combined hormone therapy eventually have a similar bleeding pattern[4].

There were no cases of endometrial hyperplasia at one year. Of 12 patients, 1 (8%) had a weakly proliferative endometrium and 2 (16.6%) had a secretory endometrium, but the majority (9, 75%) had an atrophic endometrium. In the seven cases where it was not possible to obtain a Pipelle sample of endometrium, the double thickness lining

Table 1. Endocrinology, DEXA bone densitometry and biochemical bone markers.

Median results	Baseline	One year	P*
E_2, pmol/L, median (interquartile range)	77 (41.5–153.5)	275 (152–339)	0.0007
FSH, iu/L, median (interquartile range)	73.6 (46.0–94.0)	3.65 (1.9–11.9)	0.0001
L2–L4, g/cm^2 (interquartile range)	0.939 (0.874–0.988)	0.992 (+5.6%) (0.927–1.048)	0.0050
Total femur, g/cm^2 (interquartile range)	0.872 (0.779–0.923)	0.890 (+2.1%) (0.838–0.984)	0.0978
Z score spine (%)	103.0	111.5	
Z score hip (%)	103.5	108.5	
P1CP (interquartile range)	112.0 (88.5–121.0)	114.0 (100.5–131.5)	0.0376
1CTP (interquartile range)	3.00 (2.50–3.70)	2.90 (2.45–3.30)	0.2863

* Wilcoxon signed rank test.

was <4 mm and it is presumed that this was because the endometrium was so atrophic that it was not possible to sample. In the 3/22 cases that dropped out at six months, the endometrium was secretory in nature. Others have also found a favourable effect on the endometrium using continuous combined therapy, even in a study from our unit where patients had been followed up for eight years[5]. It was encouraging that the low dose progestogen regimen used in this study adequately protected the endometrium in women using oestrogen implants for one year and unpublished data from our unit suggests this protective effect continues in patients using the same regimen for more than five years.

The effect of therapy on biochemical bone markers was encouraging. The bone formation marker increased significantly and bone resorption fell, although not significantly. Others have found a similar effect on bone markers with oral continuous combined therapy, in that bone resorption was decreased. However, bone formation was not increased with oral therapy suggesting that implants produce a more anabolic effect[6].

There was a very favourable effect on DEXA bone densitometry in the lumbar spine and total femur with a significant increase of 8.5% age matched bone density in the lumbar spine and a smaller increase in the femoral neck of 5.0% age matched bone density. These were highly significant increases compared with the matched control group of postmenopausal women who had not been on any therapy. These results were not surprising as previous work in our unit had suggested an anabolic effect on the skeleton of 25 mg oestradiol implants with sequential progestogens[2]. The degree of gain in bone density is greater than others have found with either oral continuous combined preparations or the gonadomimetic tibolone, which tend to increase bone density by approximately 2–5% per annum[7].

Public awareness of the consequences of the menopause has increased in recent years. As a result, postmenopausal women in their late 50s and 60s, as in our study, are seeking prophylaxis from the long term consequences of oestrogen deficiency; that is, osteoporosis, cardiovascular disease and Alzheimer's/multi-infarct dementia. These women have a susceptibility to the side effects of HRT (e.g. breast tenderness, progestogenic (PMS-like) side effects and a desire not to start bleeding again[8]). We should aim to tailor make their HRT to minimise side effects and maximise benefits to achieve good compliance. HRT of this nature encourages compliance by minimising undesirable side effects while maintaining the benefits on the skeleton. There have been many favourable reports of oral continuous combined therapeutic regimens and more recently transdermal systems[9].

In our opinion, our preliminary data provide encouraging evidence of the acceptability and safety of low dose oestradiol implants with low dose continuous progestogen. The recent development of a simple injection device for 25 mg oestradiol implants (Riselle, Organon Laboratories) now available in some countries should further increase the acceptability and compliance with this therapeutic regimen.

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